Issues in Radiological pathology
Index

Radiological pathology of embolic brain infarction
Radiological pathology of hemorrhagic infarction
Radiological pathology of microvascular cerebral hemorrhage
Radiological pathology of ischemic microvascular cerebral disease
Radiological pathology of transient ischemic attacks
Radiological pathology of intracranial aneurysms and subarachnoid hemorrhage
Radiological pathology of multi-infarct dementia
Radiological pathology of cerebral sino-venous thrombosis
Radiological pathology of intracranial diffuse astrocytomas
Radiological pathology of pilocytic astrocytoma
Radiological pathology of meningiomas
Radiological pathology of pituitary adenomas
Radiological pathology of cerebral butterfly tumors
Radiological pathology of brain edema
Radiological pathology of dissemination of primary brain tumors
Radiological pathology of hereditary ataxias
Radiological pathology of multi-system atrophy
Radiological pathology of developmental brain disorders
Radiological pathology of Neuro-Behcet
Radiological pathology of neurosarcoidosis
Radiological pathology of tuberous sclerosis
Radiological pathology of Wagener granulomatosis
Radiological pathology of degenerative disc disease

©www.yassermetwally.com corporation, all rights reserved
RADIOLOGICAL PATHOLOGY OF CEREBRAL INFARCTION

Stroke is the number three cause of mortality in the adult population and affects more than 400,000 people in the United States annually. Ischemic infarcts account for approximately 85% of all strokes. Previously the medical management of infarcts primarily involved diagnosis, stabilization during the acute period, and subsequent rehabilitation. As a result of the development of new therapy options, including thrombolytic agents and brain-protective drugs, stroke is increasingly becoming a treatable condition. These treatment choices have created a significant impetus for the early clinical and radiographic detection of acute infarcts.

Although magnetic resonance (MR) imaging has been shown to be more sensitive than computed tomography (CT) in detecting acute strokes within the first 24 hours, CT remains the emergent imaging test of choice to evaluate acute ischemia. It is fast, noninvasive, and readily available in almost all hospitals. Despite its limitations, CT continues to be used for all major stroke therapy trials. Until other methods of stroke
imaging, such as xenon CT and MR diffusion/perfusion, become widely and rapidly available in most institutions, CT remains the primary screening tool for acute ischemia.

**CLINICAL IMPORTANCE OF EARLY STROKE DETECTION BY CT**

Two major drug trials testing the safety and efficacy of early thrombolytic therapy have been completed in the past 4 years. Although both studies demonstrated improved clinical outcomes after the administration of intravenous thrombolytic drugs, the results were dependent on the appropriate screening of potential patients. The National Institute of Neurological Disorders (NINDS) and Stroke rt-PA Stroke Study Group treated 624 acute stroke patients with either intravenous recombinant human tissue plasminogen activator (tPA) or placebo within 3 hours of the onset of Symptoms. Despite an overall increased incidence of symptomatic intracerebral hemorrhage in the therapeutic group, this study demonstrated an improved clinical outcome with thrombolytic therapy without a significant difference in mortality. Patients treated with tPA were 30% more likely to have minimal or no disability at 3 months compared with patients given a placebo.

Further analysis of the NINDS data demonstrated that intracranial hemorrhage was a more common complication in patients with edema or infarct on the initial scan, occurring in 31% of these patients compared with 6% of cases without early CT findings. Despite this complication, this subset of patients was still more likely to have an improved clinical outcome at 3 months. The study therefore concluded that patients with edema or mass effect on the baseline CT were candidates for tPA if it was administered within 3 hours of the onset of symptoms.

A second study was conducted by the European Cooperative Acute Stroke Study (ECASS). This group treated 620 stroke patients with either intravenous thrombolytic agent or placebo within 6 hours after the onset of symptoms. Patients with evidence of major ischemic changes, defined as hypodensity lesions involving greater than 33% of the middle cerebral artery (MCA) territory already visible at the time of the first scan, were to be excluded from the protocol. Fifty-two patients with CT findings of extended infarcts were incorrectly admitted into the study because of misinterpretation of the initial film. These patients had no beneficial effect from intravenous tPA and demonstrated a mild increased rate of fatal cerebral hemorrhage compared with the remaining population. The 215 patients with small hypodensity lesions experienced an increased chance of good outcome if treated with intravenous thrombolytic therapy. ECASS originally concluded that although intravenous thrombolytic therapy was effective in improving neurologic outcome in a subset of patients with moderate to severe neurologic deficit and no evidence of extended infarct on CT scan, its use was not recommended because of difficulty in identifying this subgroup and the associated unacceptable risk of increased hemorrhagic complications and death.

A subsequent reanalysis of the ECASS data, which correctly reclassified the patients with extended ischemic changes, demonstrated that (1) response to tPA is different for patients with no, small, or large areas of edema visible on initial CT and (2) patients with large ischemic zones already apparent on the initial CT scan most likely will not benefit from
thrombolytic therapy. Treatment with tPA significantly increased the cure rate of patients with no or small cytotoxic edema by 8% and 18% but decreased the cure rate to 6% for patients with large cytotoxic edema. If patients with extended infarcts already present on the initial scans are excluded from the treatment population, the probability of clinical improvement with thrombolytic therapy increases.

The results of these two studies underscore the importance of careful clinical and radiologic screening before the administration of thrombolytic drugs. Although tPA has the potential to improve clinical outcomes of patients with acute strokes, the drug must be given to the appropriate population within a relatively small time window. If treatment is delayed or CT scans are not accurately interpreted, the potential benefits of thrombolytic therapy can be negated.

CT FINDINGS IN ACUTE STROKE

When reviewing the CT scan of potential stroke patients, the radiologist should systematically answer several questions that determine the patient's medical management. Can the cause of the neurologic problem be identified on the scan? Are the findings consistent with an acute ischemic infarct, or is there another abnormality? Many neurologic disorders can mimic an acute infarct, including tumors, subdural hematomas, hemorrhages from underlying masses or vascular malformations, and venous occlusive disease. These diagnoses can often be excluded on noncontrast CT scans; however, additional imaging, including contrast-enhanced CT or MR examinations, may be needed to confirm the diagnosis.

When the diagnosis of ischemic infarct is suspected, careful review of the film for evidence of major arterial occlusion, early parenchymal edema, or hemorrhage is indicated. These findings help determine if thrombolytic therapy is indicated and may influence how it is administered, either intravenously or intraarterially. Identification of hemorrhage is crucial because its presence precludes thrombolytic therapy.

VASCULAR FINDINGS IN ACUTE INFARCTION

Asymmetric hyperdensity within a major cerebral artery represents one of the earliest CT signs of stroke and is caused by occlusion of the vessel from either an embolus or a thrombus. The density of blood on CT is linearly related to the hemoglobin concentration. Flowing blood has a density of approximately 40 Hounsfield units (HU) with a normal range of 35 to 60 HU. When a thrombus or embolus occurs, serum is extruded from the clot producing an increase in the hemoglobin concentration and a subsequent increase in density. Intraluminal thrombus measures approximately 80 HU with a range of 77 to 89 HU. Atheromatous vessels typically have higher densities because of the presence of wall calcification and usually measure between 114 and 321 HU.
The hyperdense artery sign has been described primarily in the MCA and basilar artery. Because of their extended courses through the subarachnoid space, these arteries are easily visualized and can be directly compared with other arterial and venous structures. A few cases of calcified emboli to the anterior cerebral artery have been reported; however, noncalcified occlusion of the anterior cerebral distribution is rarely detected. Hyperdense cerebral arteries usually resolve within 1 week secondary to lysis of the clot and recanalization of the vessel.
Figure 2. A 62-year-old man who presented with sudden onset of left hemiparesis and confusion. A, Noncontrast axial CT scan performed 90 minutes after the onset of symptoms demonstrates a linear hyperdensity in the region of the right middle cerebral artery (arrow) consistent with a hyperdense middle cerebral artery sign. Compare with the normal density of the left middle cerebral artery. B, A more superior image of the initial scan demonstrates loss of the insular ribbon (arrows) consistent with early ischemic change in the right MCA distribution. Bilateral remote occipital infarcts are also noted. The patient was started on IV thrombolytic therapy; however, one hour after the infusion began, the patient developed hypotension and seizure activity. A repeat CT scan was performed to evaluate for possible hemorrhage. C, Noncontrast CT scan performed three hours after ictus demonstrates obscuration of the right lenticular nuclei representing progression of ischemic change. D, CT scan performed 24 hours later demonstrates a large infarct involving the majority of the right middle cerebral artery distribution producing mild mass effect.
The hyperdense MCA sign (HMCAS) has been well described in the literature as one of the earliest signs of MCA infarct. It is associated with occlusion of the proximal MCA or its branches and has been identified in 35% to 50% of patients presenting with clinical signs of acute MCA stroke.2,3,6,43

Proximal MCA occlusion is one of the most serious cerebrovascular occlusive conditions. Mortality associated with MCA occlusion can range from 5% to 45%, and survivors typically have severe neurologic deficits.17,32,43 If collateral circulation is inadequate, these strokes can produce malignant brain edema, uncal herniation, and subsequent compression of the midbrain. Rapid detection and early, aggressive treatment of proximal MCA occlusion is indicated to reduce both mortality and morbidity.

Studies have demonstrated that the HMCAS predicts a poorer clinical outcome compared with patients without the sign.19,31 Occlusion of the proximal M1 segment of the MCA correlates with an infarct of 100 mL or greater in the majority of cases.36 Tomsick et al. noted that the HMCAS is associated with a poor response to intravenous thrombolytic therapy. Clinical follow-up performed 3 months after intravenous tPA demonstrated that patients with a positive HMCAS had larger infarcts and were significantly less likely to be completely neurologically improved compared with the patients without an HMCAS. These results indicate that patients with an HMCAS, if detected before the formation of extensive parenchymal ischemic changes, may benefit from more aggressive initial treatment, such as intra-arterial thrombolysis.

Several conditions may mimic a hyperdense thrombosed vessel, including a high hematocrit or vessel wall calcification. To prevent false-positive results, the radiologist should closely adhere to a narrow definition of HMCAS. The HMCAS is defined as an MCA that is denser than its counterpart and denser than any visualized vessel of similar
size that is not attributable to vessel calcifications. Using this definition, the HMCAS is an accurate and moderately sensitive tool in detecting early MCA occlusion. In a blinded analysis performed by six neuroradiologists, Tomsick et al. demonstrated a sensitivity of 78%, specificity of 93%, and accuracy of 91% for the HMCAS.

**PARENCHYMAL CHANGES OF ACUTE INFARCTION**

- **Pathophysiology**

The CT detection of acute infarcts depends on the development of edema within the brain parenchyma, which produces subtle density changes and mass effect. To understand better the CT findings of acute ischemia, a brief review of the histologic changes that occur during a stroke are presented.

**Table 1. Pathological stages of cerebral infarction**

<table>
<thead>
<tr>
<th>Time</th>
<th>Gross pathology</th>
<th>Microscopical pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>From 8-18 Hr</td>
<td>The damaged zone become pale, and the demarcation between the white and gray matter is indistinct. Edematous swelling is apparent and accompanied by cortical congestion. At this stage the infarcted area is soft in consistency.</td>
<td>Ischemic neuronal death, with capillary endothelial swelling accompanied by exudation of edematous fluid and extravasation of RBCs even in anemic infarction</td>
</tr>
<tr>
<td>2-10 days</td>
<td>The edema and the swelling persist but to a decreasing degree and the infarcted zone becomes friable and its boundary becomes better defined.</td>
<td>Stage of phagocytic acivity and parenchymatous liquefaction: Exudation of neutrophil leukocytes begins for a brief time and causes inflammatory reaction and is replaced on the second day by macrophages laden with Sudanophilic breakdown products originating from disintegration of myelin sheaths. Macrophage activity becomes most marked from the 5th to the 30th day i.e. during the phase of parenchymatous liquefaction</td>
</tr>
<tr>
<td>After 10 days</td>
<td>Liquefaction begins and after 3 weeks cavitations becomes more evident. From then on the necrotic tissues is replaced by yellowish tissue which causes depression of the cerebral cortex.</td>
<td></td>
</tr>
</tbody>
</table>
Normal cerebral blood flow ranges from 50 to 60 mL/100 g tissue/min. During an ischemic infarct, blood supply to a portion of the brain is significantly reduced. As cerebral blood flow decreases, injury occurs in the brain progressing from electrical dysfunction to reversible cellular damage and eventually to cell death. At approximately 20 mL/100 g, electrical activity in the brain ceases, and water homeostasis begins to be disrupted. At critical flow rates of 10 to 15 mL/100 g, there is disruption of ion homeostasis within the cells producing rapid increases of extracellular potassium and intracellular sodium. This disruption causes water to shift into the intracellular compartment producing astrocytic swelling (cytotoxic edema).

Severe ischemia can cause a 7 to 8 HU change at 1 hour that should be visible on CT. With marginal cerebral blood flows between 15 and 20 mL/100 g, ischemic edema takes longer to develop and may not be detected on early CT scans. The development of cytotoxic edema aggravates ischemia by causing progressive compression of the microcirculation, which further decreases blood flow. As the ischemic changes worsen, capillary walls become permeable allowing leakage of intracellular proteins and subsequent accumulation of extracellular water (vasogenic edema). Worsening edema produces additional mass effect causing a decrease in cerebral perfusion pressure and collateral flow. Cytotoxic edema may be detectable within 1 hour of the onset of stroke; however, vasogenic edema usually does not develop until 6 hours or more after ictus.

Figure 4. Acute infarctions with mass effect due to edema
Table 2. Comparison between the cytotoxic and vasogenic edema of recent infarction

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cytotoxic (intracellular)</th>
<th>Vasogenic (extracellular)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>Within 1 hour of the onset of stroke</td>
<td>Does not develop until 6 hours or more after ictus.</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>At critical flow rates of 10 to 15 mL/100 g, there is disruption of ion homeostasis within the cells producing rapid increases of extracellular potassium and intracellular sodium. This disruption causes water to shift into the intracellular compartment producing astrocytic swelling (cytotoxic edema).</td>
<td>The development of cytotoxic edema aggravates ischemia by causing progressive compression of the microcirculation, which further decreases blood flow. As the ischemic changes worsen, capillary walls become permeable allowing leakage of intracellular proteins and subsequent accumulation of extracellular water (vasogenic edema).</td>
</tr>
<tr>
<td>Composition</td>
<td>Increased intracellular water and sodium</td>
<td>Plasma filtrate including plasma proteins</td>
</tr>
<tr>
<td>Location of edema</td>
<td>Gray and white matter</td>
<td>Chiefly white matter</td>
</tr>
<tr>
<td>Pathology</td>
<td>Cellular swelling, usually of astrocytes in the grey matter.</td>
<td>Grossly, the gyri are flattened and the sulci narrowed; the white matter is moist and swollen. Microscopically, there is micro-vacuolization of the white matter, poor staining, and &quot;halo's&quot; around nuclei.</td>
</tr>
<tr>
<td>Capillary permeability to large molecules</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Neuroimaging</td>
<td>Normal</td>
<td>(1) obscuration of the lentiform nucleus, (2) loss of the insular ribbon, (3) diffuse low density with loss of the gray-white interface, and (4) sulcal effacement, (5) mass effect</td>
</tr>
</tbody>
</table>

Ischemic changes that occur above 15 mL/100 g can be reversible. At flow rates below 10 to 15 mL/100 g, tissue damage is usually irrevocable after 1 hour of hypoperfusion. Other factors also play a role in the reversibility of ischemic changes. During low levels of perfusion, small amounts of glucose may be available to brain tissue for glycolysis, but oxidation cannot occur. The subsequent development of lactic acidosis adversely affects the viability of brain tissue.

- **Sensitivity of CT in Evaluating Acute Ischemia: How Early Can Stroke Be Detected?**

How quickly an acute infarct can be visualized is governed primarily by the severity of hypoperfusion; however, the duration, size, and location of ischemia also play important roles. When cerebral blood flow drops below the critical value of 10 to 15 mL/100 g, ischemic changes are usually irreversible, and edema develops fast, permitting early detections.

As edema progresses, water content within the parenchyma increases. This increase causes a subsequent decrease in the brain's specific gravity, which is linearly proportional to CT attenuations. In other words, as edema increases, brain density proportionately decreases. A 1 % change in water content changes the CT attenuation by 2.6 HU. Typically a change of 4 HU or greater is needed to detect the change visually. In cases of severe ischemia caused by proximal MCA occlusion, cytotoxic edema can produce a 3% increase in water within 1 hour of the onset of symptoms. This can increase to 6% at 2 to 4 hours. Therefore, severe ischemia can cause a 7 to 8 HU change at 1 hour that should be visible on CT. With marginal cerebral blood flows between
15 and 20 mL/100 g, ischemic edema takes longer to develop and may not be detected on early CT scans.

In the future, more advanced imaging techniques, such as MR perfusion and xenon CT, may play an important role in determining the cerebral blood flow of ischemic areas to help determine tissue viability. Until then, noncontrast CT can provide important information. If hypoperfusion is less severe and collaterals to an ischemic area are adequate, edema may not develop, and early CT scans are negative. Conversely the presence of more extensive edema on an early CT scan indicates severe hypoperfusion and may predict a less favorable outcome after thrombolytic therapy.

The sensitivity of early CT scans in detecting acute strokes also depends on the duration, location, and size of the infarct. As the time of ischemia increases, CT abnormalities become more obvious; however, the absolute presence or absence of edema primarily relies on the severity of hypoperfusion and adequacy of collateral circulation. Larger infarcts are visible earlier than smaller infarcts because of the increased volume of tissue involved (i.e., MCA infarcts are detected sooner than small cortical or lacunar infarcts).

Several researchers have studied the sensitivity and accuracy of detecting infarcts on CT. Bryan et al. performed MR imaging and CT scans on 31 stroke patients within 24 hours of the onset of their symptoms. The locations of the infarcts included the posterior fossa as well as supratentorial cortical, subcortical, and combined lesions. Eighty-two percent of early MR imaging scans showed an abnormality compared with 58% of CT scans. On follow-up examinations performed 7 to 10 days later, approximately 90% of both MR imaging and CT scans were abnormal. Mohr et al. demonstrated that although CT showed deep and brain stem infarcts less often than MR imaging, it was equally sensitive in detecting convexity lesions.

When analysis is restricted to the assessment of MCA infarcts, the overall sensitivity of CT significantly increases. Moulin et al. reviewed 100 patients with MCA stroke. Ninety-four percent of all CT scans performed within 14 hours after the onset of symptoms were abnormal; 88% of CT scans obtained within 6 hours of ictus were abnormal. These results compare favorably with data of von Kummer et al. A review of 44 patients demonstrated that CT performed within 6 hours of the onset of symptoms has an accuracy of 95% and a mean sensitivity of 82% of detecting MCA infarcts. CT scans performed within the first 2 hours of symptoms, however, were much less sensitive in detecting early ischemia. Truwit et al. and Tomura et al. described subtle findings of MCA stroke that can increase the sensitivity of CT to greater than 90% in detecting major MCA occlusions.

The presence of parenchymal changes on early CT scans also correlates with the degree of intracranial occlusive disease. Horowitz et al. studied 50 patients with ischemic strokes that produced at least hemiparesis. CT scans were performed within 4 hours of ictus and were correlated with angiography or carotid ultrasound. Acute CT abnormalities, including hypodensities and mass effect, were seen in 56% of patients. When there was major vascular occlusion, however, either occlusion of the MCA trunk or two or more MCA branches, the CT scan was positive in 86% of cases.
CT Findings

Several articles describing early CT findings of acute infarcts have been published in recent years. These findings have primarily focused on MCA ischemia and have significantly improved the overall sensitivity of CT in detecting early MCA infarcts. The major CT findings of acute MCA stroke include (1) obscuration of the lentiform nucleus, (2) loss of the insular ribbon, (3) diffuse low density with loss of the gray-white interface, (4) sulcal effacement, (5) gray matter enhancement and (6) hemorrhagic infarction.

- Obscuration of the Lentiform Nucleus.

In 1988, Tomura et al. described obscuration of the lenticular nucleus as an early sign of MCA infarct. This finding is caused by cellular edema arising within the basal ganglia and closely correlates with a proximal MCA occlusion. Twenty-five patients who had clinical evidence of MCA infarcts underwent CT scanning within 6 hours of the onset of symptoms. The scans were then retrospectively reviewed for obscuration of the lenticular nuclei as well as decreased density within the brain parenchyma and sulcal effacement. Twenty-three of the patients (92%) demonstrated an obscured outline or partial disappearance of the lentiform nucleus. This sign was visualized earlier than other CT findings and in a few cases was present within 1 hour after the onset of the stroke. Parenchymal hypodensities and sulcal effacement occurred later and were present on significantly fewer initial scans.

The lenticular nuclei receive their blood supply from the lenticulostriate arteries which arise from the MI trunk of the MCA. Collateral circulation to this area is poor compared with the cortex. Occlusion of the proximal MCA disrupts the primary blood supply to these structures. As a result of the insufficient collaterals as well as the relatively high metabolic rate of the lenticular nuclei, proximal MCA occlusion can quickly cause critically low cerebral blood flow, which produces early ischemic changes on CT.

Firlick et al. performed CT, xenon CT, and angiography on 20 patients with acute MCA infarcts. Early CT changes in the basal ganglia were associated with significantly lower cerebral blood flows in the MCA territory compared with patients with normal CT scans. An early basal ganglia hypodensity correlated with a mean cerebral blood flow in the affected MCA territory of less than 10 mL/100 g. Patients with more distally located occlusions, beyond the origins of the lenticulostriate arteries, preserve blood supply to the basal ganglia and do not develop this early sign.

Bozzao et al. evaluated 36 patients with acute MCA infarcts with CT and angiography and correlated changes on early CT scans with the angiographic findings. CT scans were performed within 4 hours, and angiograms were obtained within 6 hours from the onset of symptoms. Bozzao et al. noted that all patients with early CT findings of MCA infarcts demonstrated an arterial occlusion on angiography. Involvement of the lenticular nuclei corresponded closely with a proximal MCA occlusion.
Loss of the Insular Ribbon. (LIR)

Another early sign of acute MCA infarction is loss of the insular ribbon (LIR) which is described as loss of definition of the gray-white interface in the lateral margins of the insula. This area is supplied by the insular segment of the MCA and its claustral branches and is the region most distal from anterior and posterior cerebral collateral circulation. As a result, collateral flow to the insular region is decreased compared with other portions of the cerebral cortex.

Truwit et al performed both retrospective and prospective evaluations of CT scans in patients with clinical evidence of acute MCA distribution infarcts to evaluate the sensitivity and accuracy of the LIR sign. In a retrospective analysis of 11 cases, LIR was seen in all patients (100%). In a prospective study, the LIR sign was identified in 12 of 16 patients (75%). Obscuration of the lenticular nucleus occurred less frequently and was identified in 73% and 63% of patients. They concluded that LIR is more frequently observed in acute MCA infarcts than other early CT findings.

In two patients, the LIR was localized to the posterior segment of the insula and was associated with a more limited infarct. This situation may be due to more distal occlusion of posterior MCA branches within the operculum.

The presence of obscuration of the lenticular nucleus or LIR without other signs of extensive infarct does not preclude the use of thrombolytic agents. These patients may receive significant benefit from intravenous or intraarterial thrombolysis; because of the presence of early CT changes, however, they may be more likely to have areas of irreversible damage compared with patients with negative CT scans.

Diffuse Parenchymal Hypodensity and Sulcal effacement.

As ischemic changes progress, both cytotoxic and vasogenic edema increase producing areas of hypoattenuation throughout the affected circulation. In larger infarcts, mass effect also increases producing effacement of sulci and compression of ventricles.

Figure 6. A 52-year-old woman who presented with sudden onset of left arm weakness. A and B, CT scan performed three hours after the onset of symptoms demonstrates focal loss of the insular ribbon posteriorly (arrows). A more superior image performed through the lateral ventricles demonstrates an area of low attenuation in the right posterior frontal cortex with loss of the gray-white interface (arrows) consistent with ischemic change in the right MCA distribution.
Detection of anterior and posterior cerebral artery infarcts as well as posterior fossa lesions relies predominantly on the presence of parenchymal hypodensity and sulcal effacement. As a result of the lack of other subtle CT findings, such as obscuration of the lenticular nucleus and LIR, these infarcts may not be detected as early as large MCA strokes.

In cases of MCA infarcts, extensive parenchymal hypodensity on early CT scans is associated with a high mortality rate as well as a poor clinical outcome in survivors. When greater than 50% of the vascular territory was involved, the mortality rate increased up to 85% because of malignant brain edema. Early craniectomy decreases the mortality rate for patients with severe edema; however, clinical outcome remains poor.

Figure 7. A 67-year-old man who presented with a 5-hour history of left leg weakness. A and B, CT scan shows subtle low attenuation and loss of sulcation in the right parasagittal frontal lobe extending to the convexity (arrowheads) consistent with an anterior cerebral artery distribution infarct. C, MR diffusion scan demonstrates abnormal high signal in the right frontal parasagittal region confirming the diagnosis of an ACA infarct.

The presence of extensive ischemic change typically excludes the use of thrombolytic therapy. The likelihood of clinical improvement is low, whereas the rate of complication, including hemorrhage, is significantly increased. In the future, faster mechanical methods of removing clot within the MCA may offer benefit to these patients; however, in most cases, irreversible damage has been done.
### TABLE 3. EARLY CT SCAN FEATURES OF HYPERACUTE ISCHEMIC STROKE

<table>
<thead>
<tr>
<th>RADIOLOGICAL FEATURE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperdense thrombosed vessel,</td>
<td>When a thrombus or embolus occurs, serum is extruded from the clot producing an increase in the hemoglobin concentration and a subsequent increase in density. The hyperdense MCA sign (HMCAS) has been well described in the literature as one of the earliest signs of MCA infarct. It is associated with occlusion of the proximal MCA or its branches and has been identified in 35% to 50% of patients presenting with clinical signs of acute MCA stroke. It is defined as an MCA that is denser than its counterpart and denser than any visualized vessel of similar size that is not attributable to vessel calcifications.</td>
</tr>
<tr>
<td>Diffuse Parenchymal Hypodensity and Sulcal effacement.</td>
<td>A 1% change in water content changes the CT attenuation by 2.6 HU. Typically a change of 4 HU or greater is needed to detect the change visually. In cases of severe ischemia caused by proximal MCA occlusion, cytotoxic edema can produce a 3% increase in water within 1 hour of the onset of symptoms. This can increase to 6% at 2 to 4 hours. Therefore, severe ischemia can cause a 7 to 8 HU change at 1 hour that should be visible on CT. If hypoperfusion is less severe and collaterals to an ischemic area are adequate, edema may not develop, and early CT scans are negative. Conversely the presence of more extensive edema on an early CT scan indicates severe hypoperfusion and may predict a less favorable outcome after thrombolytic therapy.</td>
</tr>
<tr>
<td>Loss of the Insular Ribbon. (LIR)</td>
<td>Loss of definition of the gray-white interface in the lateral margins of the insula.</td>
</tr>
<tr>
<td>Obscuration of the Lentiform Nucleus.</td>
<td>Obscuration of the lenticular nucleus is an early sign of MCA infarct. This finding is caused by cellular edema arising within the basal ganglia and closely correlates with a proximal MCA occlusion.</td>
</tr>
</tbody>
</table>

- **Gray matter enhancement (GME)**

One early pattern seen with MRI is areas of increased signal intensity (long T2) involving cortical and deep gray matter structures. This may be demonstrating the selective vulnerability of these structures to ischemia and hypoxia. A CT correlate of this MRI finding may be the inconsistently visualized regions of gray matter enhancement (GME). To date, nearly all cases of GME visualized by CT have shown a corresponding area of increased signal (long T2) by MRI. This long T2 abnormality, corresponding to the region, of GME may persist for years although a frank area of infarction may not be demonstrable by CT.
○ **Hemorrhagic infarction**

This type of infarction is regarded as distinct from anemic infarction although microscopical haemorrhage is frequent in the later. It has frankly hemorrhagic features which consist of petechial zones that are frequently confluent and are situated in the cortex. These hemorrhagic areas may involve the entire infarction but tend most often to involve the boundary zones supplied by meningeal arterial anastomosis or, in case of middle cerebral infarct, in the basal ganglia. Hemorrhagic infarction is secondary cortical reirregagation which takes place in the capillary blood vessels that have been damaged by the initial hypoxia. Reirregagation takes place when lysis (natural or by therapeutic thrombolysis) or secondary mobilization of the thrombus takes place.

![Figure 8: Haemorrhagic infarctions. They have frankly hemorrhagic features which consist of petechial zones that are frequently confluent and are situated in the cortex.](image)
Figure 9. A, Plain CT scan showing middle cerebral artery hemorrhagic infarction, notice petechial zones situated in the basal ganglia. B, MRI T2 image showing a left sided hemorrhagic infarction, notice cortical hypointense petechial zones composed mainly of deoxyhemoglobin.

- **Fogging effect**

Fogging is the temporary loss of visibility of an infarct on CT which occurs in the subacute phase at about 2 weeks after stroke. It occurs in up to 40% of medium to large infarcts on CT. Cerebral infarcts therefore may be overlooked or grossly underestimated if the scan is performed during the second and third week after stroke.  

Increase of x-ray attenuation on day 10 is known as the fogging effect and appears to be a favorable prognostic factor. Fogging is generally considered to be due to macrophage invasion and proliferation of capillaries within the infarct area, but probably also represents partial restoration of some viable tissue.
Figure 10. A, Initial CT scan examination showed multiple small hypodense lesions in the right parieto-temporo-occipital lobes, left occipital and left frontal lobe representing acute infarcts. B, Repeated CT examination 10 days later in the same patient as (A) showed that the lesions are no longer apparent (fogging effect)

○ Gyral Enhancement

Superficial enhancement of the brain parenchyma is usually caused by vascular or inflammatory processes and is only rarely neoplastic. Vascular causes of serpentine (gyral) enhancement include vasodilatation after reperfusion of ischemic brain, the vasodilatation phase of migraine headache, posterior reversible encephalopathy syndrome (PRES), and vasodilatation with seizures. Serpentine enhancement from breakdown of the blood-brain barrier is most often seen in acutely reperfused cerebral infarction, subacute cerebral infarction, PRES, meningitis, and encephalitis. The primary distinction between vascular and inflammatory causes of the serpentine pattern of enhancement relies on correlation with clinical history and the region of enhancement. An abrupt onset of symptoms suggests a vascular cause, whereas a more indolent history and nonspecific headache or lethargy suggests inflammation or infection. Gyral lesions affecting a single artery territory are often vascular, whereas inflammatory lesions may affect multiple territories. The most common vascular processes affect the middle cerebral artery territory (up to 60% of cases). However, PRES lesions usually localize in the posterior cerebral artery territory.
Vascular gyral enhancement results from various mechanisms with variable time courses. The earliest enhancement can be caused by reversible blood-brain barrier changes when ischemia lasts for only several hours before reperfusion occurs. Early reperfusion may also produce vasodilatation, with increased blood volume and shortened mean transit time. These features were first observed at conventional angiography; they were described as dynamic changes and were called "luxury perfusion" because of the increased blood flow. The increased blood flow is caused by autoregulation mechanisms, which are "tricked" by the increased tissue PCO2 that accumulates before reperfusion occurs. Ischemia or infarction may demonstrate gyral enhancement on both CT and MR images within minutes (with early reperfusion). In the healing phases of cerebral infarction, from several days (5–7 days) to several weeks after the event, there will be vascular proliferation or hypertrophy. Contrast enhancement usually fades away between 4 weeks and 4 months after the stroke, and enhancement is usually replaced by brain volume loss. The vascular changes facilitate the breakdown and removal of the dead brain tissue and lead to the encephalomalacia and atrophy characteristic of old "healed" infarction. The imaging appearance of postictal states may mimic the findings of cerebral infarction in several features, including gyral swelling, increased signal intensity on T2-weighted images and decreased signal intensity on T1-weighted images, sulcal effacement, and gyral enhancement. Reperfusion, whether
acute (eg, after thrombolysis) or subacute to chronic ("healing" infarction), is required to deliver contrast material to produce enhancement.

Figure 12. Cortical gyral enhancement in embolic cerebral infarction in a 65-year-old woman. (a) On an axial nonenhanced CT scan, the sulci in the right hemisphere are normally prominent; on the left, the parietal sulci are effaced within a wedge-shaped region of abnormal hypoattenuation. The gyral surface is actually slightly hyperattenuating due to reperfusion injury with secondary petechial hemorrhage in the infarcted cortex. (b) Axial contrast-enhanced CT scan shows cortical gyral enhancement. The same endothelial damage that allows red cells to extravasate also permits contrast material to escape the vascular lumen and enter the brain parenchyma.
Figure 13. Cortical gyral enhancement in subacute thrombotic cerebral infarction. (a) Axial contrast-enhanced CT scan shows enhancement that is limited to the opercular surfaces, insula, and caudate nucleus head (all of which are gray matter). (b) Photograph of an axially sectioned gross specimen shows green staining, which is caused by bilirubin bound to serum albumin, and which outlines areas of the brain where the blood-brain-barrier is no longer intact. Note how the green stain is almost exclusively in the gray matter of the cortex (arrowheads), basal ganglia (*), caudate nucleus, and claustrum. In these areas, the healing process would have removed the infarcted tissue, resulting in encephalomalacia and atrophy, if the patient had not died (the jaundiced patient died 2 weeks after left internal carotid thrombosis caused infarction of the anterior and middle cerebral artery territories).

**RADIOLOGICAL PATHOLOGY OF OLD INFARCTION**

During the first week, there is a transient inflammatory reaction, especially around blood vessels and in the meninges, due to release of arachidonic and other fatty acids. As the core of the infarcted area disintegrates, endothelial cells from the periphery proliferate and capillaries grow into the dead tissue. Neovascularization (which accounts for contrast enhancement) peaks at 2 weeks.

Mononuclear cells from the blood stream enter the infarct through damaged vessels. They ingest the products of degradation of neurons and myelin and are transformed into lipid-laden macrophages. Macrophage reaction appears early and peaks at 3–4 weeks. Astrocytes from the surrounding undamaged brain proliferate and form a glial scar around the
infarct (astrogliosis). This is completed in approximately 2 months. After that, the infarct remains unchanged. With maturation of new capillaries and glial scar formation, the blood brain barrier is once again sealed. Neurons do not regenerate. So, some brain tissue is lost forever.

With progression of time the infarction gets more hypodense and the mass effect gradually decreases with time due to gradual reduction of brain edema because the blood brain barrier is once again sealed. Negative mass effect is the end result. It is tempting to consider that these CT changes in old infarctions represent edema. The question then arises: Is this vasogenic edema or cytotoxic edema? Because the blood-brain barrier is sealed in old infarctions, vasogenic edema is unlikely. The cells are not dead or dying, so that cytotoxic edema is also unlikely.

Figure 14. A, subacute infarction, B, old infarction with extensive gliosis and cavitations

Figure 15. (A) Old infarction with extensive gliosis, microcavitations, the infarction is hypodense with negative mass effect (B)
Perhaps the edema results from the increased number of astrocytic cells that spread apart the normal myelinated axons of the white matter. The presence of significant amount of normal appearing astrocytes (hyperplasia), with marked cytoplasmic hypertrophy and low nuclear to cytoplasm ratio result in total increase in the water content of the brain. These cells may merely have different physical and chemical properties than the normal tightly packed bundles of axons that traverse through the brain. Astrogliosis is commonly associated with widened fluid filled extracellular spaces (microcavitations and macrocavitations) which definitely increase tissues water content resulting in the characteristic CT scan/MRI picture.48,49,50

Figure 16. With progression of time (from A to C) the infarction gets more hypodense, more well defined and the mass effect gradually decreases with time due to gradual reduction of brain edema because the blood brain barrier is once again sealed. The initial hypodensity in acute infarction is due to edema (A) while the the ultimate hypodensity in old infarction (C) is due to astrogliosis with widened fluid filled extracellular spaces (microcavitations and macrocavitations). During the evolution of the infarction the edema and the swelling decreases and the infarction boundary becomes better defined, and the infarcted area becomes more hypodense.
Astrocytes have extensive vascular foots. Astrogliosis (astrocytic hyperplasia) commonly results in the formation of a mesh with enlargement of extracellular spaces and extensive fluid-filled microcavitations. This, coupled with marked cytoplasmic hypertrophy of astrocytes that results in low nuclear to cytoplasm ratio, are responsible for the CT scan picture of old infarction.

Figure 18. Reactive astrocytosis. Notice the mesh between the astrocytes.
Table 4. Comparison between CT hypodensity of recent and old infarctions

<table>
<thead>
<tr>
<th>Etiology of CT hypodensity</th>
<th>Recent infarction</th>
<th>Old infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vasogenic edema (cytotoxic edema does not contribute to CT hypodensity)</td>
<td>Astroglisis with widened fluid filled extracellular spaces (microcavitations and macrocavitations)</td>
</tr>
</tbody>
</table>

**THROMBOLYSIS: WHO AND WHEN TO TREAT**

Both the radiologist and the clinician play important roles in determining who is a candidate for thrombolytic therapy and how it is administered. The clinician must carefully assess the patient for the extent of ischemic symptoms; time of onset; and presence of other complicating factors that may preclude thrombolysis, such as recent major surgery or other contraindications for anticoagulation. The radiologist then must carefully review the imaging studies for the presence of hemorrhage or extensive ischemic change that would prevent treatment.

![Figure 19](image19.png)

**Figure 19.** A 62-year-old woman who presented with a 4-hour history of right hemiparesis and aphasia. A and B, Noncontrast CT scan demonstrates a large area of low attenuation in the left middle cerebral artery distribution with obscuration of the lentiform nuclei, loss of the gray-white interface, and effacement of sulci. Due to the presence of a well-defined infarct this patient was not considered a candidate for thrombolytic therapy. C, CT scan performed 4 days later demonstrates a large left MCA infarct with mass effect and moderate midline shift to the right. A craniectomy has been performed to relieve intracranial pressure.

Patients may be considered for three different treatment options: intravenous, intra-arterial, or combined intravenous and intra-arterial thrombolysis. The type of thrombolytic therapy is determined by the duration and severity of symptoms. If a patient
presents within 3 hours of ictus and has no contraindications to thrombolysis, he or she is a candidate for intravenous tPA therapy. Intravenous therapy is not considered if the duration of ischemia is longer than 3 hours or the time of onset is unknown.

As mentioned earlier in this article, patients with major vessel occlusion, such as internal carotid, proximal MCA, or basilar artery thrombosis, have a poorer response to intravenous therapy compared with those with smaller branch occlusions and should be considered for intra-arterial therapy, if available. Clinical and radiographic features of this group include a dense vessel sign, either MCA or basilar; clinical evidence of ischemia in these vascular distributions; and a National Institutes of Health Stroke Scale Score greater or equal to 10.

Intra-arterial thrombolysis can also be administered after longer duration of ischemia than intravenous therapy. MCA occlusions can be treated up to 6 hours after onset of symptoms. After 6 hours, the risk of hemorrhage is believed to outweigh the potential benefits. Basilar artery occlusions typically have dire clinical outcomes and therefore may be treated up to 24 or 48 hours after ictus.

CONCLUSION

Despite the development of advanced imaging techniques, such as xenon CT, MR diffusion/perfusion, and MR angiography, CT scanning continues to play a major role in the assessment of acute strokes. Although CT is less sensitive than MR imaging in detecting acute ischemia, it is useful in screening patients for potential thrombolytic therapy. When reviewing CT scans of potential thrombolysis patients, several key points should be considered. The presence of hemorrhage is a contraindication for thrombolytic agents. Stroke patients with negative CT scans or small areas of edema are candidates for treatment; however, the presence of early MCA ischemic changes indicates more severe hypoperfusion, which may predict a poorer clinical outcome. Evidence of extensive MCA infarct on the initial CT scan usually precludes treatment with thrombolysis because of the increased risk of hemorrhage and decreased clinical benefit. The presence of a hyperdense MCA sign is associated with a poorer outcome after intravenous therapy; therefore, more aggressive therapy, such as intra-arterial thrombolysis, should be considered if technically feasible.
**TABLE 5. CT SCAN FEATURES ASSOCIATED WITH A POORER OUTCOME AFTER THROMBOLYTIC FEATURES**

<table>
<thead>
<tr>
<th>Radiological feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brain edema, diffuse low density on the initial CT scan</strong></td>
<td>The absolute presence or absence of edema primarily relies on the severity of hypoperfusion and adequacy of collateral circulation. The presence of more extensive edema on an early CT scan indicates severe hypoperfusion and may predict a less favorable outcome after thrombolytic therapy. The rate of complication, including hemorrhage, is significantly increased in this subgroup of patients.</td>
</tr>
<tr>
<td><strong>Hyperdense MCA sign</strong></td>
<td>It is associated with occlusion of the proximal MCA or its branches and it is present in 30% to 50% of patients presenting with clinical signs of acute MCA stroke.</td>
</tr>
<tr>
<td><strong>Sites of occlusion</strong></td>
<td>Internal carotid, proximal MCA, or basilar artery thrombosis, have a poorer response to intravenous therapy compared with those with smaller branch occlusions and should be considered for intra-arterial therapy, if available.</td>
</tr>
</tbody>
</table>

*Figure 20. Topography of the cerebral main vascular territories*
Figure 21. Topography of the cerebral main vascular territories

References


Created by Professor Yasser Metwally

http://yassermetwally.com
INTRODUCTION

A hemorrhagic infarction can be defined as an ischemic infarct in which an area of bleeding exists within ischemic cerebral tissue. This definition includes small hemorrhages confined to minor ischemic areas in gray matter as well as much larger areas involving cortical and deep lesions. Hemorrhagic infarction has been recognized as a complication of embolic stroke. In pathological studies, cerebral embolism was associated with hemorrhagic infarction in 50% to 70% of cases (13). In an angiographic study reported by Yamaguchi et al (4), the incidence of hemorrhagic infarction in patients with cardiogenic embolism was 37.5%, which was significantly higher than the 1.5% in patients with non-embolic stroke. A prospective survey by Hornig et al (5) based on clinical and radiological studies has indicated that hemorrhagic infarction occurs in 43% of ischemic stroke
patients. Regarding the arterial distribution of hemorrhagic infarction, 90% of the patients had involvement of the anterior circulation (6). However, there was little information on the involvement of the posterior circulation. In 1996, Chaves et al (7) investigated cerebellar hemorrhagic infarction, and concluded that the causes, imaging findings and consequences of hemorrhagic infarction in posterior circulation were similar to those in anterior circulation. Anecdotal evidence implicated large embolic cerebral infarcts (5, 8, 9), uncontrolled hypertension (10), advanced age and institution of anticoagulants (10-12) or thrombolytic agents (13, 14) as special risk factors for hemorrhagic infarction. Infarct size seemed to be the most important factor for secondary hemorrhage. The reason for preferential hemorrhagic transformation of a large infarct with a mass effect might include more extensive edema, compression of small vessels in the area surrounding the lesion and stasis of blood flow. After the decrease of edema, reperfusion of these vessels occurs and because these capillaries often have a disrupted endothelium, a diapedesis of blood will occur (15, 16). Cerebellar hemorrhagic infarction was common when the full cerebellar arterial territories were involved, probably reflecting the larger size of infarcts, which is known to be a risk factor associated with hemorrhagic infarction in the anterior circulation (7). As compared to cerebellar hemorrhagic infarction, massive pontine hemorrhagic infarction was relatively uncommon. The reason why the incidence of pontine hemorrhagic infarction is low has not been clarified. (50)

The pathogenesis of hemorrhagic infarction has been investigated in experimental and clinical studies. There are three theories concerning the mechanism of hemorrhagic infarction. The most common pattern in supratentorial and cerebellar hemorrhagic infarction is complete interruption of arterial blood supply, followed by reperfusion. In 1951, Fisher and Adams (1) reported a high incidence of hemorrhagic infarction in their autopsy study of cerebral embolism. They postulated that hemorrhagic transformation occurs when an embolus fragments and migrates distally, thereby opening the previously occluded vessel and exposing the necrotic brain to the full force of arterial blood pressure. The downstream migration of the embolus after its initial impact leads to extravasation of blood via reflow into damaged vessels of the proximally infarcted zone. Reconstitution of blood flow results in hemorrhagic transformation of the embolic infarction (2, 17). This migration embolism could occur in the vertebrobasilar circulation system as well as the carotid and cerebellar systems. As suggested by Kimura et al (18) in this volume, the extensive embolic occlusion of the entire length of the basilar artery and migration of the embolus are assumed to develop into massive pontine hemorrhagic infarction.

The second mechanism is extravasation from leptomeningeal collateral vessels. Some patients with cardiogenic embolic stroke developed hemorrhagic infarction without opening of occluded vessels. In such cases, restoration of blood flow occurs through leptomeningeal collaterals. Ogata et al (19) indicated that hemorrhage into an infarct with persisting occlusion of the proximal artery may occur when the involved blood vessels are exposed to the force of arterial blood pressure from the leptomeningeal collaterals. A less common pattern is incomplete and insufficient perfusion caused by stenotic vessels, followed by gradual necrosis of cerebral tissue. (50)
Thrombolytic therapy of acute ischemic stroke patients is currently one of the most controversial topics in clinical medicine. The use of thrombolytic agents can increase the likelihood of hemorrhagic infarction (13, 14). The decision regarding whether to use thrombolytic agents should be based on thorough evaluation of the individual patients by a physician with a speciality in treating stroke patients. Patients with large infarcts and severe neurological deficits have a higher risk of hemorrhagic transformation after thrombolysis. However, it remains debatable how to prevent and manage hemorrhagic infarction caused by acute therapeutic agents in ischemic stroke patients. More clinical research is needed.

**NEUROIMAGING OF HEMORRHAGIC INFARCTION**

- **Arterial hemorrhagic infarction**

Ischemic infarction can be divided into "bland or non-hemorrhagic" infarction and infarction associated with secondary bleeding — referred to as hemorrhagic conversion or transformation (HT) — in ischemically infarcted areas. Bland infarction is characterized by bland widespread leukocyte infiltration and macrophage invasion, with only scattered red cells being found. Hemorrhagic conversion may take the form of hemorrhagic infarction (HI) or, less commonly, parenchymatous hemorrhage associated with a cerebral embolic infarction (PH). The occurrence of Hemorrhagic conversion is "predominantly a natural tissue consequence of embolism". (50)

| Bland or non-hemorrhagic | Bland infarction is characterized by bland widespread leukocyte infiltration and macrophage invasion, with only scattered red cells being found. The occurrence of Hemorrhagic conversion of infarction is "predominantly a natural tissue consequence of embolism"
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhagic conversion of infarction</td>
<td>Hemorrhagic infarction (HI)</td>
</tr>
</tbody>
</table>

An autopsy, hemorrhagic infarction may vary from patchy petechial bleeding to more confluent hemorrhages, representing multifocal extravasation of blood from capillaries or venules. Hemorrhagic infarction and Parenchymatous hemorrhage associated with a cerebral embolic infarction (PH) have different incidences, pathogenesis, and clinical outcome, but distinguishing HI and PH on CT may be difficult. Although HI and PH have often been grouped together, there are certain features on CT that help characterize these two types of hemorrhagic transformation. On CT, HI appears as a discontinuous heterogeneous mixture of high and low densities occurring within the vascular territory of the infarct. In contrast, PH appears as a discrete, homogeneous collection of blood that often exerts mass effect and may extend beyond the original infarct boundaries or even into the ventricles. (50)
Hemorrhagic infarction occurs regularly in the natural evolution of acute embolic stroke. Hemorrhagic transformation of an infarction can occur spontaneously in up to 30% of patients by serial CT brain scan. (19) Transformation of a bland embolic infarct to hemorrhagic infarction is rare in the first 6 hours. Most hemorrhagic infarctions are asymptomatic, and it is not uncommon to detect hemorrhagic infarction on CT in patients who are stable or improving. The pathogenesis of hemorrhagic conversion or transformation in ischemically infarcted areas appears to relate to reperfusion of bleeding from recanalized but ischemically injured vessels by the natural, dynamic dissolution of thrombi i.e., an embolus that represents all or part of a thrombus has a spontaneous tendency to lyse and disperse. Reperfusion into the ischemically injured vessels can therefore result in varying degrees of blood extravasation through the damaged blood-brain barrier. (50)

Hemorrhagic infarction has been often explained as a result of reperfusion of the vascular bed of the infarct, such as would occur after fragmentation and distal migration of an embolus or after early reopening of a large vessel occlusion in the setting of a large infarction; the full pressure of arterial blood into hypoxic capillaries results in a diapedesis or red cells through their hypoxic walls. The concept of restored lumen patency is consistent with greater frequency of hemorrhagic infarction in patients with cardioembolic infarcts.

The occurrence of parenchymatous hemorrhage (PH) in areas of ischemic infarction is less common that that of HI. PH appears to be associated with anticoagulation therapy, Antiplatelet therapy and thrombolytic therapy, with a low incidence of spontaneous PH in areas of ischemic infarction (on the order of 2% to 9%) in patients not receiving anticoagulation therapy. In contrast to HI, clinical deterioration is often associated with PH. It has been proposed that the pathogenesis of PH may involve "ischemic necrosis resulting in the rupture of small penetrating vessels analogous to hypertensive hemorrhage, leading to massive bleeding rather that the multifocal diapedesis of blood through capillary walls, as seen in HI". (50)

The observation that some hemorrhagic infarctions develop distal to the site of a persisting occlusion suggests that reperfusion is not always a necessary condition. Investigators from Japan (20) examined the brains of 14 patients who died from herniation of the brain after cardioembolic stroke with persistent occlusion of the internal carotid-middle arterial axis. The finding of hemorrhagic infarct in 7 of the patients contradicts the concept that reopening a previously occluded vessel is the only pathophysiologic mechanism for the development of hemorrhagic infarct. Analysis of blood pressure after stroke has revealed one or more surges of arterial hypertension or rapid rise of blood pressure in patients with
hemorrhagic stroke without a reopening of the occluded artery; it has been speculated that these blood pressure rises might explain hemorrhagic infarction in many cases. (50)

A relationship between hyperglycemia and hemorrhagic transformation has also been suggested by he observation that occluding the middle cerebral artery of markedly hyperglycemia cats was associated with 5-fold more frequent and 25-fold more extensive hemorrhage into infarcts than in normoglycemic animals (21). Compared with permanent occlusion, temporary restoration of blood flow after 4 hours caused the most extensive hemorrhage into infarcts. It was concluded that hyperglycemia and restoration of blood flow to ischemic territories were strong risk factors for hemorrhagic infarct conversion. The evidence suggests that the marked tissue energy depletion accompanied by acidosis damages brain vessels, causing leakage of edema fluid and red blood cells (21). Diffuse HI associated with marked hyperglycemia has been reported in two patients (22).

In summary, HI occurs regularly in the natural evolution of acute embolic stroke and is usually asymptomatic. Parenchymatous hemorrhage associated with a cerebral embolic infarctions (PHs) occur less frequently, but are often symptomatic due to extension and mass effect beyond the original infarct territory. Interest in these issues has been further generated by trials of thrombolytic therapy for acute ischemic stroke.

Hemorrhagic infarction is regarded as distinct from anemic infarction although microscopical haemorrhage is frequent in the later. It has frankly hemorrhagic features which consist of petechial zones that are frequently confluent and are situated in the cortex. These hemorrhagic areas may involve the entire infarction but tend most often to involve the boundary zones supplied by meningeal arterial anastomosis or, in case of middle cerebral infarct, in the basal ganglia. Hemorrhagic infarction is secondary cortical reirregation which takes place in the capillary blood vessels that have been damaged by the initial hypoxia. Reirregation takes place when lysis (natural or by therapeutic thrombolysis) or secondary mobilization of the thrombus take place.
Figure 1. Haemorrhagic infarctions. They have frankly hemorrhagic features which consist of petechial zones that are frequently confluent and are situated in the cortex.

Figure 2. Noncontrast CT brain scan within 1 hour of acute onset of aphasia and right-sided weakness (A), which demonstrates an old right posterior cerebral artery territory infarct, and 24 hours later, after thrombolytic therapy (B), demonstrating dramatic hemorrhage transformation of the cerebral infarct.
Figure 3. Parenchymatous hemorrhage associated with a cerebral embolic infarctions (PHs) occur less frequently, but are often symptomatic due to extension and mass effect beyond the original infarct territory.

- Anticoagulants and hemorrhagic infarctions (50)

The occurrence of ICH in patients receiving oral anticoagulants is generally a serious event. On one hand, the risk of ICH is increased by eight to 11 fold by the chronic use of warfarin anticoagulation. On the other hand, this mechanism of ICH often leads to larger haematomas than those in patients not receiving anticoagulants, a feature that correlates with substantially higher mortality rates.

Table 2. The clinical features of ICH in patients receiving oral anticoagulants include:

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>• A low frequency of associated bleeding elsewhere in the body.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Lack of consistent association between ICH and preceding head trauma or cerebral infarction.</td>
</tr>
<tr>
<td></td>
<td>• Larger haematoma volumes in anticoagulated patients than in non-anticoagulated patients, as a result of more prolonged bleeding periods.</td>
</tr>
<tr>
<td></td>
<td>• A bad prognosis in anticoagulant-related ICHS, with mortality rates exceeding 50-60%</td>
</tr>
</tbody>
</table>

Box 1. Other features related to the occurrence of anticoagulant-related ICH are less consistently observed, and include: (50)
1. Duration of anticoagulation prior to onset of ICH: in some reports, most haemorrhages (70%) occurred within the first year of treatment, whereas in others only about one-third of the cases occurred within that period of time.

2. Relationship between intensity of anticoagulation and risk of ICH: in some studies, ICH was more likely with excessive prolongation of the prothrombin time, but in others there was no clear relationship.

3. Role of hypertension in causing ICH in patients on oral anticoagulants: a strong association with hypertension is present.

4. Location of ICH: a relatively high frequency of cerebellar haemorrhages in anticoagulated patients has been reported in some series, but not in others.

- Thrombolytic agents and hemorrhagic infarctions

Thrombolytic agents, in particular streptokinase and recombinant tissue-type plasminogen activator (rt-PA), are widely used in the treatment of patients with acute myocardial infarction (MI). Although the frequency of ICH is low (0.4-1.3% of treated patients), especially with the intravenous use of the fibrin-specific agent rt-PA, its occurrence is always serious and often fatal. (50)

Table 3. The clinical and CT aspects of ICH related to the use of rt-PA in MI include the following

| Thrombolysis | Onset soon after treatment, close to 40% of them during the rt-PA infusion and another 25% occurring within 24 hours of onset of infusion in one series. |
| Thrombolysis | Predominantly lobar location, with rare examples of bleeding into the posterior fossa and putamen |
| Thrombolysis | Multiple simultaneous haemorrhages in about one-third of the cases. |
| Thrombolysis | Mortality rate of 44-66%. |

The mechanism of bleeding in the setting of rt-PA use is not clear. A potential role of the concomitant use of intravenous heparin in the production of ICH has been suggested. The Global Use of Strategies to Open Occluded Coronary Arteries as the majority of patients with this complication have excessively prolonged activated partial thromboplastin time (APTT) (100 seconds) at the time of onset of the ICH. Local vascular factors with bleeding potential, such as CAA, have been recently reported as the suspect substrate of ICH in the setting of thrombolysis for acute MI. Other features, such as age 65 years, history of hypertension, and previous aspirin use have been suggested as risk factors, but have not been clearly documented.
More details about hemorrhagic transformation of arterial infarctions with thrombolytic therapy (50)

The most feared complication in acute ischemic stroke is hemorrhagic transformation (HT) as it has devastating clinical consequences and is associated with an over ten-fold increase in mortality (23). Although in clinical practice this complication may be less frequent than failure of treatment to recanalized occluded cerebral artery or early reocclusion, ICH seems to represent an important obstacle to the generalization of thrombolytic therapy (24). Intracerebral hemorrhage mostly occurs in the core of the infarcted area, thus suggesting that ischemic events can have an important role (25).

In experimental models of focal cerebral ischemia, the basal lamina of the vessels and the extracellular matrix show an alteration and the adhesion between the microvessel cells and the extracellular matrix is dearranged so there can be an extravasation of blood elements. There is an increase in capillary permeability that comes along with an inrush of plasma components inside the brain tissue, an inflammatory reaction with thrombin activation, and an increasing of many mediators such as platelet-activating factor, tumor necrosis factor ? and bradykinin, which contribute to increase endothelial permeability. In addition, oxidative damage may increase hemorrhagic risk (26).

Metalloproteinases (50)

Matrix metalloproteinases (MMP) are involved in the hemorrhagic transformation, and their activation is partly responsible for the BBB disruption. MMPs represent a family of proteolytic enzymes combined with zinc, which acts normally on the remodeling of the extracellular matrix. Inappropriate activation can induce proteolysis of the matrix of the neurovascular unity (endothelium, astrocyte, and neuron). MMPs are liberated by the endothelium and the polynucleates at the inflammatory stage of ischemia and utilize type IV collagen and laminin as substrates. (27). In some animal models of focal cerebral ischemia, activation of MMP-9 is associated with increased permeability of the BBB that leads to edema formation and hemorrhagic transformation (27).

MMP-2 and MMP-9 released during the ischemic event can damage the vessel components, particularly type IV collagen, fibronectin, and laminin, thus altering the basal lamina of the cerebral vessels. In humans, elevation of MMP-9 is linked to the severity of ischemic stroke (28), and the pretherapeutic MMP-9 rate is an independent predictor of the risk of hemorrhagic transformation related to thrombolysis (29).

Risk factors for HT after thrombolytic therapy (50)

Exact knowledge of mechanisms related to ICH after thrombolysis and the role of biomarkers could be useful in selecting patients that can benefit from such treatment. Other elements must be taken in account for the genesis of rt-PA-related ICH: age, hypertension, diabetes mellitus or cerebral amyloid angiopathy, extent of early ischemic signs shown on brain CT scan or the volume of cerebral ischemic lesions on diffusion weighted MRI, and the presence of leukoaraiosis (30).
The first trials on rt-PA have provided evidence that higher doses of lytic agents lead to higher rates of sICH, so the dose was limited to 0.9 mg/kg up to 90 mg in total (31).

Age has been consistently found to be a risk factor for sICH after thrombolysis for acute ischemic stroke (8). Recent data from several open-label studies on use of rt-PA have shown that the risk of sICH in the elderly is comparable to that of younger patients. Certain trial showed that the benefit-risk ratio of intravenous rt-PA can be favorable in carefully selected elderly stroke patients treated within three hours. The sICH rate was 4.4% in the group of patients aged 80 years or older included in this study (32). The Stroke Survey Group rt-PA analysis also concluded that it was not justified to systematically contraindicate thrombolysis for patients older than 80 years (33).

Many authors have shown the importance of the baseline stroke severity in hemorrhagic risk after thrombolysis (9). The Multicentre tPA Acute Stroke Survey study showed that the NIHSS score was an independent marker of ICH, with an odds ratio of 1.38 for a one-point increase in the NIHSS score (33).

Some authors on their report did not find a significant association of severity of neurological deficit at baseline with increased risk of sICH (10). Moreover, the ECASS I trial showed that severity of neurological deficit at admission represented a risk factor for hemorrhagic transformation and not for parenchymal hematoma (31). Another factor which may contribute to the development of rt-PA-related sICH is hypertension during the first 24 hours after ischemic stroke (34).

Experimental and human studies indicate that hyperglycemia predicts higher stroke mortality independently from stroke severity, stroke type, or age. These data suggest that hyperglycemia may directly contribute to poor outcomes by exacerbating acute brain injury (29). In the PROACT II study, there was an increased risk of sICH in patients with pretherapeutic glycemia higher than 200 mg/dl (35).

The mechanism of hyperglycemia-related ICH is not clear. There are numerous animal experimental proofs that hyperglycemia provokes microvascular lesions as well as BBB damage, leading to hemorrhagic transformation of the cerebral infarction (36). However Some authors did not find that a history of diabetes mellitus was a risk factor for sICH, despite the fact that many patients with diabetes mellitus had elevated serum glucose at stroke onset (25). The significance of early ischemic changes on baseline brain CT scan as predictors of hemorrhagic transformation scan remains controversial (26). With the advent of advanced MRI such as diffusion- (DWI) and perfusion-weighted imaging (PWI), It has been demonstrated in recent studies that in anterior circulation strokes, an acute DWI lesion volume >70 cm3 has a high specificity for poor outcomes with or without therapy (37).

A retrospective multicenter study evaluated whether leukoaraiosis is a risk factor for sICH in patients treated with alteplase for anterior circulation stroke. All patients had received magnetic resonance imaging evaluation before thrombolysis and for statistical analysis. Leukoaraiosis in the deep white matter was dichotomized into absent or mild versus
moderate or severe. The rate of sICH was significantly higher in patients with moderate to severe leukoaraiosis than in patients without relevant leukoaraiosis (37).

The risk of ICH after thrombolysis in ischemic stroke patients carrying old asymptomatic microbleeds (which can considered as a marker of microangiopathy, and of amyloid angiopathy) remains a controversial subject (38). In a published pooled analysis of 570 patients, the presence of microbleeds was not predictive of sICH after thrombolysis except grade 3 microbleeds (39).

Some authors have suggested that the differences between symptomatic and asymptomatic ICHs are due to the intensity of bleeding rather than physiopathologic differences. For others, hemorrhagic infarctions and parenchymal hematomas after t-PA have a different clinical, etiologic, and biological significance (40). Benign hemorrhagic transformation can be associated with the natural history of ischemic stroke while parenchymal hematomas, especially the PH-type 2 (homogeneous hematomas with mass effect occupying 30% of ischemic lesion volume) could be linked to the t-PA itself and particularly to its impact on homeostasis (as demonstrated by elevation of fibrin degradation products after treatment) (41).

Any extension of the thrombolytic treatment window also implies an increased risk of HT. Data shows that the occurrence of HT in patients treated within three hours of symptom onset was 4.8%, while for those treated between three and six hours after onset the occurrence rose to 6.4% (42).

Although tPA can cause fatal or symptomatic brain hemorrhage, patients treated with tPA strictly following protocol have a higher likelihood of functional neurologic recovery. Thus, only physicians experienced in stroke management should use tPA to treat patients with acute stroke; inexperienced physicians are more likely to violate protocols, resulting in more brain hemorrhages and deaths (43,44,45).

- **Venous infarction**

In sinovenous thrombosis, the mechanism for venous infarction is obstruction of venous drainage with increasing venous pressure in the affected region of the brain. The venous congestion results in significant extravasation of fluid into the brain, producing focal cerebral edema and hemorrhage. The edema may be transient, if venous flow is re-established, or be associated with permanent tissue infarction if the increased venous blood pressure eventually exceeds the arterial blood pressure. In the latter situation, there is insufficient delivery of arterial blood and regional ischemic infarction (50). Recently, MR imaging studies utilizing diffusion-weighted imaging (DWI) have demonstrated cytotoxic edema early in acute CSVT, preceding the onset of vasogenic edema. These findings support the presence of primary neuronal injury early in venous infarction (50).

Once the initial thrombus has formed, the resultant obstruction and venous stasis can promote propagation of the initial thrombus. Anticoagulant therapy is aimed at preventing extension of the initial thrombus and allowing the fibrinolytic system to achieve dissolution
of the existing thrombus. Unlike an arterial ischemic stroke, relief of venous obstruction, even if very delayed, may relieve the circulatory congestion in CSVT with clinical benefit.

Figure 4. Deep venous thrombosis: male newborn born at term developed hypernatremia, dehydration, and seizures at day 8 of life; axial noncontrast CT shows bilateral thalamic hemorrhagic infarction secondary to deep venous thrombosis. Note increased density in the internal cerebral veins and the vein of Galen (arrow).

Thrombotic occlusion of the superior sagittal sinus or the dominant lateral sinus interferes with the absorption of cerebrospinal fluid (CSF) through impaired function of the “arachnoid granulations” that line the superior sagittal sinus. The latter mechanism further increases the extent of cerebral swelling and results in a communicating hydrocephalus (50).

In addition to the intracerebral and intravascular events in CSVT, pressure on the optic nerves secondary to raised intracranial pressure initially causes papilloedema, which if unrelieved over time can progress to permanent visual loss.

- Imaging of venous infarction

Venous infarction may be evident on CT as a diffuse low-attenuating lesion. Mass effect is common, and, in one study, 40% of symptomatic patients showed CT evidence of hemorrhage (50). Bilateral, parasagittal, hypoattenuating lesions on CT is a common feature of venous thrombosis in the superior sagittal sinus. These lesions do not conform to an arterial distribution but do involve the cortex. Early changes are often subtle, with edema and swelling of the frontal/parietal gyri. In addition, isolated involvement of the temporal lobe is common and found in cerebral sinus thrombosis of the transverse sinus. Bilateral thalamic hypoattenuating lesions on CT may be evident in deep venous thrombosis and on non-contrast-enhanced CT, thrombus may be seen in the straight sinus.
Figure 5. Deep venous thrombosis in a 27-year-old woman with antiphospholipid antibody syndrome who presented with headache, nausea, and vomiting that progressed to aphasia and a decreased level of consciousness. Axial noncontrast CT (A) and T2-weighted MRI (B) show bilateral thalamic ischemia or infarction (open arrow). On CT, a small hemorrhage is seen in the right lateral ventricle (solid arrow). (C) T1-weighted sagittal MRI demonstrates subacute thrombus in the vein of Galen and straight sinus.

Figure 6. Bilateral parasagittal hemorrhages secondary to superior sagittal sinus thrombosis (A) Axial noncontrast CT shows a high attenuation in the superior sagittal sinus (solid arrow) and bilateral parasagittal hemorrhages (open arrows). (B) Fluid-attenuated inversion-recovery sequence in another patient shows mixed-signal-intensity lesions in both frontal lobes with a fluid-fluid level (arrow) in a hematoma cavity on the left.
MRI is sensitive to the parenchymal changes seen in cerebral sinus thrombosis. Cortical and subcortical high-signal-intensity lesions on fluid-attenuated inversion-recovery sequence and T2-weighted imaging may highly suggest cerebral sinus thrombosis when the lesions do not correspond to an arterial territory (50). Restriction of diffusion on diffusion-weighted imaging (DWI) with a corresponding decrease in the apparent diffusion coefficient (ADC) value is often irreversible in arterial infarction and correlates with a permanent neurologic deficit (4). Diffusion techniques have been used in cerebral sinus thrombosis to differentiate reversible ischemic tissue from irreversible ischemia (4). Preliminary results have shown some potential in predicting the prognosis of the cerebral sinus thrombosis (50). Recent investigations of cerebral sinus thrombosis have revealed that mixed signal intensity on DWI may represent both cytotoxic and vasogenic edema (50). A reduced ADC value in CVT may not correlate with neuronal death and a permanent neurologic deficit (50). Therefore, a decrease of ADC in cerebral sinus thrombosis may not have the same prognostic value as it does in arterial stroke (50), and venous ischemia may be reversible despite decreased ADC values. This correlates with the important clinical improvement that may occur after an initial major cerebral sinus thrombosis-related neurologic deficit.

Figure 7. Diffusion imaging. T2-weighted (A) and fluid-attenuated inversion-recovery sequence (B) MRIs show scattered high-signal-intensity lesions (arrows). (C) Diffusion-weighted imaging demonstrates a mixed-signal-intensity area (arrow) suggesting both cytotoxic and vasogenic edema. (D) ADC map reveals that the lesions are predominantly hyperintense (arrows).
Pathophysiology of cerebral sinus thrombosis and its parenchymal changes

The pathophysiology of brain parenchymal involvement in venous occlusion differs from that in arterial occlusion. Parenchymal changes may be secondary to cytotoxic edema, vasogenic edema, or intracranial hemorrhage. The primary underlying mechanism is likely to be increased venous pressure. If collateral pathways of venous drainage are insufficient, especially in the presence of cortical venous involvement, subsequent parenchymal changes may occur. If venous pressure continues to increase, with a consequent diminishment in arterial perfusion pressure, cell death may ensue. If adequate collateral pathways develop or recanalization occurs before cell death or intracranial hemorrhage, the parenchymal changes may resolve partly or completely. Vasogenic and cytotoxic edema patterns may coexist.
Comment

Venous thrombosis produce effects on the vein that include increase in diameter and length of the thin walled vein, kinking, folding, stenosis, and sometimes occlusion. This has been described as a hemodynamic effect caused by pressure and flow of arterial blood in a vein.

In the presence of venous thrombosis, a subpial or cortical vein dilates, lengthens, and may kink at the junction with the sinus. It may also balloon to the point of rupture or thromboses. The deep venous collector in the galenic malformations (the embryonic precursor to the vein of Galen) typically shows a dilatation and focal stenosis at the outlet to the straight sinus or a falcine sinus. Occasionally, this structure spontaneously thromboses.

Under normal conditions, there is negative venous pressure in the dural sinuses relative to the heart. There are no valves and pulsatile flow in the sinuses. Blood is effectively sucked through the shunt rather than pushed. An increased resistance to flow occurs when the venous pressure rises. This may occur transiently during a Valsalva maneuver or chronically in severe right heart failure or when there is a stenosis in the venous sinuses due to sinus thrombosis. When there is increased venous pressure, there is a corresponding decrease in water resorption by the arachnoid granulations, which is reflected in an increased amount of water in the ventricles and subarachnoid spaces. The third and lateral ventricles become prominent, and the cerebral sulci enlarge. If the fontanelles are open, the head enlarges (macrocrania). Normally, the posterior fossa drainage relies on the petrosal sinuses draining anteriorly to the cavernous sinus and caudally to the jugular bulb. In the absence of anterior drainage and restricted caudal drainage, there is an increase in cerebellar water, which results in a small fourth ventricle and tonsillar herniation.

With persistent increase of the venous pressure due to venous thrombosis, there will be reduction of the venous return, stasis of blood, or even reversal of flow of blood (cerebral venous reflux) depending on the degree of venous pressure rise. Stasis of blood in the venous sinuses predisposes to further thrombosis. Cerebral venous reflux predisposes to dilatation of superficial, deep venous system, transcerebral vein, white matter congestive encephalopathy with edema, petechial haemorrhages and mass effect. Increase of intravenous pressure often results in venous wall remodelling with increase in diameter and length of the thin walled vein, kinking, folding, stenosis, and sometimes occlusion of thrombosis.

Venous infarction or ischemic cerebral changes can occur due to increased venous pressure - secondary to venous thrombosis, the mechanism for venous infarction is obstruction of venous drainage with increasing venous pressure in the affected region of the brain. The venous congestion results in significant extravasation of fluid into the brain, producing focal cerebral edema and hemorrhage. The edema may be transient, if venous flow is re-established, or be associated with permanent tissue infarction if the increased venous blood pressure eventually exceeds the arterial blood pressure. In the latter situation, there is insufficient delivery of arterial blood and regional ischemic infarction. MR imaging studies utilizing diffusion-weighted imaging (DWI) have demonstrated cytotoxic edema early in acute venous thrombosis, preceding the onset of vasogenic edema. These findings support the presence of primary neuronal injury early in venous infarction.

Under normal conditions, there is negative venous pressure in the dural sinuses relative to the heart. There are no valves and pulsatile flow in the sinuses. Blood is effectively sucked through the shunt rather than pushed. An increased resistance to flow occurs when the
venous pressure rises. This may occur transiently during a Valsalva maneuver or chronically in severe right heart failure or when there is a stenosis in the venous sinuses due to sinus thrombosis. Venous hypertension probably passes into three stages depending upon the degree of venous hypertension and the chronicity of the condition.

Table 5. **Stages of cerebral venous hypertension** (50)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Absence of any parenchymal changes. When there is increased venous pressure, there is a corresponding decrease in water resorption by the arachnoid granulations, which is reflected in an increased amount of water in the ventricles and subarachnoid spaces. The third and lateral ventricles become prominent, and the cerebral sulci enlarge. If the fontanelles are open, the head enlarges (macrocrania). Normally, the posterior fossa drainage relies on the petrosal sinuses draining anteriorly to the cavernous sinus and caudally to the jugular bulb. In the absence of anterior drainage and restricted caudal drainage, there is an increase in cerebellar water, which results in a small fourth ventricle and tonsillar herniation. At this stage the thrombosed sinus will show the characteristic MRI signal changes but without any parenchymal changes.</td>
</tr>
<tr>
<td>Stage II</td>
<td>Early cerebral congestive encephalopathy with reversible parenchymal changes. With persistent increase of the venous pressure due to venous thrombosis, there will be reduction of the venous return, stasis of blood, or even reversal of flow of blood (cerebral venous reflux) depending on the degree of venous pressure rise. Stasis of blood in the venous sinuses predisposes to further thrombosis. Cerebral venous reflux predisposes to dilatation of superficial, deep venous system, transcerebral vein, white matter congestive encephalopathy with edema, petechial haemorrhages and mass effect. Increase of intravenous pressure often results in venous wall remodelling with increase in diameter and length of the thin walled vein, kinking, folding, stenosis, and sometimes occlusion of thrombosis. Parenchymal changes in this stage are due to reversible edema edema and petechial hemorrhage once venous flow is restored.</td>
</tr>
<tr>
<td>Stage III</td>
<td>Late cerebral congestive encephalopathy with irreversible parenchymal changes. Venous infarction or ischemic cerebral changes can occur due to increased venous pressure -secondary to venous thrombosis, the mechanism for venous infarction is obstruction of venous drainage with increasing venous pressure in the affected region of the brain. The venous congestion results in significant extravasation of fluid into the brain, producing focal cerebral edema and hemorrhage. The edema may be transient, if venous flow is re-established, or be associated with permanent tissue infarction if the increased venous blood pressure eventually exceeds the arterial blood pressure. In the latter situation, there is insufficient delivery of arterial blood and regional ischemic infarction. MR imaging studies utilizing diffusion-weighted imaging (DWI) have demonstrated cytotoxic edema early in acute venous thrombosis, preceding the onset of vasogenic edema. These findings support the presence of primary neuronal injury early in venous infarction.</td>
</tr>
</tbody>
</table>

Acute dural sinus thrombosis leads to distinct stages of parenchymal changes, the severity of which depends on the degree of venous congestion, which, in turn, is closely related to intradural sinus pressure. As intradural sinus pressure increases, progression from mild parenchymal change to severe cerebral edema and/or hematoma may occur if thrombolysis is delayed.
In the analysis of 29 patients with dural sinus thrombosis (by MRI, and dural sinus pressure measurement using a Tracker 18 end-hole catheter proximal to the thrombus and connected to a pressure transducer at ear level with the waveform displayed on either an Alpha 9 pressure monitor), Fong, et al, (49) could identify five stages of brain parenchymal changes secondary of sinus thrombosis, each stage relates to the dural intrasinus pressure.

Table 6. Parenchymal changes, and intrasinus pressure in dural sinus thrombosis (49)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Parenchymal Changes</th>
<th>Symptoms</th>
<th>Pressure Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No parenchymal change</td>
<td>Severe headache, papilledema, weakness, changed mentation, drowsiness, right hemiparesis (one patient only)</td>
<td>One patient placed in this category had pressure measurements taken left transverse sinus = 14 mm Hg; superior sagittal sinus = 17 mm Hg</td>
</tr>
<tr>
<td>II</td>
<td>Brain swelling, sulcal effacement and mass effect, no signal change</td>
<td>Increased headache, double vision, seizures, decreased mentation, extreme drowsiness, difficulty rousing, right lower extremity weakness (one patient)</td>
<td>Four patients had measurements taken 20-25 mm Hg</td>
</tr>
<tr>
<td>III</td>
<td>Increased intensity of signal change as mild to moderate edema</td>
<td>Inability to rouse, obnubilation, hemiparesis, seizure</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Severe edema, with or without hemorrhage</td>
<td>Hemiparesis, seizure, loss of consciousness, coma</td>
<td>Three patients had measurements taken 32-38 mm Hg</td>
</tr>
<tr>
<td>V</td>
<td>Massive edema and/or hemorrhage</td>
<td>Coma, response to deep pain only</td>
<td>No measurements were taken</td>
</tr>
</tbody>
</table>

Acute dural sinus and cerebral venous thrombosis may lead to various stages of parenchymal changes of venous infarction, with the degree of severity depending on the degree of venous congestion and elevated dural sinus pressure. The prognosis of venous thrombosis depends to a significant extent on the use of thrombolytics. Severe neurologic symptoms, including coma, may be reversible if treatment with thrombolytics is started before massive cerebral edema or hemorrhage has developed. Stage I may be treated with anticoagulants alone; however, if the patient deteriorates clinically, prompt thrombolysis is probably needed. All other stages should be treated with thrombolysis. A progression from mild brain swelling to severe cerebral edema and/or hemorrhage from increasing dural sinus pressure may occur if treatment with thrombolysis is delayed. (50)
Table 7. Biochemical stages of sinus thromboses (50)

<table>
<thead>
<tr>
<th>STAGE</th>
<th>MRI PICTURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>The acute deoxyhemoglobin stage of blood</td>
<td>In the acute stage of thrombus formation (0–5 days), the signal is predominantly isointense on T1-weighted images and hypointense on T2-weighted images because of deoxyhemoglobin in red blood cells trapped in the thrombus. A venous thrombus in the acute stage may have a signal intensity that mimics a normal flow state, and such a finding may lead to diagnostic error. The signal may be very hypointense on T2-weighted images and may be mistakenly thought to indicate a flow void. According to some estimates, in 10%–30% of cases of sinus thrombosis, the thrombus at initial presentation or imaging examination is in the acute stage of formation. Contrast-enhanced MR venography or CT venography is usually necessary to achieve a definitive diagnosis at this stage.</td>
</tr>
<tr>
<td>products (days I through 5)</td>
<td></td>
</tr>
<tr>
<td>The subacute extracellular methemoglobin</td>
<td>In the subacute stage of thrombus development (6–15 days), the signal is predominantly hyperintense on both T1-weighted images and T2-weighted images because of methemoglobin in the thrombus. Subacute-stage thrombus has been found in 55% of patients at clinical presentation with cerebral venous thrombosis. This stage of formation is the easiest stage at which to detect a thrombus on MR images, as the signal intensity of the sinus is most different from that in normal flow states. The finding of increased signal intensity on both T1-weighted images and T2-weighted images is almost always abnormal.</td>
</tr>
<tr>
<td>stage of blood products (from day 5 through day 15)</td>
<td></td>
</tr>
<tr>
<td>Chronic dural sinus thrombosis</td>
<td>The thrombus becomes hypointense and heterogeneous because of partial resolution and recanalization and might enhance after gadolinium administration. Enhancement within the occluded dural sinus is due to organization of the thrombus. Chronic thrombosis with incomplete recanalization of the sinus may present a diagnostic challenge at MR imaging. As many as 15% of patients in whom sinus thrombosis is diagnosed at MR imaging may have a chronic (&gt;15-day-old) thrombus. Compared with the MR signal in normal brain parenchyma, the signal in a chronic thrombus is typically isointense or hyperintense on T2-weighted images and isointense on T1-weighted images; however, significant variability in thrombus signal intensity exists. The signal intensity may be similar to that of very slowly moving oxygenated blood.</td>
</tr>
</tbody>
</table>

Sinus enhancement in sinus thrombosis is presumably secondary to an organized thrombus with intrinsic vascularization as well as to slow flow in dural and intrathrombus collateral channels.

www.yassermetwally.com
Parenchymal changes secondary to congestive encephalopathy are shown by MRI as subcortical white matter precontrast T1 hypointensity, with patchy, irregular and linear enhancement and T2 hyperintensity mixed with linear and patchy hypointensity and signal void structures. Changes are due to edema, petechial hemorrages and dilated veins. Parenchymal changes commonly show positive mass effect and are usually focal rather than diffuse. Bilateral parenchymal changes are not uncommon. Although parenchymal changes may occur in areas of the brain that are directly drained by the occluded venous sinus, in some patients the parenchymal changes may not closely correlate with the location of venous occlusion.

Parenchymal swelling without abnormalities in attenuation or signal intensity on images may occur in as many as 42% of patients with cerebral venous thrombosis. Sulcal effacement, diminished cistern visibility, and a reduction in ventricular size may occur. Patients with brain swelling and without parenchymal signal intensity changes tend to have intrasinus pressures in the intermediate range (20–25 mm Hg); however, intrasinus pressures also may be markedly elevated. Such patients typically have more prominent clinical symptoms than would be expected on the basis of imaging findings. (50)

In view of the variable nature of the parenchymal abnormalities that may occur in cerebral venous thrombosis, the use of the term venous infarct in reference to these lesions should be discouraged because that term implies irreversibility. In contrast with arterial ischemic states, many parenchymal abnormalities secondary to venous occlusion are reversible. It is much better to refer to these parenchymal changes secondary to cerebral sinus thrombosis as cerebral venous encephalopathy. Persistence of parenchymal MRI signal changes over a long time might warrant the usage of the terminology venous infarction. (50)

- Parenchymal hemorrhage in cerebral sinus thrombosis

Parenchymal hemorrhage can be seen in one-third of cases of cerebral venous thrombosis. Flame-shaped irregular zones of lobar hemorrhage in the parasagittal frontal and parietal lobes are typical findings in patients with superior sagittal sinus thrombosis and should prompt additional imaging evaluations (eg, with MR venography or CT venography). Hemorrhage in the temporal or occipital lobes is more typical of transverse sinus occlusion. Hemorrhage in cerebral venous thrombosis is typically cortical with subcortical extension. Smaller zones of isolated subcortical hemorrhage also may be seen and may be accompanied by minimal edema. MR imaging with GRE sequences is sensitive in the depiction of these zones of parenchymal hemorrhage. (50)
The mechanism of hemorrhage in cerebral venous thrombosis is multifactorial. Hemorrhage may be precipitated by continued arterial perfusion in areas of cell death, as can be seen at reperfusion in arterial ischemia. Elevation of venous pressure beyond the limit of the venous wall also is likely operative. Hemorrhage was noted in patients with intrasinus pressures higher than 42 mm Hg but not in those with lower pressures.

- **Contrast Enhancement**

Parenchymal enhancement in 1%–29% of cases of cerebral venous thrombosis has been reported. The enhancement is typically gyral in location and may extend into the white matter. Parenchymal enhancement, which indicates disruption of the blood-brain barrier, may be seen in areas of cytotoxic or vasogenic edema and in the presence of either irreversible or reversible brain abnormalities. Increased tentorial enhancement (likely related to dural venous collaterals), adjacent leptomeningeal enhancement, and prominent cortical venous enhancement (secondary to venous congestion) also may be visible after the administration of contrast material. (50)
Figure 9. Axial MR image series with a color overlay represents the major superficial cortical venous drainage territories. Most of the superior cerebrum (green) is drained primarily into the superior sagittal sinus, which also receives drainage from the parasagittal cortical regions at lower levels. The sylvian veins drain blood from the peri-insular region (yellow) into the basal dural sinuses. The transverse sinuses receive blood from the temporal, parietal, and occipital lobes (blue). The Labbé vein, if dominant, may drain much of this territory. Parenchymal abnormalities such as hemorrhage or edema in this territory may be indicative of thrombosis of the transverse sinus or Labbé vein.
Figure 10. Axial MR image with color overlay shows the drainage territory of the deep cerebral veins (internal cerebral vein, vein of Galen) (pink), in which parenchymal abnormalities due to deep venous occlusion typically are found. The deep white matter (medullary) venous drainage territory (blue) also is shown.

References


Haemorrhagic microvascular brain disease constitutes the other facet of the bad coin (the microvascular brain disease) the first facet of which is the ischemic microvascular brain disease. Both the haemorrhagic and the ischaemic microvascular brain disease share common haemorheological, metabolic endocrinial abnormalities (The metabolic syndrome) and cardiac changes(LVH).

In microvascular brain disease, the small penetrating arterioles of the subependymal and the pial microvascular systems tend to become stenosed and undergo lipohyalinosis or they may dilate to form microaneurysms. From the pathological point of view both
Lipohyalinosis and microaneurysms, almost invariably, coexist in the same individual, thus making the patient liable to develop either the ischaemic or the haemorrhagic microvascular brain.

Microaneurysmal formation occurs predominantly in the territory of the subependymal microvascular system, thus making the incidence of the haemorrhagic microvascular events much more frequent in the periventricular gray matter (thalamus, basal ganglia and the internal capsule) or the immediate periventricular white matter. The coexistence of lipohyalinosis and microaneurysms in the periventricular regions will explain the propensity of the diseased microvascular system either to thrombose (resulting in lacunar infarctions) or to rupture and leak resulting in periventricular haematoma formation. Lacunar infarctions and hypertensive cerebral haemorrhages are two facets of one and the same bad coin (the microvascular brain disease).
Figure 2. Microaneurysms are predominately distributed in the immediate periventricular region

Microaneurysmal formation should weaken the arteriolar wall so that rupture and leakage can occur even in normotensive states. When microaneurysmal rupture occurs, the bleeding will result in haematoma formation. The bleeding will then be arrested by occlusive thrombosis of the bleeding microaneurysms. Following microaneurysmal rupture and bleeding, the size of the resulting haematoma will be determined by the bleeding time. The bleeding time is a function of the whole blood viscosity in general and the platelet aggregability in particular.

Should microaneurysmal bleeding occurs during periods of higher blood viscosity, the bleeding time will be shorter and subsequently the size of the resulting haematoma will be smaller. In fact during high blood viscosity the bleeding is not infrequently arrested before forming haemorrhages adequate to give rise to immediate clinical sequelae. Patients with higher blood viscosity and thrombotic tendency, although less likely to develop serious haemorrhagic microvascular events, they are particularly liable to develop serious ischaemic microvascular events.

During periods of lower blood viscosity and thrombotic tendency of the blood, microaneurysmal bleeding might result in huge haematoma formation that may split along the planes of the white matter forming a substantial space occupying clot, or may rupture into the ventricular system resulting in massive ventricular haemorrhage. In general inverse correlation is present between the haematoma size and the current blood viscosity at the time of microaneurysmal bleeding.
Patients with microvascular brain disease might have recurrent events which could be purely haemorrhagic or purely ischaemic, however, it is not uncommon for some patients to fluctuate between the haemorrhagic and the ischaemic events, developing haemorrhagic events at certain times and ischaemic events at other times. In general ischaemic microvascular events are much more common and much more frequent than the haemorrhagic events.

**PATHOGENESIS OF HYPERTENSIVE CEREBRAL HEMORRHAGE**

Hypertension causes fibrinoid necrosis of these penetrating arterioles. The massive intracerebral hemorrhage which is a complication of hypertension, arises from rupture of a necrotic arteriole or from rupture of a minute "miliary" aneurysm formed at the site of necrosis. These aneurysms were first described by CHARCOT and BOUCHARD. The frequency of fibrinoid necrosis and miliary aneurysm formation in vessels within basal ganglia and thalamus accounts for the frequency of intracerebral hemorrhage in those locations. Fibrinoid is identified by its structureless or sometimes granular red appearance on H&E stain and by the fact that, unlike hyalinized smooth muscle which is also eosinophilic, the fibrinoid areas stain with stains for fibrin such as PTAH or Putz stain or with certain trichrome stains. The fibrinoid change in these vessels was called lipohyalinosis by Miller-Fisher in a very influential series of articles. However that term is confusing because hyalinized arteries are arteries whose media has undergone a pathologic change which is not fibrinoid necrosis and which by itself does not lead to rupture. Indeed hyalinized arterioles are common in hypertension. The term lipohyalinosis stresses the presence of fat in the degenerate arteriolar wall but again this change is not the hallmark of the arterioles that are in danger of rupturing or forming miliary aneurysms. The fibrinoid change is the critical change in these diseased arteriolar segments looks and stains just like the fibrinoid seen in renal and other arterioles in malignant hypertension. The important point to remember is that, for unknown reasons, the brain arterioles can undergo fibrinoid necrosis even in so-called benign hypertension—that is in patients with only modest blood pressure elevation. For that reason it is important to treat even benign hypertension. The series figures below illustrates the pathologic processes that can lead to rupture.
Figure 3. A, The figure shows the wall of an arteriole stained with H&E. The amorphous pink [eosinophilic] material in the wall could be either fibrinoid or amyloid. To prove that it is fibrinoid the section or its close neighbor should be stained with any one of several techniques that stain fibrin [e.g. Putz stain-blue; or the PTAH stain-blue; or a trichrome stain such as the azo carmine stain; the azo carmine is particularly good because it distinguishes fibrinoid from garden variety hyalinization by staining fibrin/fibrinoid red while staining collagen or hyalinized collagen blue.]. B, This section was stained with azocarmine. An arteriole in the subarachnoid space has an amorphous red material occupying a good portion of its wall. This is fibrinoid. Fibrinoid is frequently segmental in distribution so that the entire circumference may not be involved and other areas along the length of the vessel may also be spared. C, This figure was also stained with azocarmine. The arteriole wall is replaced by red fibrinoid and displays aneurysmal dilation.
Figure 4. A,B Sometimes a miliary aneurysm thrombosis rather than ruptures. It then appears as a fibrous ball which may be separated from the parent vessel due to the plane at which the section has been cut. If the section is close to the parent arteriole there will be elastic tissue at the margin of the ball. This elastic tissue stains black with the VVG stain in (B)

Figure 5. The pathologist got lucky when this section was taken. Here a miliary aneurysm that has been converted to a fibrous ball or globe, shown in this longitudinal section, still connected to the parent arteriole by a thin neck.

PATHOLOGY

Cerebral Haematomas occur much more frequently at the putameno-capsular and the thalamic regions and may rupture into the ventricular system. Less common sites include the cortical and the immediate subcortical white matter, especially in the parietal region, the pons and the cerebellum.

The resulting haematoma is dark red in colour due to the existence of deoxyhaemoglobin inside the intact RBCS. During the subacute stage (3 days - one month) the dark red colour
of the haematoma is replaced by a brownish discoloration, which starts at the periphery of
the haematoma and then extends to its center. This brownish discoloration occurs due to
the replacement of deoxyhaemoglobin by the oxidized methemoglobin.

Acute hematoma usually spreads between white matter tracts resulting in island of viable
brain tissues within the hematoma itself. Bleeding usually stops shortly after the initial
ictus, however in a substantial minority of patients the hematoma continues to expand
usually within the first hour after the presentation. Expansion after one hour is unusual.
Once hematoma forms, vasogenic edema forms around the clot as osmotically active serum
proteins are released from the hematoma. Edema peaks at about 48 hours and usually
begins to resolve after 5 days. Whether the brain tissues surrounding the acute hematoma
is ischemic -due to vascular compression- or not is controversial. Functional suppression
(diaschisis) of brain activity rather than ischemia is more probable.

- **Risk of Hematoma Enlargement**

In nearly one quarter of initially alert patients presenting with spontaneous intracerebral
hemorrhage, secondary deterioration in level of consciousness occurs within the first 24
hours after onset. Hematoma expansion and edema formation are believed to be the major
factors involved in several large prospective and retrospective studies, investigators have
evaluated the rate of hematoma enlargement after initial presentation and report rates
ranging from 14 to 38% within the first 24 hours of admission.[27,28]

In their review of 627 patients with spontaneous intracerebral hemorrhage Fujii, et al.[27]
reported that CT scanning within 24 hours of admission demonstrated enlargement of the
hematoma in 14% of patients. Five factors were found to be associated with enlargement:
admission shortly after onset of symptoms, heavy alcohol consumption, irregularly shaped
hematoma, reduced level of consciousness, and low level of fibrinogen.
Figure 6. Cerebral (A) and pontine (B) acute haemorrhage, C, acute cerebellar hemorrhage

Gradually the haematoma is surrounded by reactive gliosis and macrophages laden with haemosiderin granules (Ferric hydroxide). The clot is gradually absorbed starting with its periphery and is replaced by a yellow fluid, this is called an apoplectic cyst. Reactive gliosis progressively increases and ultimately transforms the haematoma into a slit-like scar.

Figure 7. A, acute putameno-capsular & intraventricular hemorrhage, B, apoplectic cyst

Pathologically the brains of patients with cerebral haemorrhages very frequently show evidence of past microvascular ischaemic events such as lacunar infarctions, leukoaraiosis, etc.

**INCIDENCE OF COMMON ANATOMICAL SITES IN HYPERTENSIVE INTRACEREBRAL HAEMORRHAGE**
Figure 9. Incidence (in % ) of the common anatomical sites in hypertensive intracerebral haemorrhage

STRUCTURAL NEUROIMAGING OF MICROVASCULAR CEREBRAL HAEMORRHAGE

- CT imaging of haematoma.

A cerebral haematoma, in the acute stage, has higher attenuation values on precontrast scan (hyperdense). The higher attenuation values of fresh blood is due to the existence of packed haemoglobin in the haematoma. In particular the globin component of the haemoglobin is responsible for the increased CT density on precontrast scan. With progressive absorption of haemoglobin, (this usually starts from the periphery of the haematoma) the attenuation value of the haematoma gradually decreases until the high density haematoma is replaced by a low density space occupying cyst.

Figure 10. A, Acute haematoma, B, an apoplectic cyst and C, an old haematoma (slit-like scar)
The evolution of the haematoma from a high density clot to a low density cyst usually takes a period that ranges between one month to three months. The walls of this cyst might enhance and the haematoma at this stage might be mixed with abscess or glioma. History is of paramount significance at this stage. Very old haematoma appears by CT scan as a slit-like hypodense area with negative mass effect.

In general Haematomas are space-occupying with positive mass effect and are commonly surrounded by a hypodense oedema area. The most common sites are the putameno-capsular and the thalamic sites and either of them might rupture intraventricularly. Less common sites includes the parietal lobe, pons and cerebellum.

The diagnosis of acute ICH is virtually 100% reliable with non-contrast CT due to the characteristic mass of blood of high attenuation value, due to the presence of the globin component of the haemoglobin molecule. Under exceptional circumstances, patients with profound anaemia, with a haematocrit of 20% or less have presented with an acute haematoma which was isointense to brain on account of the low haemoglobin contents of the fresh haematoma. Fresh blood has an attenuation value of 55-85 Hounsfield units, the high attenuation (50-70 Hounsfield units) is from high protein concentration within intact red blood cells and not iron content.

As the fresh clot starts to retract after 24-48 hours from onset, there is serum extrusion around its periphery, resulting in a ring of hypointensity that surrounds the haematoma. In the subacute stage, the haematoma maintains its mass effect but becomes progressively less dense, from the periphery toward the center, until reaching isointensity with the adjacent brain parenchyma. The infusion of intravenous contrast at this stage can demonstrate an area of ring enhancement at the periphery of the haematoma. In the chronic stage, the mass effect of the haematoma is no longer present, post-contrast enhancement has disappeared after about 6 weeks from onset, and the residual is a hypointense cavity, at times in the form of a slit that can be indistinguishable from an area of old cavitated infarction.

○ More detailed description of the CT scan appearance of brain hemorrhage

The CT appearance of hemorrhage is determined by the degree of attenuation of the x-ray beam, which is proportional to the density of hemoglobin protein (relative to plasma concentration) within the hematoma.

Immediately following vessel rupture, the hematoma consists of a collection of red blood cells, white blood cells, platelet clumps, and protein-rich serum that has a heterogeneous appearance on CT with attenuation in the range of 30–60 Hounsfield units (HU), depending on the degree of plasma extrusion [20]. In this hyperacute phase, hemorrhage may be difficult to distinguish from normal cortex because of similar attenuation. Over minutes to hours, a fibrin clot forms with an increase in attenuation to 60–80 HU (Fig. 11) [20]. Clot retraction and extrusion of serum can further increase attenuation to as high as 80–100 HU in the center of the hematoma. The degree of attenuation may be reduced in patients with severe anemia [21], impaired clot formation due to coagulopathy, or volume
averaging with adjacent tissue. Vasogenic edema evolves around the hematoma within hours and may continue to increase for up to 2 weeks after hemorrhage onset [22].

![CT appearance of hemorrhage. Serial CT scans of right thalamic hematoma.](image)

(A) Acute ICH in the right thalamus with mean attenuation 65 HU. (B) CT performed 8 days later than (A); the periphery of the hematoma is now isodense to the brain while the center of the hematoma has mean attenuation 45 HU. (C) CT performed 13 days later than (A) shows continued evolution of the hematoma with decreasing attenuation. (D) CT performed 5 months later than (A) shows a small area of encephalomalacia in the location of the previous hemorrhage.

Over the following days, cells and protein are broken down and scavenged by macrophages, leading to slowly decreasing attenuation, with the greatest decrease at the periphery of the hematoma and more gradual evolution toward the center (Fig. 11) [23]. Within 4 to 9 days, the hematoma attenuation decreases to that of normal cortex, and within 2 to 3 weeks to that of normal white matter [20].

The CT recognition of subacute intracerebral hematoma can be challenging because the attenuation is similar to that of normal brain tissue, although mass effect may still be present. MR imaging can confirm subacute hematoma. As time goes on, attenuation continues to decrease to levels below that of the normal brain. Eventually, the hematoma resolves into a fluid-filled or slit-like cavity that may be difficult to visualize on CT (Fig. 11). Contrast enhancement is not present in the initial days following ICH but may develop at the periphery in weeks to months [24], sometimes leading to diagnostic confusion with brain tumor or abscess.

A blood-fluid level may be seen in medium to large ICH within the first hours after onset; the dependent portion displays higher attenuation (Fig. 12) due to sedimentation of cellular elements [25]. This finding may be more common in ICH caused by anticoagulation [26], but it is not specific and has also been described in ICH due to hypertension, trauma, tumor, or arterial-venous malformation. The association with shorter time interval from ICH onset, and in some cases with anticoagulation, has led to speculation that incomplete clotting is required for blood-fluid level formation.
Figure 12. CT with blood-fluid level. A 77-year-old woman was admitted with coma of 4 hours' duration. CT scan shows massive left hemispheric hematoma with blood-fluid level. No history of anticoagulation or coagulopathy.

Box 1. As the hemorrhage evolves, different characteristic appearances can be identified on CT, depending on the age of the bleed. CT findings over time are as follows:

- After 7-10 days, the high density of blood begins to decrease, starting from the periphery of the lesion.
- From 1-6 weeks, peripheral enhancement can be seen, mimicking the appearance of an abscess, possibly related to hypervascularity at the periphery of a resolving hematoma or disruption of the blood-brain barrier.
- By 2-4 months, decreased density indicates cavity formation. A residual cavity is the final stage, which is reached after complete absorption of necrotic and hemorrhagic tissue.

MRI Imaging of cerebral haematoma

Imaging of haematoma by MRI is time dependent as follow:

- The hyperacute stage (0 - 12 hour)

The acute hematoma less than 12 hours old is composed mostly of intracellular oxyhemoglobin with the edematous brain undergoing necrosis. On T2-weighted MR images, hyperacute hematoma will exhibit inhomogeneous signal due to hypointense deoxyhemoglobin and hyperintense, edematous cortical tissue. MR is less sensitive than CT in the hyperacute stage because diamagnetic intra-cellular oxyhemoglobin lacks unpaired electrons and thus clot signal is close to normal brain parenchyma-normal to slightly lower signal on T1-weighted images and slightly higher signal on T2-weighted images. Repeat imaging is indicated to monitor the size of the hemorrhage and the development of delayed hemorrhage and vasogenic edema.

- The acute stage (12 Hr - 3 days)
Due to the presence of the magnetoically susceptible deoxyhaemoglobin. The T2 relaxation time will be markedly shortened, so that fresh blood appears hypointense (black) on the T2 weighted MRI images. This hypointensity is commonly surrounded by a wider hyperintense area that represents oedema. On the T1 weighted images fresh blood appears isointense or slightly hyperintense.

Acute hematoma one to three days old are composed mostly of paramagnetic intracellular deoxyhemoglobin. The deoxyhemoglobin is formed by the dissociation of oxygen from hemoglobin, a process that begins within several hours. Because the deoxyhemoglobin within intact, clotted hypoxic red blood cells does not cause T1 shortening, the hematoma will have normal to slightly lower signal on T1-weighted MR images. The concentration of red blood cells with clot and the concentration of fibrin cause T2 shortening, with areas of very low signal on T2-weighted spin echo and T2 *-weighted gradient echo images.

Figure 13. A 62-year-old female with hypertension presented with acute-onset ataxia and confusion. Noncontrast CT exam of the head [left image] showed a large, right cerebellar hemorrhage, which was evacuated to relieve the mass effect on the brainstem and fourth ventricle. The cerebellar hemorrhage is seen hypointense on the T2 image due to Deoxyhemoglobin [right image].

Figure 14. The concentration of red blood cells with clot and the concentration of fibrin cause T2 shortening, with areas of very low signal on T2-weighted spin echo and T2 *-weighted gradient echo images.

- The subacute stage (3 days - one month)

The picture of hematoma is determined by the oxidation of deoxyhemoglobin to methemoglobin and its shift from the intracellular to the extracellular compartment. The picture of haematoma, during this period is governed by the progressive reduction in the concentration of deoxyhaemoglobin and the progressive increase in the concentration of the oxidized methemoglobin. These changes take place from the periphery of the haematoma to its center. Intracellular oxidized methemoglobin induces shorting of T2
relaxation time while extracellular oxidized methemoglobin induces prolongation of T2 relaxation time

Progressive reduction in the concentration of deoxyhaemoglobin and shift of oxidized methemoglobin from the intracellular to the extracellular compartment, due to lyse of RBCs, results in progressive disappearance of the T2 hypointensity observed in the acute stage. Absence of the deoxyhaemoglobin and appearance extracellular oxidized methemoglobin will result in progressive prolongation of the T2 relaxation time that starts from the periphery of the haematoma to its center, this results in progressive increase of the T2 signal intensity (it becomes brighter); At first the periphery of the haematoma becomes brighter on the T2 weighted images, and this brightness progressively extends to the center.

Within a few days, the subacute hematoma start to undergo liquefaction with development of vasogenic edema. As the edema increases over the first week, it may be great enough to cause herniation. The edema has fluid or water characteristics: iso- to hypointense on T1-weighted images, and hyperintense on T2-weighted images. With oxidation of deoxyhemoglobin to strongly paramagnetic intracellular methemoglobin, proton-electron dipole-dipole interactions between hydrogen atoms and the paramagnetic centers of methemoglobin will cause marked T1 shortening and very high signal intensity on T1-weighted images \(^4\) within the periphery of the hematoma. The intracellular methemoglobin will cause T2 shortening and very low signal on T2-weighted images.

After erythrocyte membrane breakdown and extracellular migration of methemoglobin, there is neovascularization with removal of blood components and debris by macrophages. The new blood vessels at the periphery of the lesion lack the tight endothelial junctions of an intact blood brain barrier, and so there is intense enhancement of the margins on both contrast CT and MR \(^1\). The fragile granulation tissue vessels predispose the patient to additional episodes of acute hemorrhage. CT will show a decrease in the density of the hemorrhage and decrease in the mass effect, the latter due to a decrease in edema. MR will exhibit the persistent high signal of extracellular methemoglobin on T1- and T2-weighted images \(^4\) for up to a year. The peripheral rim of hemosiderin and ferritin has slightly low signal on T1- and marked low signal on T2-weighted images \([201\text{ from the susceptibility effect of hemosiderin within macrophage lysosomes.}])

![Images](image1.jpg)
Figure 15. MRI T2 image (A) and proton density image (B) showing a subacute haematoma, notice the peripheral hypointense hemosiderin ring

Because the extracellular oxidized methemoglobin has a paramagnetic quality it results in shortening of the T1 relaxation time, so that the haematoma in the subacute stage appears hyperintense (bright) on the T1 weighted MRI images. This again starts from the periphery of the haematoma and progresses to its center, because as mentioned before methemoglobin starts to appear at the periphery of the haematoma, this results initially in ring hyperintensity on the T1 images.

Figure 16. Early subacute hemorrhagic contusion in a 78-year-old male. Sagittal TI-weighted image demonstrates high signal intensity at the periphery of the hematoma, consistent with extracellular methemoglobin.

The haemosiderin pigmentation that surrounds the haematoma in the subacute and chronic stages is responsible for the rim of hypointensity that surrounds the haematoma on the T2 weighted and proton density images.

Figure 17. The hypointense hemosiderin ring of subacute haematoma

- Chronic stage (one month to 3 months)

Due to complete absorption of the deoxyhaemoglobin and diffuse and homogeneous increase of the oxidized methemoglobin within the haematoma; it appears diffusely hyperintense (bright) on both the T1 and T2 weighted images.
Clot resorption begins from the periphery inward, and depending on the size of the hematoma, may vary from one to six weeks in duration. Necrotic tissue is sloughed and cystic cavities are formed over the next 6 to 12 months. Focal atrophy is characterized by a decrease in the size of cortical gyri, with compensatory enlargement of cerebrospinal fluid spaces and dilatation of the adjacent ventricle. Cystic cavities are surrounded by gliosis and hemosiderin scarring.

Table 1. The MRI biochemical stages of cerebral hematomas

<table>
<thead>
<tr>
<th>Biochemical substance</th>
<th>MRI changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxyhemoglobin</td>
<td>Oxyhemoglobin lacks unpaired electrons and thus clot signal is close to normal brain parenchyma-normal to slightly lower signal on T1-weighted images and slightly higher signal on T2-weighted images</td>
</tr>
<tr>
<td>Paramagnetic intracellular deoxyhemoglobin</td>
<td>Because the deoxyhemoglobin within intact, clotted hypoxic red blood cells does not cause T1 shortening, the hematoma will have normal to slightly lower signal on T1-weighted MR images. The concentration of red blood cells with clot and the concentration of fibrin cause T2 shortening, with areas of very low signal on T2-weighted spin echo and T2 *-weighted gradient echo images</td>
</tr>
<tr>
<td>Paramagnetic intracellular methemoglobin</td>
<td>Proton-electron dipole-dipole interactions between hydrogen atoms and the paramagnetic centers of methemoglobin will cause marked T1 shortening and very high signal intensity on T1-weighted images within the periphery of the hematoma.</td>
</tr>
</tbody>
</table>
The intracellular methemoglobin will cause T2 shortening and very low signal on T2-weighted images.

Extracellular migration of methemoglobin. MR will exhibit the persistent high signal of extracellular methemoglobin on T1 - and T2-weighted images for up to a year. The peripheral rim of hemosiderin and ferritin has slightly low signal on T1- and marked low signal on T2-weighted images [20] from the susceptibility effect of hemosiderin within macrophage lysosomes.

Clot resorption begins from the periphery inward, and depending on the size of the hematoma, may vary from one to six weeks in duration. Necrotic tissue is sloughed and cystic cavities are formed over the next 6 to 12 months.

Focal atrophy is characterized by a decrease in the size of cortical gyri, with compensatory enlargement of cerebrospinal fluid spaces and dilatation of the adjacent ventricle. Cystic cavities are surrounded by gliosis and hemosiderin scarring.

### SUMMARY

**Table 2. The biochemical stages of cerebral hematomas**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperacute stage [0-12 Hr]</td>
<td>Immediately after an intracerebral bleed, the liquefied mass in the brain substance contains oxyhemoglobin but no paramagnetic substances. Therefore, it looks like any other proteinaceous fluid collection.</td>
</tr>
<tr>
<td>Acute stage [4Hr -3 days]</td>
<td>Reduction in oxygen tension in the hematoma results in the formation of intracellular deoxyhemoglobin and methemoglobin in intact red cells. These substances have a paramagnetic effect that produces T2 shortening. A thin rim of increased signal surrounding the hematoma on T2-weighted images represents edema.</td>
</tr>
<tr>
<td>Subacute stage [3days-3 weeks]</td>
<td>As red blood cells lyse, redistribution of methemoglobin into the extracellular space changes the effect of this paramagnetic substance to one of predominantly T1 shortening. The longer T2 results from(1) a combination of red blood cell lysis (T2 shortening disappears), (2) osmotic effects that draw fluid into the hematoma, and (3) the repetition times (TR) that are in general use for T2-weighted sequences, which are not sufficiently long to eliminate T1 contrast effects in the image.</td>
</tr>
<tr>
<td>Chronic stage [3 weeks-3 months]</td>
<td>Phagocytic cells invade the hematoma (starting at the outer rim and working inward), metabolizing the hemoglobin breakdown products and storing the iron as superparamagnetic hemosiderin and ferritin.</td>
</tr>
</tbody>
</table>
### Table 3. Effect of blood products on the MRI signal

<table>
<thead>
<tr>
<th>Phase</th>
<th>Time</th>
<th>Hemoglobin</th>
<th>T1</th>
<th>T2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperacute stage [0-12 Hr]</td>
<td></td>
<td>Oxyhemoglobin</td>
<td>T1 lacks unpaired electrons and thus clot signal is close to normal brain parenchyma - normal to slightly lower signal on T1-weighted images and slightly higher signal on T2-weighted images</td>
<td></td>
</tr>
<tr>
<td>Acute stage [4Hr -3 days]</td>
<td></td>
<td>Deoxyhemoglobin within intact, clotted hypoxic red blood</td>
<td>No effect</td>
<td>T2 shortening, with areas of very low signal on T2-weighted spin echo and T2 * - weighted gradient echo images</td>
</tr>
<tr>
<td>Early subacute stage [3days-3 weeks]</td>
<td></td>
<td>Strongly paramagnetic intracellular methemoglobin,</td>
<td>TI shortening and very high signal intensity on T1-weighted images within the periphery of the hematoma</td>
<td>The intracellular methemoglobin will cause T2 shortening and very low signal on T2-weighted images</td>
</tr>
<tr>
<td>Late subacute stage [3days-3 weeks]</td>
<td></td>
<td>extracellular migration of methemoglobin</td>
<td>MR will exhibit the persistent high signal of extracellular methemoglobin on T1 - and T2-weighted images for up to a year</td>
<td></td>
</tr>
<tr>
<td>Chronic stage[3 weeks-3 months]</td>
<td></td>
<td>Focal atrophy is characterized by a decrease in the size of cortical gyri, with compensatory enlargement of cerebrospinal fluid spaces and dilatation of the adjacent ventricle. Cystic cavities are surrounded by gliosis and hemosiderin scarring.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 4. Effect of blood products on the MRI signal

<table>
<thead>
<tr>
<th>Phase</th>
<th>Time</th>
<th>Hemoglobin</th>
<th>T1</th>
<th>T2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperacute</td>
<td>&lt;24 hours</td>
<td>Oxyhemoglobin (intracellular)</td>
<td>Iso or hypo</td>
<td>Hyper</td>
</tr>
<tr>
<td>Acute</td>
<td>1-3 days</td>
<td>Deoxyhemoglobin (intracellular)</td>
<td>Iso or hypo</td>
<td>Hypo</td>
</tr>
<tr>
<td>Early subacute</td>
<td>&gt;3 days</td>
<td>Methemoglobin (intracellular)</td>
<td>Hyper</td>
<td>Hypo</td>
</tr>
<tr>
<td>Late subacute</td>
<td>&gt;7 days</td>
<td>Methemoglobin (extracellular)</td>
<td>Hyper</td>
<td>Hyper</td>
</tr>
</tbody>
</table>
CEREBRAL EDEMA ASSOCIATED WITH NONTRAUMATIC CEREBRAL HEMORRHAGE

Traditionally, ICH was believed to cause permanent brain injury directly by mass effect. However, the importance of hematoma-induced inflammatory response and edema as contributors to secondary neuronal damage has since been recognized. At least three stages of edema development occur after ICH (Table 5). In the first stage, the hemorrhage dissects along the white matter tissue planes, infiltrating areas of intact brain. Within several hours, edema forms after clot retraction by consequent extrusion of osmotically active plasma proteins into the underlying white matter. The second stage occurs during the first 2 days and is characterized by a robust inflammatory response. In this stage, ongoing thrombin production activates the coagulation cascade, complement system, and microglia. This attracts polymorphonuclear leukocytes and monocyte/macrophage cells, leading to up-regulation of numerous immunomediators that disrupt the blood-brain barrier and worsen the edema. A delayed third stage occurs subsequently, when red blood cell lysis leads to hemoglobin-induced neuronal toxicity. Perihematomal edema volume increases by approximately 75% during the first 24 hours after spontaneous ICH and has been implicated in the delayed mass effect that occurs in the second and third weeks after ICH.

Thrombin is an essential component of the coagulation cascade, which is activated in ICH. In low concentrations thrombin is necessary to achieve hemostasis. However, in high concentrations, thrombin induces apoptosis and early cytotoxic edema by a direct effect. Furthermore, it can activate the complement cascade and matrix metalloproteinases (MMP) which increase the permeability of the blood brain barrier.

Delayed brain edema has been attributed, at least in part, to iron and hemoglobin degradation. Hemoglobin is metabolized into iron, carbon monoxide, and biliverdin by heme oxygenase. Studies in animal models show that heme oxygenase inhibition attenuates perihematomal edema and reduces neuronal loss. Furthermore, intracerebral infusion of iron causes brain edema and aggravates thrombin-induced brain edema. In addition, iron induces lipid peroxidation generating reactive oxygen species (ROS), and deferoxamine, an iron chelator, has been shown to reduce edema after experimental ICH.
Table 5. Stages of edema after ICH

<table>
<thead>
<tr>
<th>First stage (hours)</th>
<th>Second stage (within first 2 days)</th>
<th>Third stage (after first 2 days)</th>
</tr>
</thead>
</table>
| • Clot retraction and extrusion of osmotically active proteins | • Activation of the coagulation cascade and thrombin synthesis  
• Complement activation  
• Perihematomal inflammation and leukocyte infiltration | • Hemoglobin induced neuronal toxicity |

References


11. Fazekas F, Kleinert R, Roob G: Histopathologic analysis of foci of signal loss on
gradient-echo T2*-weighted MR images in patients with spontaneous intracerebral
hemorrhage: evidence of microangiopathy-related microbleeds. AJNR Am J Neuroradiol


13. Gomori JM, Grossman RI: Mechanisms responsible for the MR appearance and


15. Robertson CS, Contant CF, Gokaslan ZL: Cerebral blood flow, arteriovenous oxygen
difference, and outcome in head injured patients. J Neurol Neurosurg Psychiatry 1992 Jul;
55(7): 594-603.

16. Ruscallada J, Peiro A: Prognostic factors in intraparenchymatous hematoma with

17. Spangler KM, Challa VR, Moody DM: Arteriolar tortuosity of the white matter in


19. Welch KMA, Caplan LR, Reis DJ, Weir B, Siesjo BK, eds.: Primer on Cerebrovascular
Diseases. Morgan Kaufmann; 1997.


1977;13(5):265–266.

22. Inaji M, Tomita H, Tone O, et al.. Chronological changes of perihematomal edema of

23. Messina AV. Computed tomography: contrast enhancement in resolving intracerebral

24. Ichikawa K, Yanagihara C. Sedimentation level in acute intracerebral hematoma in a


Created by Professor Yasser Metwally

http://yassermetwally.com
INTRODUCTION & PATHOGENESIS:

Microcirculatory brain disease is a collective terminology that comprises vascular arteriolar pathology, metabolic endocrinal abnormalities and haemorheological abnormalities. Clinically it is characterized by the existence of cerebral ischaemic events that have a peculiar tendency for recurrence and progression to multi-infarct dementia. These ischaemic events are commonly associated with increased incidence of depression,
parkinsonian manifestations, essential hypertension and blood hyperviscosity. The associates of the microvascular brain disease are collectively called the metabolic syndrome. (See table 1). Microvascular brain disease is occasionally associated with a special subtype of large vessel disease called arterial ectasia or fusiform aneurysm of the vertebrobasilar system. 140

Table 1. Microvascular brain disease associates (the metabolic syndrome)

<table>
<thead>
<tr>
<th>Microvascular associate</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical picture</td>
<td>Stroke, TIAs, multi-infarct dementia, essential hypertension, depression, parkinsonism</td>
</tr>
<tr>
<td>Metabolic, endocrinal changes</td>
<td>Type VI hyperlipidaemia (Hypertriglyceridemia), hyperuricemia, type 2 diabetes, Insuline resistance, truncal obesity (The metabolic syndrome)</td>
</tr>
<tr>
<td>Vascular pathology</td>
<td>Lipohyalinosis, astrogliosis and interstitial edema, etc</td>
</tr>
<tr>
<td>Haemorheological changes</td>
<td>Increased whole blood viscosity and hypercoagulability characterized by an increased plasminogen activator inhibitor-1 (PAI-1) level.</td>
</tr>
</tbody>
</table>

The endocrinal and metabolic abnormalities characteristic of the microvascular brain disease include non-insulin dependent diabetes mellitus, Type IV hyperlipidaemia (increased triglyceride and reduced HDL), truncal obesity and hyperuricemia (The metabolic syndrome).

Although the association between parkinsonian manifestations (vascular parkinsonism) and microvascular brain disease can be attributed to the pathologic findings of multiple basal ganglia cavitations (etat crible) and infarcts (etat lacunaris) that are encountered in the ischemic microvascular brain disease, however a link between the idiopathic parkinson disease and type 2 diabetes was demonstrated by Hu, et al, [122]. Hu, G, et al, 122 found that individuals who developed type 2 diabetes have an 83% increased risk for PD compared with the general population. The mechanism of the association between type 2 diabetes and PD is, however, poorly understood. Insulin might play a role in the regulation of central dopaminergic transmission. 122 According to the study of Hu, et al, 122 The association between type 2 diabetes and PD is independent of sex, smoking, alcohol and coffee intake, and body weight. The demonstrated link between the idiopathic parkinson disease and type 2 diabetes could result in increased incidence of the idiopathic parkinson disease in the microvascular brain disease that is independent of any structural ischemic cerebral pathology.

- Microvascular brain disease and Alzheimer disease (AD)

There seems to be a complex interrelationship between Alzheimer disease (AD) and cerebrovascular disease that extends beyond the coexistence of these 2 disease processes. Imaging features of small vessel disease are seen at higher frequency in Alzheimer’s disease (AD) than in healthy controls. Cerebrovascular disease and Alzheimer disease (AD) often
coexist, whereas stroke often exacerbates preexisting, sometimes previously subclinical, disease. Furthermore, Alzheimer disease (AD), Vascular dementia and microvascular brain disease share common risk factors, such as diabetes and hypertension, as well as genetic factors for brain tissue vulnerability (presenilins, amyloid precursor protein, APOE genes).

- Insuline resistance, the metabolic syndrome and the ischemic microvascular brain disease

The mechanisms that are responsible for the insulin resistance syndromes (IRS) include genetic or primary target cell defects, autoantibodies to insulin, and accelerated insulin degradation. Obesity, the most common cause of insulin resistance, is associated with a decreased number of receptors and postreceptor failure to activate the tyrosine kinase. Insulin resistance plays a major pathogenic role in the development of the metabolic syndrome that may include any or all of the following: hyperinsulinemia; type 2 diabetes or glucose intolerance; central obesity; hypertension; dyslipidemia that includes high triglycerides (TG); low high-density lipoprotein cholesterol (HDL-C) and small, dense low-density lipoprotein (LDL) particles; and hypercoagulability characterized by an increased plasminogen activator inhibitor-1 (PAI-1) level.

THE ISCHEMIC MICROVASCULAR BRAIN DISEASE

As a point of departure a quick overview on the cerebral microcirculation will be given. Two microvascular systems were described. The centrifugal subependymal system and the centripetal pial system. The centrifugal subependymal microvascular system originates from the subependymal arteries which are terminal branches of the choroidal arteries, then extends centrifugally outward into the periventricular gray matter (Basal ganglia and thalamus) and the immediate periventricular white matter.

The centripetal pial vascular system originate from the pial arteries then extends centripetally inwards towards the ventricular system. This system supply the cortical gray
matter and the immediate subcortical white matter. Accordingly the microcirculation is heavily concentrated in the cortical and the immediate periventricular regions.

![Figure 2. The cerebral microcirculation](image)

The microvascular pathology includes initially vascular smooth muscle cell (VSMC) proliferation associated with increased sensitivity of the VSMCs resulting in increased contractibility of the microvascular smooth muscle cells. This is reflected in increased tendency of the fine penetrating intracerebral arterioles for vasospasm. At an advanced stage microvascular remodelling occurs resulting in VSMCs degeneration coupled with excessive deposition of the ground substance (collagen fibres and Lipohyaline material) in the arteriolar walls resulting in what is termed pathologically lipohyalinosis. VSMCs degeneration coupled with lipohyalinosis ultimately result in loss of the physiological autoregulatory process.

![Figure 3. Lipohyalinosis is seen in the smaller penetrating arteries (<200 micrometers in diameter) and occurs almost exclusively in patients with hypertension. It has features of both atheroma formation and fibrinoid necrosis with lipid and eosinophilic fibrinoid deposition in the media.](image)

The haemorheological changes associated with microvascular brain disease include increase in the whole blood viscosity and thrombotic tendency of the blood. In general a significant increase of blood, plasma and serum viscosity and a decrease of whole blood filterability are observed in the metabolic syndrome, and this significantly impair flow in the microcirculation and contribute to the development of the ischemic microvascular brain disease. 118,119,120,121

A negative relationship is observed between directly measured whole-blood viscosity and insulin sensitivity as a part of the insulin-resistance syndrome (The metabolic syndrome), and a positive relationship is observed between insulin resistance and whole blood viscosity. In general, obesity and insulin resistance both impair blood rheology by acting on red cell
rigidity and plasma viscosity. Whole blood viscosity reflects rather obesity than insulin resistance. 118,119,120,121

Whole blood viscosity is a collective terminology that include blood viscosity and plasma viscosity. Blood viscosity is determined by the haematocrit value and plasma viscosity is determined by serum fibrinogen. Increase of the haematocrit value and serum fibrinogen - even within the normal range - increases the whole blood viscosity. Increase of the platelet aggregation also increases whole blood viscosity.

Figure 4. PLATELETS AGGREGATION

Reduced RBCs deformability and increased RBCs aggregability also increase whole blood viscosity. Normally the RBCs must be deformed (they usually become parachuted) in order to pass through the microcirculation. Reduction of the RBCs deformability results in poor RBCs flow through the microcirculation and subsequently poor tissue oxygenation.

Figure 5. RBCs deformability [left] and rigidity [right]

It should also be noted that increased fibrinogen level, especially when associated with increase of the RBCs and platelet aggregability, reflects a hypercoagulable state that selectively affects the microcirculation of the brain. Microvascular occlusion can occur either by Local aggregation of hyperaggregatable platelets or by red cell aggregation with impaction of rigid red cell in the microcirculation.

Increase of the blood viscosity results in global reduction of brain perfusion, however, this is normally compensated for by the physiological process of autoregulation. In response to critical reduction of brain perfusion, the brain microvascular bed dilates thus increasing brain perfusion. Normally the autoregulatory process keeps the brain perfusion at a constant level despite the normal daily fluctuation of the whole blood viscosity.

Loss of the autoregulatory physiological process, secondary to microvascular arteriolar pathology, will simply mean that brain perfusion will fluctuate with fluctuation of the whole blood viscosity. The microvascular brain disease is the end result of a vicious circle that starts at one end of the circle with loss of the autoregulatory process and restarts at the other end of the circle by increase of the whole blood viscosity. This vicious circle should mean that in microcirculatory brain disease there is critical and chronic reduction of whole brain perfusion that is interrupted by frequent microvascular thrombo-occlusive episodes of sudden onset and regressive course. These episodes are secondary to the
hypercoagulable state and increased thrombotic tendency of the blood. The metabolic syndrome, which is commonly associated with the microvascular brain disease, are so commonly associated with increased blood viscosity to the point that it can be called the blood hyperviscosity syndrome.

In general hypertension, an elevated hematocrit value above 45, increased fibrinogen level, old age, cigarette smoking and the metabolic syndrome are significantly linked with silent and symptomatic lacunar infarctions and the microvascular brain disease. Cigarette smoking is significantly linked with the metabolic syndrome (The insulin resistance syndrome). Smoking increases insulin resistance and is associated with central fat accumulation.

CEREBRAL PARENCHYMAL CONSEQUENCES OF MICROVASCULAR BRAIN DISEASE

- Central and cortical atrophy

This is secondary to chronic global reduction of brain perfusion.

- Leukoaraiosis

Leukoaraiosis is an ischaemic demyelination of the immediate periventricular white matter associated with astrogliosis, enlarged extracellular spaces and white matter microcavitations. It is secondary to chronic global reduction of brain perfusion. Leukoaraiosis, which appears as an area of hyperintense signal in the white matter on MR images, is an age-related neurodegenerative condition that, when severe, correlates with dementia. It is characterized histologically by demyelination, loss of glial cells, and spongiosis. The pathogenesis of leukoaraiosis is not yet established, but it is thought to be related to ischemia. Periventricular venous collagenesis, thickening of the vessel wall by multiple layers of collagen, has been reported to occur in aging brains and to be more severe in brains with leukoaraiosis. In postcapillary venules and small veins, the stenosis
that results from severe periventricular venous collagenosis may be one contributing factor in chronic localized ischemia, with consequent cell injury and death.

Figure 7. A, Central and cortical atrophy, notice the associated leukoaraiosis and lacunar infarctions, more on the left side. B, leukoaraiosis. The CT scan periventricular hypodensities are mainly due to astrogliosis and interstitial edema.

- **Histopathology of leukoaraiosis**

Postmortem studies reveal that leukoaraiosis can be due to a heterogenous assortment of tissue changes that differ in histopathologic severity. In most cases, periventricular leukoaraiosis consists of variable degrees of axonal loss, demyelination, astrogliosis, and finely porous, spongy, or microcystic changes in the neuropil. 34,79,96 These changes are frequently associated with arteriosclerotic vasculopathy and, in more severe cases, with frank lacunae infarction. 54 On MR imaging the mild degree of leukoaraiosis almost always present adjacent to the angles of the frontal horns is usually due to focal gaps in the ependymal epithelium with mild underlying gliosis. 86 This change, known as ependymitis granularis, increases in frequency with age and is believed to be due to the wear and tear effects of ventricular CSF pulsations on an ependymal lining incapable of self-repair. 82 Leukoaraiosis may also be related to histologic characteristics of the normal frontal horn subependymal region (fasciculus subcallosus) where finely textured fibers may have different T2-relaxation properties than the deeper white matters.
Figure 8. Etat cribe seen in a cognitively and neurologically normal 81-year-old woman. Fast spin echo: A, Proton density image. B, Second echo: dilated perivascular space permeate the basal ganglia bilaterally.

Subcortical regions of leukoaraiosis seen on MR imaging share many of the histologic features characteristic of the periventricular pattern. Pathologic correlation studies based on postmortem MR image scanning have demonstrated reduced axonal and oligodendroglial density, astrocytosis, pallor on myelin staining, diffuse neuropil vacuolation, and hyalinotic arteriolar thickening. In some cases, these diffuse changes are found to surround variably sized foci of cystic infarction. Subcortical leukoaraiosis, particularly when highly circumscribed or punctate, can often be explained by dilated Virchow-Robin spaces surrounding ectatic and sclerotic arterioles. Such changes may occur in 40% of patients with hypertension, and, when severe, corresponds to the phenomenon of etat cribe originally described by Durand-Fardel in 1843.

Figure 9. Neurologically normal patient with leukoaraiosis affecting the basis pontis and tegmentum.

Rarely, patients with extensive leukoaraiosis can be diagnosed as having Binswanger's disease. This condition, sometimes referred to as lacunar dementia, etat lacunaire, or subcortical arteriosclerotic encephalopathy, is characterized pathologically by extensive athero and arteriosclerosis, multiple foci of white matter infarction, diffuse white matter demyelination with sparing of the subcortical "U" fibers, and variable evidence for cortical
These white matter changes are more destructive than those of typical leukoaraiosis and are clinically associated with combinations of hemiparesis, gait dysfunction, spasticity, Parkinsonism, dysarthria, incontinence, pseudobulbar palsy, and dementia. These abnormalities generally accumulate over months or years in a nonuniform and sometimes stroke-like fashion. There is a tendency for patients to be hypertensive but exceptions have been described. 

Figure 10. Radiographic/histopathologic correlation for a case of diffuse and extensive periventricular LE occurring in an 86-year-old patient. A, Antemortem coronal MR image of left occipital lobe. Note extensive white matter hyperintensity adjacent and superior to the occipital horn of the lateral ventricle sparing the subcortical arcuate fibers. B, Postmortem coronal MR image of left occipital lobe. Note topographically coextensive white matter changes compared with A. C, Bielschowsky-stained postmortem specimen (2X) corresponding to A and B. D, Photomicrograph (hematoxylin-eosin, original magnification x 140) from involved white matter demonstrating perivascular parenchymal rarefaction and macrophage infiltration. E, Photomicrograph (GFAP, original magnification x 660) from involved white matter demonstrating reactive astrocytes. No regions of cystic (lacunar) infarction could be identified in this case.
In contrast to the severe and necrotizing changes of Binswanger's disease, it is apparent that the histology underlying most other forms of leukoaraiosis is far less destructive. This observation may explain why individuals with radiographically widespread leukoaraiosis are often unimpaired. In MS, extensive demyelinative plaques with relative axonal preservation can frequently evolve silently while affecting even neurofunctionally critical regions such as the brain stem and thoracic spinal cord. 37, 38,50, 64, 72 Given the pathology associated with these clinically silent lesions, the dilated perivascular spaces, isomorphic gliosis and low-grade demyelination of leukoaraiosis might be also expected to have limited clinical consequences.
Pathophysiology of leukoaraiosis

Several pathophysiologic mechanisms have been proposed to explain the histology of leukoaraiosis. In addition to ependymitis granularis and Virchow-Robin space dilatation, more extensive regions of leukoaraiosis have been attributed to the ischemic effects of chronic oligemia and to perivascular edema and retrograde axonal degeneration.

- Chronic hypoperfusion

In the severe (Binswanger's disease) form of leukoaraiosis, chronic microvascular oligemia and intermittent thrombotic occlusion appear responsible for the observed pattern of multiple lacunar infarcts with interspersed areas of edema, demyelination, and gliosis. Unlike the richly collateralized cerebral cortex, the leukoaraiosis vulnerable white matter is perfused by long penetrating corticofugal endarteries with few side branches, a vascular architecture that provides little protection from the ischemic effects of microvascular stenosis. 22, 80

The extent to which the more common and histologically milder forms of leukoaraiosis can also be explained by ischemic mechanisms is currently unclear. The term "incomplete white matter infarction" has been proposed to designate regions of mild demyelination, oligodendroglial loss, astrocytosis, and axonal rarefaction that occur in proximity to cystic infarcts or in association with arteriolar hyaline vasculopathy. 26 These changes, which characterize most forms of diffuse leukoaraiosis and can be seen in association with the cystic lacunes of Binswanger's disease, may represent the long-term consequences of chronic hypoperfusion due to senescence and hypertension-related microvascular stenosis.

Direct evidence for hypoperfusion as an explanation of leukoaraiosis pathogenesis is conflicting. Several studies have demonstrated diminished cerebral blood flow (CBF) in
white matter regions affected by leukoaraiosis, but it is unclear whether such hypoperfusion is itself causative or occurs as a secondary response to reduced metabolic activity of the leukoaraiosis tissue. Using, 18 F fluoromethane positron emission tomography (PET), one study revealed that while severe leukoaraiosis regions were associated with ipsilateral cortical hypoperfusion, the hypoperfused regions typically spared the anterior and posterior cortical watershed territories. The authors use this finding to argue that the blood flow reductions seen in leukoaraiosis cases result from the lower metabolic demands of cortex rendered electrophysiologically isolated by subjacent zones of disrupted white matter tissue. The implication is that chronically inadequate hemispheric perfusion may not play a role in leukoaraiosis pathogenesis. While this interpretation gains support from the observation that hemodynamically significant extracranial carotid stenosis does not correlate with the presence of ipsilateral leukoaraiosis, others have seen leukoaraiosis to progress in concert with a severely stenosed ipsilateral carotid that advanced to complete occlusion. In a more recent study, an increased oxygen extraction fraction (OEF) for white matter was found in four nondemented subjects with severe leukoaraiosis. If replicated, this result would support chronic hypoperfusion as an etiologic mechanism by revealing leukoaraiosis lesions to experience a metabolic demand out of proportion to the local CBF.

- **Fluid accumulation and edema**

The subependymal accumulation of interstitial fluid has been proposed as an alternative explanation for leukoaraiosis. Approximately 10% to 20% of CSF may be produced intraparenchymally and transependymally absorbed into the lateral ventricles. Such a drainage pattern might increase the water content of the periventricular region and result in leukoaraiosis, particularly if exacerbated by the effects of age-related ependymal degeneration (ependymitis granularis).

Feigin and Budzilovich observed leukoaraiosis-like white matter changes including demyelination, hyalinized microvessels, cystic necrosis, and astrocytosis in the edematous regions surrounding intracerebral tumors. These authors proposed that Binswanger’s disease might result from a self-reinforcing cycle of tissue destruction where chronic hypertension combined with episodes of local hypoxia and acidosis contribute to the formation of extracellular edema. The edema would then trigger cytotoxicity, gliosis, and demyelination and potentiate the degenerative microvascular changes. Based on this model, others have suggested that exudation of serum proteins from arterioles made leaky from the effects of hypertensive vasculopathy might explain the milder white matter changes of subcortical leukoaraiosis.

- **Axonal degeneration**

Ischemic axonopathy may also account for leukoaraiosis. Ball described the presence of leukoaraiosis with cortical layer III laminar necrosis in the postmortem brains of four elderly patients who experienced episodic systemic hypotension during life. Because the leukoaraiosis regions consisted of rarefied white matter without necrosis or microvascular sclerosis, this author proposed that distal axonopathy secondary to cortical neuronal...
ischemia was the underlying process. Supporting the hypothesis that retrograde degenerative white matter changes can account for at least some leukoaraiosis lesions is the finding of MR image hyperintensities within pyramidal tract locations distal and ipsilateral to internal capsule infarcts. 76

- **Neuroimaging of leukoaraiosis**

Radiographic LA has been correlated with a variety of neuropathological findings. Punctuate hyperintensities are caused by perivascular demyelination and gliosis, dilated Virchow-Robin spaces, or small lacunae. Diffuse or extensive LA consists of areas of loss of axons and glial cells, predominantly oligodendrocytes, and myelin rarefaction (sparking the U fibers) accompanied by spongiosis. 106, 107 Multiple lacunae and multiple sclerosis plaques have also been found in areas of radiological LA. Periventricular rims, thin caps, and halos correlate with subependymal glial accumulation associated with loss of the ependymal lining. The consensus is that small vessel disease is associated with LA. 108 However, a variety of vasculopathies have been found to produce LA on imaging studies. Lipohyalinosis of the long penetrating arteries originating from the pial network and the ventrofugal branches of the choroidal arteries is the most common abnormality in patients with LA. Other vasculopathies can also lead to the neuropathological abnormalities described earlier. 108 Cerebral amyloid angiopathy consisting of amyloid deposition in the media and adventitia of small and mid-sized arteries of the cerebral cortex and leptomeninges is believed to lead to LA in patients with Alzheimer disease. 108 In CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) electron-dense, eosinophilic deposits are found in the media of small vessels; this leads to lumen narrowing. 109

The implications of finding LA on computed tomographic scan or magnetic resonance imaging are varied. Some studies have found that it is a predictor of vascular death in elderly neurological patients; when found in patients with ischemic strokes, it adds extra risk of future strokes from large and small vessels. While some studies have found that LA is not an independent risk factor for intracerebral hemorrhage, 108 the increased severity of WMCs was found to correlate with a 7-fold increased risk of bleeding from anticoagulation in the SPIRIT Study. 110

- **Lacunar infarctions**

lacunar infarctions are secondary to the microvascular thrombo-occlusive episodes. They are most numerous in the periventricular gray matter (thalamus and basal ganglia) and the immediate periventricular white matter. Spasm of the fine penetrating arterioles (secondary to increased VSMCs sensitivity) can also result in Lacunar infarctions.

- **Background**

The lacunar hypothesis proposes that (1) symptomatic lacunes present with distinctive lacunar syndromes and (2) a lacune is due to occlusion of a single deep penetrating artery generated by a specific vascular pathology. This concept is controversial because different
definitions of lacunes have been used. Lacunes may be confused with other empty spaces, such as enlarged perivascular (Virchow-Robbins) spaces, in which the specific small vessel pathology occasionally is absent. Originally, lacunes were defined pathologically, but lacunes now are diagnosed on clinical and radiological grounds. This problem is compounded by the present inability to image a single penetrating artery.

Lacunes may be defined as small subcortical infarcts (less than 15 mm in diameter) in the territory of the deep penetrating arteries and may present with specific lacunar syndromes or may be asymptomatic. Unfortunately, neither the 5 classical lacunar syndromes nor the radiological appearances are specific for lacunes. Lacunes occur most frequently in the basal ganglia and internal capsule, thalamus, corona radiata, and pons.

**Pathophysiology**

Lacunes are caused by occlusion of a single penetrating artery. The deep penetrating arteries are small nonbranching end arteries (usually smaller than 500 micrometers in diameter), which arise directly from much larger arteries (eg, the middle cerebral artery, anterior choroidal artery, anterior cerebral artery, posterior cerebral artery, posterior communicating artery, cerebellar arteries, basilar artery). Their small size and proximal position predispose them to the development of microatheroma and lipohyalinosis.

![Figure 13](image)

Figure 13. Lacunar infarctions are secondary to the microvascular thrombo-occlusive episodes. They are most numerous in the periventricular gray matter (thalamus and basal ganglia) and the immediate periventricular white matter.

Initially, lipohyalinosis was thought to be the predominant small vessel pathology of lacunes; however, microatheroma now is thought to be the most common mechanism of arterial occlusion (or stenosis). Occasionally, atheroma in the parent artery blocks the orifice of the penetrating artery (luminal atheroma), or atheroma involves the origin of the penetrating artery (junctional atheroma).

A hemodynamic (hypoperfusion) mechanism is suggested when there is a stenosis (and not occlusion) of the penetrating artery. When no evidence of small vessel disease is found on
histologic examination, an embolic cause is assumed, either artery-to-artery embolism or cardioembolism. About 25% of patients with clinical radiologically defined lacunes had a potential cardiac cause for their strokes.

- **Histologic Findings**

Lacunes are not examined histologically except at necropsy. Histologically, lacunes are no different from other brain infarcts. Cells undergoing necrosis initially are pyknotic, then their plasma and nuclear membranes break down. Polymorphonuclear cells appear followed by macrophages, and the necrotic tissue is removed by phagocytosis. A cavity surrounded by a zone of gliosis is the end result. Careful examination may reveal the underlying small vessel pathology.

![Figure 14. Pontine lacunar infarctions](image)

Microatheroma causing occlusion or stenosis of a deep penetrating artery is the most common small vessel pathology, usually involving the artery in the first half of its course. Histologically, microatheroma is identical to large vessel atheroma with subintimal deposition of lipids and proliferation of fibroblasts, smooth muscle cells, and lipid-laden macrophages.

Lipoxyalnosis is seen in the smaller penetrating arteries (<200 micrometers in diameter) and occurs almost exclusively in patients with hypertension. It has features of both atheroma formation and fibrinoid necrosis with lipid and eosinophilic fibrinoid deposition in the media.
Neuroimaging of lacunar infarctions

Lacunar infarctions are punctate lesions mostly seen in the periventricular gray matter (thalamus and basal ganglia) and the immediate periventricular white matter, and are also seen in the brain stem. These lesions are hypodense on CT scan and hypointense of T1 weighted images and hyperintense on the T2 weighted images. Contrast enhancement might occur in acute lesions. Marked hypointensities on the T1 weighted images (black holes) are consistent with extensive tissue damage and axonal loss.

On FLAIR images acute lacunar infarctions are diffusely hyperintense. However with the passage of time central necrosis and cavitations occur in the lacunar infarction and the infarction is transformed into a cavity filled with a CSF-like fluid and surrounded by a gliotic wall, subsequently very old lacunar infarction is demonstrated by FLAIR images as a markedly hypointense (black) small lesion (representing the nulled CSF signal inside the central cavity of the lacunar infarction), this hypointense lesion (black hole) is surrounded by a hyperintense rim representing the gliotic walls of the lacunar infarction. In lacunar infarctions, FLAIR MRI images are thus very helpful in demonstrating the age of the infarction.

Figure 15. A, lipohyalinosis, B, lacunar infarction
Figure 16. Periventricular lacunar infarctions and calcifications

Figure 17. Lacunes. Small cavitary infarcts, resulting from hypertension, most frequently involving the basal ganglia (caudate nucleus, globus pallidus, putamen, and amygdala) and basis pontis. Compare right with left.

- **Granular atrophy (Cortical laminar necrosis)**

Granular atrophy is defined pathologically as infarctions localized to the cerebral cortex and not extending to the subcortical white matter. It is characterized by the presence of small punched-out foci of cavitated cicatricial softening situated entirely in the cortex and accompanied by focal glial scar and thinning of the cortical ribbon. The lesions are bilateral and situated along the crest of the gyri. The presence of arteriolar pathology over the cerebral convexity points to its ischemic aetiology.

Chronic brain infarcts are typically seen as low-intensity lesions on T1-weighted and high-intensity lesions on T2-weighted MR images due to prolonged T1 and T2 values. In some infarcts, high-intensity lesions may be seen on T1-weighted images. High intensity lesions on T1-weighted MR images can be due to methaemoglobin, mucin, high protein concentration, lipid or cholesterol, calcification and cortical laminar necrosis. In ischemic stroke, high intensity laminar lesions can be cortical laminar necrosis, hemorrhagic
infarcts, or a combination of the two. Initially thought to be caused by hemorrhagic infarction, histopathological examination has demonstrated these cortical short T1 lesions to be cortical laminar necrosis without hemorrhage or calcification. Although, the mechanism of T1 shortening in cortical laminar necrosis remains unclear, high cortical intensity on a T1-weighted image is believed to occur by neuronal damage and reactive tissue change of glia and deposition of fat-laden macrophages.

The gray matter has six layers. The third layer is the most vulnerable to depletion of oxygen and glucose. Cortical laminar necrosis is a specific type of cortical infarction, which usually develops as a result of generalized hypoxia rather than a local vascular abnormality. Depletion of oxygen or glucose as in anoxia, hypoglycemia, status epilepticus, and ischemic stroke has been attributed as an underlying cause of cortical laminar necrosis. Immunosuppressive therapy (cyclosporin A and FK506), and polychemotherapy (vincristine and methotrexate) have been observed to cause laminar necrosis due to hypoxic-ischemic-insult. Hypoxic insult leads to death of neurons, glia and blood vessels along with degradation of proteins.

The cortical laminar necrosis, seen as a laminar high-signal lesion on T1-weighted MR images, was first described by Swada et al. in a patient of anoxic encephalopathy. Early cortical changes usually show low signal intensity on T1-weighted, which could be due to acute ischemic changes (tissue edema). Usually, cortical high intensity lesions on both T1-weighted and FLAIR images appear 2 weeks after the ictus indicating short T1 and long T2 lesions. Proton-density images are more sensitive than T1-weighted MR images. On proton-density images, cortical laminar necrosis may be seen as high intensity due to increased mobile protons in the reactive tissue.

To conclude, cortical laminar necrosis shows characteristic chronological signal intensity changes, and T1-weighted, FLAIR and proton-density MR images are especially helpful in depicting these changes.

Figure 18. Granular atrophy, notice laminar necrosis with early cavitation. Note persistence of the outer most gray matter.
Figure 19. Cortical laminar necrosis. Sagittal T1-weighted MR image (A) depicts the gyriform increased signal area in right temporal and parietal region. T2-weighted MR and FLAIR images show these areas as dark signal areas.

- **Basal ganglionic calcifications**

  These are calcification of the arteriolar walls within the basal ganglia.
Figure 20. **Basal ganglionic calcification**

- **Dilated Virchow-Robin spaces (VRSs)**

Virchow-Robin spaces (VRSs) are perivascular spaces that surround the perforating arteries that enter the brain. The spaces are normally microscopic, but when dilated, they may be seen on MR images. Even in the normal brain, some VRSs are usually seen in the area of the substantia innominata at the level of the anterior commissure, and a small number of dilated spaces may also be seen in the basal ganglia (BG) in up to 60% of individuals. Virchow-Robin Spaces can be identified by a combination of their typical location and their signal intensity characteristics. They are classically described as isointense to CSF on images obtained with all pulse sequences, and they are round or linear depending on the imaging plane, although their characteristics may vary from this pattern for a number of reasons. First, the small size of the Virchow-Robin Spaces makes partial-volume effects common; therefore, measured signal intensities seldom equal those seen in pure CSF, although the changes in signal intensity between sequences are closely correlated. In addition, T1-weighted images with substantial flow sensitivity may show high signal intensity due to inflow effects. Even if we allow for these effects, the measured signal intensity in the VRS often slightly differs from that of true CSF. This finding has been attributed to the fact that Virchow-Robin Spaces around intracerebral arteries may represent interstitial fluid trapped in the subpial or interpial space.

Pathologic dilatation of Virchow-Robin Spaces is most commonly associated with arteriolar abnormalities that arise due to aging, diabetes, hypercholesterolemia, smoking, and hypertension and other vascular risk factors. This dilatation forms part of a histologic spectrum of abnormalities, which include old, small infarcts (type 1 changes); scars from small hematomas (type 2 changes); and dilatations of Virchow-Robin Spaces (type 3 changes) (124). The presence of these abnormalities on histologic examination is believed to result from moderate-to-severe microangiopathy characterized by sclerosis, hyalinosis, and lipid deposits in the walls of small perforating arteries 50 – 400 μm in diameter (124, 125). As the severity of the microangiopathy increases, microvessels demonstrate increasingly
severe changes, with arterial narrowing, microaneurysms and pseudoaneurysms, onion skinning, mural calcification, and thrombotic and fibrotic luminal occlusions (124–126)

Although microvascular disease is common, few reliable surrogate imaging markers of its presence have been described. The extent and severity of deep white matter (WM) and periventricular hyperintensity on T2-weighted images have been widely studied as potential surrogate markers for small-vessel disease. However, the correlation between these abnormalities and clinical characteristics, such as diagnosis, vascular risk factor, or neuropsychological deficit, is often poor (127).

Figure 21. MRI T2 (A), MRI FLAIR (B) and precontrast MRI T1 (C) images showing dilated Virchow-Robin Spaces associated with diffuse white matter changes (leukoaraiosis)

- More details about etiology and pathogenesis of dilatation of Virchow-Robin Spaces

Virchow-Robin Spaces are potential perivascular spaces covered by pia that accompany arteries and arterioles as they perforate the brain substance. Deep in the brain, the Virchow-Robin Spaces are lined by the basement membrane of the glia limitans peripherally, while the outer surfaces of the blood vessels lie centrally. These pial layers form the Virchow-Robin Spaces as enclosed spaces filled with interstitial fluid and separated from the surrounding brain and CSF. Dilatation of Virchow-Robin Spaces results in fluid filled perivascular spaces along the course of the penetrating arteries.
Abnormal dilatation of Virchow-Robin Spaces is clinically associated with aging, dementia, incidental WM lesions, and hypertension and other vascular risk factors (123). Pathologically, this finding is most commonly associated with arteriosclerotic microvascular disease, which forms a spectrum of severity graded from 1 to 3 on the basis of histologic appearances (124, 126). Grade 1 changes include increased tortuosity and irregularity in small arteries and arterioles (124). Grade 2 changes include progress sclerosis, hyalinosis, lipid deposits, and regional loss of smooth muscle in the vessel wall associated with lacunar spaces that are histologically seen to consist of three subtypes. Type 1 lacunes are small, old cystic infarcts; type 2 are scars of old hematomas; and type 3 are dilated Virchow-Robin Spaces (129). Grade 3 microangiopathy represents the most severe stage and is especially related to severe chronic hypertension. Typical changes described in lower grades are accompanied by fibrotic thickening vessel wall with onion skinning, loss of muscularis and elastic lamina, and regional necrosis in the vessel walls. The brain parenchyma contains multiple lacunae, and diffuse abnormality of myelin is present in the deep hemispheric white matter.

Several mechanisms for abnormal dilatation of Virchow-Robin Spaces have been suggested (130,131). These include mechanical trauma due to CSF pulsation or vascular ectasia (123), fluid exudation due to abnormalities of the vessel wall permeability (132), and ischemic injury to perivascular tissue causing a secondary ex vacuo effect (133).

In the Western world, ischemic vascular dementia is seen in 8–10% of cognitively impaired elderly subjects (134) and commonly associated with widespread small ischemic or vascular lesions throughout the brain, with predominant involvement of the basal ganglia, white matter, and hippocampus (134). Several groups have shown that a severe lacunar state and microinfarction due to arteriolosclerosis and hypertensive microangiopathy are more common in individuals with IVD than in healthy control subjects, and they have emphasized the importance of small vascular lesions in the development of dementia (134, 135). On CT or MR imaging, white matter lesions are commonly used as potential biomarkers of vascular abnormality. Many groups have suggested that simple scoring schemes for white matter lesion load and distribution are useful in the diagnosis of vascular dementia (136). Although white matter lesions are more severe in patients with vascular dementia (136), they are more prevalent in all groups with dementia than in healthy control subjects.

Dilation of Virchow-Robin Spaces provides a potential alternative biomarker of microvascular disease (small vessel disease). Virchow-Robin Spaces in the centrum semiovale were significantly more frequent in patients with fronto-temporal dementia (FTD) than in control subjects (P .01). This finding is not associated with increases in basal ganglionic Virchow-Robin Spaces and is closely correlated with measures of forebrain atrophy, suggesting that these changes are probably representative of atrophy, which is more marked in this patient group than in those with other dementing conditions (128).

The ischaemic microvascular brain disease is the interaction between the haemorheological changes, the vascular arteriolar pathology and the neuronal diminished glucose and oxygen entry.
In general all the pathological consequences of the microvascular brain disease are restricted to either the cortical zone (cortical atrophy, granular atrophy) or the periventricular zone (central atrophy, leukoaraiosis and lacunar infarctions, dilated Virchow-Robin Spaces), i.e. All the ischemic events occurred in the distribution of either the pial or the subependymal microvascular systems. This should mean that hypoperfusion, in microvascular brain disease, is restricted to either the cortical or the periventricular brain regions. The left cerebral hemisphere is more often and more severely affected than the right cerebral hemisphere.

It must be noted that in microvascular brain disease one always see a mix of pathology, i.e. in the same patient lacunar infarctions with leukoaraiosis and central and cortical atrophy might coexist.

**Figure 22.** Leukoaraiosis showing central hypoperfusion on spect study

**Figure 23.** Left hemispherical [mainly frontal] hypoperfusion on spect study

- Cerebral Microbleeds

Cerebral microbleeds are small brain hemorrhages that are presumed to result from leakage of blood cells from damaged small vessel walls. They were first detected on MR imaging only in the mid-1990s, as MR imaging sequences sensitive to blood-breakdown products became available (eg, T2-weighted gradient-echo technique), which are essential for microbleed detection (Figure 24). 37 Histologically, these small black dots on MR imaging represent hemosiderin-laden macrophages that are clustered around small vessels (Figure 25). The choice of field strength, sequence parameters (particularly echo time), and postprocessing (eg, susceptibility-weighted imaging technique) have all been found to have a major influence on the detection rate of cerebral microbleeds. 148,149,150,151 With these advances in imaging, the prevalence of microbleeds has been estimated to be more than 20% in persons aged 60 years and older, increasing to nearly 40% in those older than 80 years. 151 Microbleeds are also commonly associated with microvascular brain disease. Microbleed location is generally divided into deep (ie, basal ganglia, thalamus) and infratentorial versus lobar brain regions (Figure 26). In the aging population, microbleeds in lobar locations share apolipoprotein E (APOE) e4 genotype as a common risk factor with cerebral amyloid angiopathy (CAA) and Alzheimer’s disease (AD), suggestive of a potential link between vascular and amyloid neuropathology. 151,152 This link has further been corroborated by the finding that topography of lobar microbleeds in community-dwelling elderly individuals follows the same posterior distribution as is known from amyloid disease in cerebral amyloid angiopathy (CAA) and Alzheimer’s disease (AD). 153
Furthermore, some reports show that presence of microbleeds, and particularly those in lobar locations, relates to worse cognitive function, both in healthy elderly individuals \cite{154,155} and in patients diagnosed with Alzheimer's disease (AD) \cite{156}. In contrast, deep or infratentorial microbleeds in aging individuals are primarily linked to classic cardiovascular risk factors and are more likely caused by hypertensive vasculopathy. \cite{151} Longitudinal studies indicate that incident microbleeds commonly occur over time: annually, 3\% of presumed healthy elderly individuals develop new microbleeds, increasing to more than 7\% of those who already have microbleeds at baseline. \cite{157} In comparison, these rates are doubled in patients attending a memory clinic. \cite{157}

The increasing evidence that microbleeds reflect both vascular disease as well as amyloid angiopathy has led to the belief that these may well represent the missing link between the vascular and amyloid hypotheses in the pathogenesis of Alzheimer's disease (AD).

**Figure 24.** Microbleed imaging. T1-weighted (left), T2-weighted (middle), and T2-weighted (right) images. Cerebral microbleeds, depicted by arrows, are visualized only on the T2-weighted image and not on the T1-weighted or T2-weighted images. The T2-weighted image is susceptible to paramagnetic properties of hemosiderin, causing the microbleeds to appear as black dots of signal loss.
Figure 25. Radiologic-pathologic correlation of cerebral microbleeds on MR imaging (3 T). Postmortem brain MR imaging shows on T2-weighted imaging a hypointense focus on the gray-white matter interface (white arrow). MR image in the middle of the isolated tissue block containing this hypointense focus. Pathologic analysis of this tissue block (hematoxylin and eosin stain) shows macrophages containing hemosiderin (black arrows), confirming that the hypointense lesion on MR imaging is compatible with a microbleed.

Figure 26 Microbleed location. T2-weighted MR images showing microbleeds (arrows) in lobar (left), deep (middle), and infratentorial (right) locations.
Table 2. Pathology of ischemic microvascular brain disease

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central and cortical atrophy</td>
<td>This is secondary to chronic global reduction of brain perfusion.</td>
</tr>
<tr>
<td>Leukoaraiosis (diffuse periventricular white matter disease)</td>
<td>Leukoaraiosis is an ischaemic demyelination of the immediate periventricular white matter with axonal loss, astrogliosis and interstitial edema. It is secondary to chronic global reduction of brain perfusion.</td>
</tr>
<tr>
<td>Lacunar infarctions</td>
<td>Lacunar infarctions are secondary to the micro vascular thrombo-occlusive episodes. They are most numerous in the periventricular gray matter (thalamus and basal ganglia) and the immediate periventricular white matter. Spasm of the fine penetrating arterioles (secondary to increased VSMCs sensitivity) can also result in Lacunar infarctions.</td>
</tr>
<tr>
<td>Granular atrophy</td>
<td>Granular atrophy is defined pathologically as infarctions localized to the cerebral cortex and not extending to the subcortical white matter.</td>
</tr>
<tr>
<td>Basal ganglionic calcifications</td>
<td>These are calcification of the arteriolar wall of the microcirculation within the basal ganglia.</td>
</tr>
<tr>
<td>Dilated Virchow-Robin Spaces</td>
<td>Dilation of Virchow-Robin Spaces provides a potential alternative biomarker of microvascular disease (small vessel disease).</td>
</tr>
<tr>
<td>Cerebral Microbleeds</td>
<td>The increasing evidence that microbleeds reflect both microvascular brain disease as well as amyloid angiopathy has led to the belief that these may well represent the missing link between the vascular and amyloid hypotheses in the pathogenesis of Alzheimer's disease (AD).</td>
</tr>
</tbody>
</table>

VERTEBROBASILAR ECTASIA (FUSIFORM ANEURYSM, VERTEBROBASILAR DOLICOECTASIA)

A dolichoectatic vessel is one that is both too long (elongated) and too large (distended). Basilar artery elongation is present, by strict criteria, when the artery lies lateral to either the clivus or dorsum sellae or terminates above the suprasellar cistern. A basilar artery larger than 4.5 mm in diameter is defined as ectatic (too large). The term "fusiform aneurysm" has, unfortunately, been used interchangeably in the scientific literature with dolichoectatic change and ectasia, all referring to diffuse tortuous enlargement and elongation of an artery. Dolichoectasia occurs with greatest frequency in the vertebrobasilar system (Fig. 23) but may also involve the intracranial internal carotid and middle cerebral arteries. A contour deformity of the pons resulting from basilar artery ectasia is a not uncommon incidental finding on MRI in the elderly population. Traction or displacement of cranial nerves can, however, lead to symptoms. Depending on the segment of the basilar artery involved, cranial nerve II, III, VI, VII, or VIII can be affected. The lower cranial nerves can be affected with vertebral artery involvement.
Symptomatic vertebrobasilar dolichoectasia exists in two different patient populations: those with isolated cranial nerve involvement and those with multiple neurologic deficits. The latter population includes patients with combinations of cranial nerve deficits (resulting from compression) and central nervous system deficits (resulting from compression or ischemia). A tortuous, but normal-caliber, basilar artery is more likely to produce isolated cranial nerve involvement, whereas ectasia is more likely to cause multiple deficits of either compressive or ischemic cause. Ectasia of the vertebro-basilar system is occasionally associated with microvascular brain disease as explained above 140.

Figure 27. Partially thrombosed giant intracranial aneurysm. A large low-signal intensity lesion is noted on the spin echo scan with intermediate T2-weighting (A) in the region of the left cavernous sinus. A pulsation artifact (black arrows) is seen extending in the phase encoding direction posteriorly from the lesion but originating from only the more medial portion. Comparison of pre(B) and postcontrast (C) T1-weighted scans reveals enhancement in only the more anterior and medial portions of the lesion (white arrow). Three-dimensional time-of-flight magnetic resonance angiography depicts a patent lumen.
within the mass corresponding in position to that suggested by the pulsation artifact and contrast enhancement. The majority of this giant aneurysm of the cavernous and distal petrous carotid artery is thrombosed. Only a crescent of residual lumen remains. The precontrast scans are misleading because the clotted portion of the aneurysm has very low signal intensity on the T2-weighted scan and intermediate to low signal intensity on the T1-weighted scan. But normal-caliber, basilar artery is more likely to produce isolated cranial nerve involvement, whereas ectasia is more likely to cause multiple deficits of either compressive or ischemic cause.

Finally it should be noted that microvascular brain disease is invariably associated with hypertensive concentric left ventricular hypertrophy with unfailing 1:1 relationship.

Table 3. MICROVASCULAR BRAIN DISEASE & CARDIOVASCULAR ASSOCIATES

- LACUNAR INFARCTION
- LEUKOARAIOSIS
- CENTRAL & CORTICAL ATROPHY
- GRANULAR ATROPHY
- SPONTANEOUS HYPERTENSIVE CEREBRAL HAEMORRHAGE
- BASAL GANGLIONIC CALCIFICATION

- DUPLEX SCANNING OF CAROTID ARTERIES SHOWS NORMAL FINDINGS OR NON SIGNIFICANT CHANGES

- LEFT VENTRICULAR HYPERTROPHY WITH STRAIN PATTERN
### SUMMARY

<table>
<thead>
<tr>
<th>PATHOLOGY</th>
<th>CT SCAN</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacunar infarctions</td>
<td><img src="example1.png" alt="CT Scan Image" /></td>
<td><img src="example2.png" alt="MRI Image" /></td>
</tr>
<tr>
<td>Leukoaraiosis</td>
<td><img src="example3.png" alt="CT Scan Image" /></td>
<td><img src="example4.png" alt="MRI Image" /></td>
</tr>
<tr>
<td>Central and cortical atrophy</td>
<td><img src="example5.png" alt="CT Scan Image" /></td>
<td><img src="example6.png" alt="MRI Image" /></td>
</tr>
</tbody>
</table>

www.yassermetwally.com
References


60. Leifer D, Buonanno F, Richardson E: Clinicopathologic correlations of cranial magnetic resonance imaging of periventricular white matter. Neurology 40:911-918, 1990


www.yassermetwally.com


INTRODUCTION

Most patients with TIAs have normal CT scans. The incidence of associated infarction as demonstrated by CT has varied from 0 to 20%. These CT abnormalities have frequently consisted of lacunae or more extensive ill-defined periventricular regions of decreased density or watershed infarctions. The gray matter enhancement associated with cortical infarction and cerebral dysautoregulation has been an infrequent finding. Other observed CT findings have been equally nonspecific, including ventriculomegaly and cortical atrophy.

The MRI is abnormal in 70% of cases with TIAs. All abnormalities seen by CT are also visualized by MRI. Moreover, MRI commonly visualized more extensive involvement than is appreciated by CT. The MRI findings can be divided into four categories according to their anatomical distribution and morphology as follows.
• Periventricular abnormality
• Cortical-subcortical abnormality
• Watershed abnormality
• Normal MRI

• Periventricular white matter changes (leukoaraiosis)

This category is composed of the oldest patients (average age 73.8 years) and had the highest percentage of hypertensives (75%). Of all the groups, this group tended to have a more Polymorphic appearance, being combined on occasion with cortical and subcortical abnormalities as well as extending into clear watershed zones. Abnormalities of the immediate periventricular area, especially bordering the dorsolateral surfaces of the ventricles, are relatively nonspecific since this region may be injured by a wide variety of disease states.

The diversity of possible causes (embolic, hemodynamic, and hypertensive) is present within this group. The incidence of a cardiac history consisting of arrhythmias (chronic atrial fibrillation and ventricular arrhythmias), mitral annular calcifications, and aortic sclerosis, as well as myocardial infarction and angina is very low in this group. It is of interest that this group has the lowest degree of hemodynamically significant carotid stenosis. TIAs and RINDS in this group is one of the clinical manifestations of microvascular brain disease.

Figure 1. CT scan image showing leukoaraiosis

Although there are a diverse number of disease states that may cause these periventricular changes, it seems apparent that the most common etiology would be the vascular changes associated with hypertension. Such changes perhaps are best illustrated by a common disease, namely, subcortical arteriosclerotic encephalopathy (SAE). SAE and the high incidence of lateral periventricular abnormalities encountered have been the topic of much debate. Although none of the patients in this group have a symptom complex composed of dementia, stroke, gait disturbance, ventriculomegaly, or urinary incontinence it seems reasonable to expect that SAE may initially present with TIA or reversible ischemic neurologic deficit (RIND). This group had the highest percentage of RIND symptoms.

• Cortical-Subcortical abnormality

This is the largest Population of abnormalities found, representing 43% of all abnormal studies. The average age of this group was 66.6 years, which is considerably lower than that of the periventricular group. This group also had a relatively large percentage of disease states.
hypertensive individuals (61%). The incidence of a cardiogenic source for the emboli such as atrial fibrillation, ventricular arrhythmias, prolapsed mitral valve, atherosclerotic heart disease with angina, and recent myocardial infarction is low. The incidence of significant carotid stenosis defined as greater than 80% by carotid ultrasound or angiography is also very low in this group. CT scans might be abnormal in this group demonstrating periventricular lacunae or focal gray matter enhancement. This group has the lowest percentage of recurrent TIAS. TIAs and RINDS in this group is one of the clinical manifestations of microvascular brain disease.

- **Watershed abnormality**

This category has an average age of 70.3 years and, interestingly, the lowest percentage of hypertension (58%), comparable to the cortical-subcortical group. All of these patients have abnormalities lying in a deep posterior wedge distribution extending posteriorly and dorsally from the lateral ventricles. Some of them have abnormalities extending along the dorsolateral aspect of the lateral ventricles. Others have the abnormality extending along the cortex and subcortical region between the anterior and middle cerebral arteries. Abnormalities within watershed zones, within the cerebellum and between the distributions of the posterior inferior and superior cerebellar arteries is occasionally demonstrated. Many of these patients have significant carotid stenosis with or without coronary artery stenosis. Myocardial infarctions or ventricular arrhythmias are occasionally present. This group has the highest percentage of multiple or recurrent TIAs (67%).

- **Normal MRI**

This group has the youngest average age (58.6 years), the second highest percentage of hypertensives (67%), and the second highest number of recurrent TIAs. incidence of significant carotid disease or cardiac disease is very low.

**SUMMARY**

<table>
<thead>
<tr>
<th>Type</th>
<th>Incidence</th>
<th>Age</th>
<th>Carotid stenosis</th>
<th>Hypertension</th>
<th>Possible aetiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periventricular white matter changes</td>
<td>Common in Egypt</td>
<td>73.8</td>
<td>Low incidence</td>
<td>75%</td>
<td>Microvascular brain disease</td>
</tr>
<tr>
<td>(leukoaraiosis)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortical-Subcortical</td>
<td>Common in Egypt</td>
<td>66.6</td>
<td>Low incidence</td>
<td>61%</td>
<td>Microvascular brain disease</td>
</tr>
<tr>
<td>Watershed</td>
<td>Rare in Egypt</td>
<td>70.8</td>
<td>High incidence</td>
<td>Low</td>
<td>Carotid bifurcation disease</td>
</tr>
<tr>
<td>Normal</td>
<td>Common in Egypt</td>
<td>58.6</td>
<td>Low incidence</td>
<td>76%</td>
<td>Microvascular brain disease</td>
</tr>
</tbody>
</table>
References

INDEX

- BERRY ANEURYSMS
- PATHOGENESIS OF BERRY ANEURYSMS
- PERIPHERAL ANEURYSMS
- MULTIPLE ANEURYSMS
- COMPLICATION OF INTRACRANIAL ANEURYSMS
  - HAEMATOMA
  - INFARCTION
  - HERNIATION
  - HYDROCEPHALUS
- CAROTID-CAVERNOUS ANEURYSMS
- VASCULAR ECTASIA (FUSIFORM ANEURYSMS)
By far the most commonly encountered lesion of all is the congenital saccular or berry aneurysm, arising from the circle of Willis and the medium-sized arteries along the base and infoldings of the brain. Pathologic studies then formed the basis for most of the investigations concerning aneurysms for more than 100 years. Angiography has given more information about the importance of aneurysms and the complications of their rupture in living subjects.

**Figure 1. COMMON ANATOMICAL SITES OF BERRY ANEURYSMS**

<table>
<thead>
<tr>
<th>Location</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior cerebral</td>
<td>Anterior cerebral 5%, anterior communicating 25%</td>
</tr>
<tr>
<td>Internal carotid</td>
<td>Ophthalmic 4%, posterior communicating 18%, bifurcation 4%</td>
</tr>
<tr>
<td>Middle cerebral</td>
<td>25%</td>
</tr>
<tr>
<td>Posterior cerebral</td>
<td>2%</td>
</tr>
<tr>
<td>Basilar</td>
<td>Bifurcation [tip] 7%, trunk 3%</td>
</tr>
<tr>
<td>Vertebral, PIC A</td>
<td>3%</td>
</tr>
</tbody>
</table>
Pathogenesis of aneurysms

The theory that intracranial aneurysms originate because of developmental defects in arterial walls is widely accepted. It is also generally recognized that an aneurysm is usually found in the fork between two arterial branches. At a point of normal branching, the wall between the two limbs opposite the channel of the undivided vessel usually contains the average amount of muscular and elastic tissue in the tunica media. In addition, there are extra layers of intimal cells in the fork usually referred to as "intimal pads." A collar-like intimal pad is also present proximal to the point of bifurcation of an artery in the cerebral vessels of man, the tunica media is often defective at the fork of a dividing vessel, containing less smooth muscle than in an average normal artery and also having poorly developed elastic fibers. The finding of such medial defects constitute the bases for the development of aneurysms.

Figure 2. A, "Berry" or saccular aneurysm, posterior cerebral artery., B, Ruptured saccular or berry aneurysm, anterior cerebral artery.

In addition to the basic anatomic defects, the age of the patient and arterial hypertension are important factors in the initiation, growth, and rupture of cerebral berry aneurysms. With advancing age, elastic degeneration gradually increases. The degeneration appears first beneath the intimal pads around the arterial bifurcation, then in the more superficial lastica over the medial defects, finally becoming diffuse along the arterial trunks. Approximately two-thirds of patients with ruptured aneurysms have hypertension. Large medial defects are found to be much commoner at middle cerebral arterial forks than at other sites, apparently accounting for the greater frequency of aneurysms at the middle cerebral bifurcation than elsewhere. Aneurysms may also develop at sites of arterial
fenestration, when there is forking and then rejoining of a vessel not normally divided. Tunica media defects are frequently found in the forks of a fenestration.

Figure 3. Elastic stain to show defect in wall of "berry" or saccular aneurysm.

There has been considerable misunderstanding about the frequency of occurrence of aneurysms at various sites because some think in terms of aneurysms of clinical importance that have ruptured or caused neurological changes while others think in terms of total incidence. If all aneurysms are considered, both ruptured and unruptured, then the middle cerebral bifurcation is the most common site for aneurysms to be found. Aneurysms arising from the internal carotid artery, at the site of origin of the posterior communicating artery, are the second most frequent.
An almost equal percentage applies to the forks between the anterior communicating artery and the two anterior cerebral arteries. The fourth most common location is at the bifurcation of one of the carotid arteries into the anterior and middle cerebral arteries. Together, these four locations (middle cerebral, posterior communicating, anterior communicating, and carotid bifurcation) account for 90% of berry aneurysms. The distribution of the remaining 10% comprises the basilar bifurcation (2%), the vertebral artery at the posterior inferior cerebellar arterial origin (2%), lesions of the basilar trunk probably arising at the site of origin of one of the Pontine branches or an "experimental vessel" (1%), distal anterior or middle cerebral artery (2%), and the proximal and distal portions of the posterior cerebral artery (3%).
As noted above, only the minority of aneurysms rupture. The location of an aneurysm affects the probability of its bleeding. Anterior communicating aneurysms, for example, carry the highest risk for the production of a subarachnoid hemorrhage. An aneurysm at the site of origin of the posterior communicating artery has the second highest probability of bleeding among the more frequently occurring lesions, the rare peripheral aneurysms having a slightly higher bleeding tendency. The responsibility for a subarachnoid hemorrhage is attributable to anterior and posterior communicating aneurysms in a high percentage of cases, this depicts not only the anatomic distribution of berry aneurysms but the probability of an individual aneurysm having bled if there are two or more lesions present in different locations.
Aneurysms have certain features in common and yet they are all different, with regard to their shape, size, and to a lesser extent their direction of growth. It is important to assess angiographically the orifice or mouth of the aneurysm, the neck or cervical portion formed by the proximal third of the sac, the body or middle third, and the fundus or apex of the lesion. The vast majority of aneurysms rupture through the apex. Perhaps 10% rupture laterally from the body of the sac, whereas a rupture through the neck is rare.

Figure 7. Multiloculated berry aneurysm filled by a blood clot, in general an aneurysm has a neck, body and a fundus.

Size is also important in the assessment of rupture. The great majority of aneurysms rupture when they are between 5 and 15 mm in diameter. It is unusual for an aneurysm less than 4 mm in its smallest diameter to produce a subarachnoid hemorrhage. Larger multiloculated aneurysms are much more likely to rupture than the smaller unilocular lesions; however, size is more important than multiloculation. Many unruptured aneurysms also have more than one loculus at their domes. The presence of multiple apices or secondary bubbles or pseudopods on the surface is indicative of the pattern of past growth of the aneurysm but does not predict its future prospect for rupture. In addition, some loculations are caused by external structures crossing the aneurysm rather than changes in the wall of the lesion.
PROBABILITY OF ANEURYSMAL RUPTURE AND BLEEDING

<table>
<thead>
<tr>
<th>Factor</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td>Anterior communication artery aneurysms, followed by the posterior communicating artery aneurysms carry the highest probability for rupture and bleeding than other aneurysms</td>
</tr>
<tr>
<td>Size</td>
<td>Larger multiloculated aneurysms are more likely to rupture and bleed than smaller aneurysms with a single locule. Increase in the size of the aneurysm or the development of more loculations greatly increase the likelihood of rupture and bleeding</td>
</tr>
<tr>
<td>Location</td>
<td>Proximal aneurysm are more likely to rupture than distal one</td>
</tr>
</tbody>
</table>

When an intracranial aneurysm ruptures, it may do so suddenly and completely. Blood escapes from its lumen, leading to what is termed clinically "spontaneous subarachnoid hemorrhage." The blood may pass only into the subarachnoid space, or it may pass partly into the brain substance and partly into the subarachnoid space. The blood may, on occasion, be entirely within the cerebral substance, forming an intracerebral hematoma. Some aneurysms, upon rupturing, tear the arachnoid and an accumulation of blood may be found in the subdural space as well as in the subarachnoid space. Aneurysms of the anterior communicating and middle cerebral arteries are often associated with an intracerebral hematoma.

Figure 8. Anterior communicating artery aneurysm hemorrhage. Axial CT scan shows typical subarachnoid hemorrhage from rupture of anterior communicating artery aneurysm. Hemorrhage is present in the septal region (arrows). B, Ruptured anterior communicating aneurysm causing intraventricular and interfrontal haemorrhage
An aneurysm may also rupture with extravasation of blood through the intima but not beyond the wall of the vessel. At other times a local thinning and bulging of the wall may occur without intramural hemorrhage; in this way the pseudopods or multiloculations of the surface are produced. In these cases the size of the aneurysmal sac increases rapidly and the patient may complain of headache, or there may be involvement of the cranial nerves which are adjacent to the aneurysm.

![Figure 9. Ruptured middle cerebral artery aneurysm with hemorrhage into brain parenchyma.](image)

Cerebral angiograms carried out as soon as the patient is brought into the hospital usually show the aneurysm, and only rarely has the contrast material been seen to spurt out of the ruptured sac. In this particular instance, it is possible that angiography may have contributed to the second rupture of the aneurysmal sac. For the most part, however, cerebral angiography does not appear to cause significant deterioration of the patient's condition when carried out at almost any stage of the clinical course.

It is very common to see arterial spasm in the region of a ruptured aneurysm. It is common, also, for all of the major vessels on the side of the lesion to be involved by spasm with poor filling of minor branches. Spasm may be seen affecting the carotid systems bilaterally, and the basilar branches as well when diffuse spasm is present; however, it often is most severe in the neighborhood of the bleeding lesion. In occasional cases spasm may be seen only contralateral to a ruptured aneurysm. Severe, localized spasm is one useful feature in deciding which aneurysm has bled, when more than one aneurysm is present. In cases where intracerebral bleeding has occurred and a localized hematoma has been formed, the usual signs of a mass may be encountered in the angiogram. Aneurysms of the anterior cerebral-anterior communicating artery junction rupture, not uncommonly, into the medial portion of the contralateral frontal lobe. Lesions of the medial cerebral surface elsewhere, not adjacent to the falx, may adhere to the opposite hemisphere and rupture contralateral to their origin.
Arterial narrowing indicative of spasm is seen predominantly in the first 3 weeks after bleeding of ruptured intracranial aneurysms and it is maximal between 6 and 12 days. Thereafter, the incidence of spastic narrowing decreases.

Spasm is much less common in patients over 50 years of age and its absence is possibly a manifestation of arteriosclerosis. From the above it is evident that the presence of spasm and an avascular mass are most important in assessing aneurysms in patients with subarachnoid hemorrhage. In addition, the size of an aneurysm, especially an increase in size between two observations, and, in some cases, the configuration of the sac are helpful in diagnosis.

- **Peripheral Aneurysms**

Lesions arising from the secondary or tertiary branching or branches of the major cerebral arteries can be considered peripheral. Such an aneurysm may be congenital in origin. They may also be the result of embolism and trauma.

The peripheral congenital aneurysms are usually found at secondary or tertiary branching of the anterior and posterior cerebral arteries. For some reason, they are not as frequently seen along the distal segments of the middle cerebral artery. The lesions are saccular in type and have the other features frequently observed with berry aneurysms of the circle of Willis. Large aneurysms are seldom seen peripherally. Most often such lesions attain a size of 5 to 6 mm in diameter, which are their average proportions when the patient is seen with a subarachnoid hemorrhage. There would appear to be a very strong tendency for such congenital peripheral lesions to bleed; they are seldom seen as an incidental finding in patients with brain tumors, or with aneurysms elsewhere that have bled.

Embolic aneurysms may be either infective or neoplastic. The middle cerebral arterial branches are most commonly affected. Before the advent of antibiotics, mycotic aneurysms accounted for at least 5% of intracranial aneurysms. Delayed or inadequate treatment of bacterial endocarditis is now associated with most cases, although such lesions can occur in
drug addicts. Of the patients who have active subacute bacterial endocarditis, one-third have visceral emboli and one-half of the latter are to the brain. Congenital cardiac lesions may be complicated by infection and result in septic emboli lodging in distal cerebral arterial branches.

In many cases, hemorrhage from a mycotic intracranial aneurysm leads to death; it is not unusual for such a patient to have no clinically recognizable embolic episode preceding the hemorrhage. At other times, however, patients with bacterial endocarditis have neurologic problems of strokes or meningoencephalitis when first seen. If an embolic episode is recognized, angiography after an appropriate interval is advocated. From the best information available, it would appear that if a mycotic aneurysm develops, approximately 3 weeks elapse between the septic embolism and rupture of the aneurysm.

A local arteritis with destruction of the vessel wall and the development of a false aneurysm is the usual sequence. Such aneurysms are remarkably round in shape and they rarely attain a diameter of more than 5 mm before bleeding ensues. Since the hemorrhage from such a destructive vascular lesion may be fatal, or a secondary infection with meningitis or a brain abscess may develop, the lesions are usually treated by surgically.

Occasionally, a sizable group of neoplastic cells will metastasize as an embolus and lodge in one of the smaller cerebral vessels. Such tumor cells often come from malignant pulmonary lesions but, occasionally, a benign intracavitary tumor of the heart, a cardiac myxoma, may be the cause. The tumors, the majority of which arise in the left atrium, frequently embolize and approximately one-half of the emboli are cerebral. The myxomatous emboli cause arterial occlusions and damage to the walls of the vessels. Cerebral infarction and hemorrhage are common complications. The embolic myxomatous cells invade and destroy the normal elements of arterial walls and because their growth is slow, and accompanied by connective tissue proliferation, false aneurysms may develop.

Occasionally, somewhat similar findings may be encountered in the primary arteritis of lupus erythematosus or the secondary arteritis of bacterial meningitis and mycotic embolism.

- **Multiple Aneurysms**

Approximately one-third of patients with aneurysms have multiple lesions. The great majority of these patients have two aneurysms.

It is important to be able to identify a bleeding aneurysm among multiple lesions in order to avoid a delay in proper treatment or the institution of inappropriate treatment. In patients with multiple aneurysms the problem of finding angiographic clues as to which aneurysm has caused the subarachnoid hemorrhage may arise when there are no neurologic findings to localize the hemorrhage. Through a radiologic-pathologic correlative study of a large number of cases of multiple aneurysms, well documented anatomically, it was found possible to identify the ruptured aneurysm from the angiogram in 95% of instances. In 83% of the patients, it was found that, on the basis of major vascular
displacements, caused by a large hematoma, or the combination of a smaller displacement and spasm, the site of hemorrhage could be identified. When an aneurysm is isolated on one main cerebrovascular system apart from a second aneurysm or other aneurysms, it may be identified as the lesion that ruptured if there are lateralizing angiographic changes. These would include a generalized vascular dislocation by the mass of a large hematoma, usually manifested as a midline shift or a middle cerebral artery elevation or deformity. The situation of two aneurysms, one located on one major vascular system and the other on another, will pertain approximately one-half of the time. In an additional almost 10%, more than two aneurysms will be found arranged so that the ruptured aneurysm is on one side, whereas the unruptured aneurysms are contralateral. Thus, in approximately 60% of instances, the anatomic relationships are such that if angiographic lateralization of a subarachnoid hemorrhage to the side of an isolated aneurysm is possible, this is tantamount to identification of the aneurysm that ruptured. When a ruptured aneurysm is situated on the same cerebrovascular system as other unruptured lesions, correct diagnosis is dependent upon more sharply localizing angiographic changes. The finding in combination of a minor mass effect of a small hematoma and localized vascular spasm of moderate to marked severity usually constitutes reliable evidence for identifying the aneurysm that has caused a subarachnoid haemorrhage.

A posterior communicating aneurysms is a common cause of third nerve palsy. The aneurysms often grow backward and downward from their origin in the fork of the internal carotid and posterior communicating vessels. Such an extension causes compression of the oculomotor nerve as it passes from the subarachnoid space into the lateral wall of the cavernous sinus, the piercing of the dura occurring between the anterior and posterior clinoid processes. Since the oculomotor nerve is superior to the other orbital nerves, it is the neural structure most often affected by enlarging unruptured aneurysms in this area.

**COMPLICATIONS OF CEREBRAL ANEURYSMS**

The volume of blood that extravasates when an intracranial aneurysm ruptures is relatively small in comparison with the hemorrhages from aneurysms in other parts of the body. The acute appearance of blood in the subarachnoid space is not, in itself, a threat to life. On the other hand, death may rapidly ensue when there is trauma to important centers in the brain by a rapidly dissecting hemorrhage. Complications more often occur later owing to the secondary compression and displacement effects of a hematoma, the prolonged occurrence of cerebral ischemia leading to infarction or the development of both hematoma and infarction. Infarction, through the development of associated edema, may produce a mass effect which at times can induce herniation.

**Hematoma**

The rupture of approximately two-thirds of cerebral aneurysms results in the formation of hematomas which may be large or small. In less than one-half of patients in whom an intracerebral hematoma develops, the lesion is caused by a direct dissection of blood into the cerebral substance from the ruptured aneurysm. In the majority of the cases there is
first an extravasation into the subarachnoid space with subsequent or indirect dissection into the cerebral substance. In a small number of patients (2%) the rupture of an aneurysm may be accompanied by tearing of the arachnoid, with direct hemorrhage into the subdural space or dissection of subarachnoid blood between the arachnoid and dura mater. Many patients with ruptured aneurysms have hematomas that remain confined to the subarachnoid space, where they produce the effects of a localized extracerebral mass.

Figure 11. Massive subarachnoid hemorrhage

Certain patterns of subarachnoid hematoma formation and of intracerebral dissection are found with aneurysms in specific locations. These patterns have been worked out pathologically and can be recognized by angiography, as described below. However, it is now more satisfactory to diagnose and follow intracerebral hematomas by the atraumatic technique of computerized tomography, once the cause of bleeding has been established.

Figure 12. Ruptured aneurysm with subarachnoid hemorrhage.

Aneurysms of the anterior communicating artery are not only responsible for subarachnoid hemorrhage more often than lesions at any other single site, but the rupture results in an intracerebral hematoma more often than with lesions at other sites. Inferior frontal or olfactory hemorrhages may dissect upward, and break into a frontal horn of the ventricular system.
Figure 13. Subarachnoid hemorrhage

At other times an anterior communicating artery aneurysm may rupture into the subarachnoid space between the medial surfaces of the frontal lobes and form an interfrontal subarachnoid hematoma. Such hematomas may dissect upward into the septum pellucidum, often distending the potential cavum between the layers of the septum pellucidum. At any point the dissecting subarachnoid hematoma may burst into the substance of the frontal lobe or into the ventricular system.

The anterior cerebral artery aneurysms are the most likely to rupture

Figure 14. A, ruptured anterior communicating aneurysm inducing interfrontal and intraventricular haematoma, B, ruptured anterior communicating aneurysm inducing callosal haematoma. Notice the bilateral medial frontal anterior cerebral artery infarction, mostly due to vasospasm.

Anterior communicating artery aneurysms are also the most common lesions to produce injury of the hypothalamus. Less frequently, extension of an interfrontal hematoma may pass around the corpus callosum to form a hematoma in the callosal sulcus or in the intercingulate region. Dissection into the corpus callosum itself may take place and occasionally and intracerebral hematoma developing primarily in the frontal lobe, or extending into it from the subarachnoid space, may dissect laterally into the external
capsule. Aneurysms of an anterior cerebral artery distal to the circle of Willis produce hematomas in the proximity of the lesion.

Figure 15. Anterior communicating artery aneurysm hemorrhage. Axial CT scan shows typical subarachnoid hemorrhage from rupture of anterior communicating artery aneurysm. Hemorrhage is present in the septal region (arrows). B, Ruptured anterior communicating aneurysm causing intraventricular and interfrontal haemorrhage.

Figure 16. Ruptured anterior communicating aneurysm inducing interfrontal and intraventricular haematoma. Notice the bilateral medial frontal anterior cerebral artery infarction, mostly due to vasospasm.

The more proximal anterior cerebral aneurysms most often rupture into the frontal lobe substance, whereas the more peripheral aneurysms produce hematomas in the callosal sulcus or in the intercingulate fissure.

Aneurysms extending upward and forward from the bifurcation of the internal carotid artery often are imbedded in the frontal lobe and rupture directly into its substance; thence the hematoma may burst into a frontal horn of a lateral ventricle. Aneurysms at the bifurcation that extend backward and upward may rupture into the hypothalamic nuclei or through the lamina terminalis into the third ventricle.
Aneurysms of the cerebral segment of the internal carotid artery, which usually arise at the site of origin of the posterior communicating artery and extend backward, most often rupture into the anterior temporal lobe substance, thence into the temporal horn. At other times, a subarachnoid hematoma may develop above the uncus and dissect along the choroidal fissure into a temporal horn. The hemorrhage may also extend beneath the uncus. Bleeding from the fundus of a forward pointing aneurysm may result in a subarachnoid collection beneath the frontal lobes.

Middle cerebral artery aneurysms often result in the formation of a hematoma deep in the Sylvian fissure over the central lobe or island of Reil. Such Sylvian hematomas then may dissect into the external capsule. There also may be direct rupture into the external capsule or into the frontal or temporal lobe. A hematoma may dissect forward from the external capsule or from the frontal horn of a lateral ventricle. At other times there may be dissection backward from the external capsule or temporal lobe with rupture into the atrium of a lateral ventricle.

Figure 17. Left sylvian haematoma

Figure 18. Ruptured middle cerebral artery aneurysm with hemorrhage into brain parenchyma.

Correlating well with the pathologic changes described above, the frontal carotid angiogram may display following features denoting hematoma formation from rupture of an anterior communicating artery aneurysm, an aneurysm of the carotid bifurcation, or an aneurysm of the ending portion of the anterior cerebral artery: (a) elevation of the proximal transverse limb of an anterior cerebral artery when a hematoma occurs in the subfrontal region; (b) lateral bowing of the proximal ending portions of the anterior cerebral arteries caused by a frontal intracerebral hematoma (in the case of anterior communicating artery aneurysms that point toward the opposite hemisphere from which they arise, there may be cross-frontal rupture and ipsilateral bowing of the anterior cerebral arteries); (c) widening of the space between the anterior cerebral arteries owing to separation by an interfrontal hematoma in the subarachnoid space.
The corresponding lateral angiogram may reveal, as a result of rupture of an aneurysm of the anterior communicating artery, a lesion of the carotid bifurcation or a forward pointing aneurysm of the supraclinoid portion of the internal carotid artery, (a) backward bowing of the cerebral segment of the internal carotid artery or “closure” of the carotid siphon caused by a subfrontal or inferior intrafrontal hematoma; (b) elevation of the forward extending segment of the anterior cerebral artery, corresponding to the change shown in the proximal transverse limb in the frontal view; (c) depression of the pericallosal artery if there has been dissection of a subarachnoid hematoma over the corpus callosum into the callosal sulcus or intercingulate area. If an aneurysm situated distally on an anterior cerebral artery ruptures into the corpus callosum, or if a subarachnoid hematoma dissects into this structure, the arc of the pericallosal artery may be widened or there may be a localized elevation of this vessel. Differentiation from the wide anterior cerebral sweep of hydrocephalus may be made if there is a normally inclined thalamostriate vein. If there is a subarachnoid hematoma between the corpus callosum and cingulate gyri or in the intercingulate fissure, the pericallosal arteries may be depressed.

Aneurysms of the internal carotid artery that project and rupture backward and ruptured aneurysms at the division of the middle cerebral artery may exhibit in the frontal angiogram, as a result of hematoma formation: (a) widening of the angle formed by the supraclinoid portion of the carotid artery and the proximal portion of the middle cerebral artery due to the presence of a subtemporal or anterior Sylvian hematoma; (b) displacement of the anterior choroidal artery by a hematoma lateral or medial to this structure or as a result of tentorial herniation; (c) a deformity of the orderly columnar arrangement of the middle cerebral branch loops over the island of Reil if a subarachnoid hematoma of the Sylvian fissure is present or if there is a hematoma in the external capsule. Of particular importance is the effect of a subarachnoid hematoma on the medial or lateral lenticulostriate arteries, or the anterior perforating ganglionic arteries. Such hematomas produce obliteration of the perforating arteries at the point where they pass through the pia with the result that their subarachnoid course is seen for a few millimeters in the angiogram, followed by an abrupt termination of the shadows, often along an almost straight line.

In the lateral angiogram internal carotid artery aneurysms that rupture backward and bleeding lesions of the middle cerebral bifurcation that produce hematomas exhibit a loss of undulation, flattening, straightening, or bowing of the anterior choroidal artery, depending upon the exact location of the hematoma in relation to the vessel. When a subuncal hematoma is present, the anterior choroidal artery is elevated. A Sylvian hematoma will produce deformity of the orderly triangular arrangement of the middle cerebral arterial branches over the island of Reil. The looped arrangement is obliterated with straightening, stretching, and separation of the middle cerebral branches, if the hematoma is anterior. Rostral displacement and crowding of the branches may be shown if a posterior Sylvian hematoma is present. The deformity of the Sylvian triangle is accentuated by the presence of a hematoma in the external capsule.
Figure 19. A CT scan revealing a right frontotemporal hematoma secondary to a right MCA aneurysm rupture.

Figure 20. A CT scan revealing interhemispheric and bilateral (right–left) inferior frontal lobe hematomas secondary to an ACoA aneurysm rupture.
Aneurysms at the rostral end of the basilar artery may rupture directly into the third ventricle, the lesions often being imbedded in the structures forming the posterior portion of the ventricular floor. At other times a hematoma may form in the cisterna interpeduncularis. Such a subarachnoid hematoma may then dissect caudal into the midbrain and pons, following the course of perforating branches of the basilar and posterior cerebral arteries. A posterior inferior cerebellar aneurysm may produce a hemorrhage in the brainstem and in the subarachnoid cisterns. Some posterior inferior cerebellar aneurysms are peripheral in position and produce a cerebellar hematoma in the proximity of the lesion.

- Site of Ruptured Aneurysm

The most frequent site of aneurysm rupture in patients with an associated hematoma was the MCA (38% of patients) followed closely by the ACoA (36% of patients). The incidence of a hematoma was higher in patients with MCA (56%) and distal ACA aneurysms (50%), and it was lower in patients with ICA (24%) and PCoA aneurysms (15%). Intracerebral hematomas were very rare in patients with VBA aneurysms (1%).
Relationship Between Aneurysm Site and Hematoma Location

The types of ICH can classified into seven groups according to CT findings on admission: 1) frontal; 2) temporal, 3) sylvian; 4) basal ganglia; 5) interhemispheric; 6) callosal; and 7) cerebellar.

The location of the ICH is related to the location of the ruptured aneurysm. In patients with MCA aneurysms, the sylvian fissure was by far the most common location for hematoma occurrence. Frontal and temporal lobe hematomas also occurred in patients with MCA aneurysms (Fig. 9). In patients with ACoA aneurysms, frontal lobe hematomas occurred most frequently along with several cases of interhemispheric clots (Fig. 10). Temporal lobe hematomas were most frequent in patients with PCoA aneurysms (Fig. 11). In patients with distal ACA aneurysms, ICHs were most commonly frontal and callosal in a typical butterfly-type pattern (Fig. 12). In patients with ICA aneurysms hematomas were most often found in the temporal lobe but were also associated with basal ganglia hematomas (Fig. 13) and one sylvian clot. Only one patient experienced a hematoma (fourth ventricle/cerebellar) that occurred in conjunction with a VBA aneurysm.

It is generally accepted that the second bleeding of an aneurysm is more apt to result in serious complications, or even a terminal event, than is the first rupture. One important reason for the more serious prognosis is the fact that a second rupture usually occurs directly into the brain substance, owing to the fact that the first hemorrhage produces subarachnoid adhesions in the neighborhood of the aneurysm or the development of adhesions binding the sac of the aneurysm to the pia mater. In a high percentage of fatal intracerebral hemorrhages there is bleeding into the ventricular system. Under such circumstances, the ventricles may become rapidly distended with blood, which is evident on CT scan, MRI or in the venous phase of the angiogram, especially if there is impairment of decompression by adhesions about the foramina of the fourth ventricle and in the basal cisterns.
Figure 22. A CT scan revealing a butterfly-pattern interhemispheric hematoma secondary to rupture of a distal ACA aneurysm.
Figure 23. A CT scan revealing a temporal lobe/basal ganglia hematoma (with ventricular extension) secondary to an ICA aneurysm rupture.

Table 1. Hemorrhage sites after aneurysmal rupture

<table>
<thead>
<tr>
<th>ARTERY</th>
<th>SITE OF HAEMORRHAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANTERIOR COMMUNICATING ARTERY ANEURYSM</td>
<td>1-Inferior frontal, olfactory hemorrhage that may dissect into the frontal lobes or hypothalamus</td>
</tr>
<tr>
<td></td>
<td>2-Interfrontal hemorrhage that may dissect into septum pellucidum, corpus callosum or intercingulate area</td>
</tr>
<tr>
<td>INTERNAL CAROTID ANEURYSM</td>
<td>Frontal lobe hemorrhage.</td>
</tr>
<tr>
<td>POSTERIOR COMMUNICATING ARTERY ANEURYSM</td>
<td>Anterior temporal lobe hemorrhage that may dissect into temporal horns</td>
</tr>
<tr>
<td>MCA ANEURYSM</td>
<td>Sylvian fissure haematoma that may dissect into the external capsule</td>
</tr>
<tr>
<td>BASILAR TIP ANEURYSM</td>
<td>Commonly rupture into the third ventricle, pons, midbrain or cisterna interpeduncularis</td>
</tr>
<tr>
<td>PICA ANEURYSM</td>
<td>Brain stem or cerebellar haematoma</td>
</tr>
</tbody>
</table>
Infarction

Cerebral infarction is a more common fatal complication of the rupture of an intracranial aneurysm than intracerebral hematoma formation associated with ruptured aneurysms. It is commonly pale and ischemic, not hemorrhagic in type. Cerebral infarction occurs most often after the rupture of aneurysms (1) of the internal carotid artery where the posterior communicating vessel originates, (2) of the middle cerebral artery, (3) of the anterior communicating artery, and in that order of frequency. The order is just the reverse of that found for intracerebral hematomas. Aneurysms at the origin of the posterior communicating artery produce infarction over a wider area than other aneurysms, probably because they are more proximal on the carotid arterial vascular tree. The infarcted area is most often found in the distribution of the middle cerebral artery, which is the main continuation of the internal carotid. The rupture of aneurysms at the posterior communicating level also produces more ganglionic infarcts than aneurysms at other sites. Bilateral infarction occurs frequently after the rupture of aneurysms of the anterior communicating artery. Such infarction is usually in the cortical distribution of the anterior cerebral arteries and, although the survival rate is relatively high, many patients exhibit mental changes.

Table 2. Infarction sites after aneurysmal rupture

<table>
<thead>
<tr>
<th>Aneurysmal site</th>
<th>Infarction site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior communicating artery aneurysm</td>
<td>1. Aneurysms at the origin of the posterior communicating artery produce infarction over a wider area than other aneurysms, probably because they are more proximal on the carotid arterial vascular tree. The infarcted area is most often found in the distribution of the middle cerebral artery, which is the main continuation of the internal carotid.</td>
</tr>
<tr>
<td></td>
<td>2. The rupture of aneurysms at the posterior communicating level also produces more ganglionic infarcts than aneurysms at other sites.</td>
</tr>
<tr>
<td>Internal carotid artery aneurysm</td>
<td>Massive middle cerebral artery infarction.</td>
</tr>
<tr>
<td>Anterior communicating artery aneurysm</td>
<td>Bilateral infarction occurs frequently after the rupture of aneurysms of the anterior communicating artery. Such infarction is usually in the cortical distribution of the anterior cerebral arteries.</td>
</tr>
</tbody>
</table>

There appear to be three overriding angiographic observations that can be made in the presence of cerebral infarction, or in anticipation of an impending infarction. Recognition of these changes may be of the utmost importance in making decisions concerning treatment.
1. **Spasm.** Infarction occurs most often along the distribution of the artery bearing a ruptured aneurysm, and in many cases this is the result of prolonged spasm of the vessel. The possibility of infarction is always suggested when there is severe localized narrowing of the lumen, usually seen in the immediate vicinity of the ruptured aneurysm; it may also occur when there is only mild diffuse spasm.

2. **Atherosclerosis.** The existence of atherosclerosis may be an important contributing factor to the development of infarction as a complication of hemorrhage from an aneurysm. Infarction is more probable if blood flow in a cerebral vessel is reduced by stenosis of a large atheromatous plaque.

3. **Hematoma.** The more common angiographic changes denoting the presence of intracerebral or subarachnoid hematomas are described above. Subarachnoid hematomas apparently produce infarction more often by pressure on vessel while intracerebral hematomas cause early and marked spasm. Although it is possible to differentiate a subarachnoid from an intracerebral hematoma by CT scan or MRI, angiographic clues are often found, such as elevation of the anterior choroidal artery by a subunca!al hematoma, widening of the space between the anterior cerebral arteries by an interf!rontal mass, or the production of a local deformity of the pericallosal artery by a supracallosal collection. The most common subarachnoid hematoma to produce infarction along the arborization of adjacent vessels occurs after rupture of an anterior communicating artery aneurysm. Other observations that can be made from angiograms do not appear to have nearly as great a significance as spasm, atherosclerosis, and hematoma formation.

Anomalies of the circle of Willis, the dominance of one side over the other in blood flow through the circle, and the overall circulation rate are not often of great value in anticipating or predicting the development of infarction. Computerized tomography is very useful in diagnosing cerebral infarction secondary to spasm. The infarction may or may not be associated with angiographic signs of infarction such as vascular occlusion or early filling veins, and only spasm may be present; but the computerized tomography scan [CT scan or MRI] demonstrate the typical findings of cerebral infarctions .

**Herniation**

The development of a herniation may be a critical event, regardless of where it occurs. Acute herniations follow most often the rapid development of massive intracerebral, intraventricular or subdural hematomas, or massive infarction associated with significant oedema .

The subfalcine herniations occurring with hematomas and infarction are similar to those commonly seen in association with tumors. The anterior cerebral arteries and their branches and the deep cerebral veins are the structures usually displaced to the greatest extent. In some cases hematomas may not only produce generalized or localized displacement of the internal cerebral and basal veins but may also deform the septal and Sylvian veins. Other cerebral hernias that may be seen in supratentorial tumours are not encountered in connection with rupture of aneurysms of the carotid system. In some
instances, however, hematomas that form along the course of the vertebral-basilar system may cause an upward transtentorial herniation or a downward herniation at the foramen magnum.

Figure 24. Subfalcine herniation (arrows). Subfalcial herniation is displacement of the cingulate gyrus from one hemisphere to the other, under the falx cerebri. Subfalcial herniation can compress the pericallosal arteries, causing an infarct in their distribution.

✔ Hydrocephalus

A sizable number of patients who have a subarachnoid hemorrhage develop hydrocephalus. The onset may be acute or gradual. Acute ventricular dilatation occurs when the initial hemorrhage extends directly into the ventricular lumen. Acute enlargement may also develop when an intracerebral hematoma dissects by pressure necrosis through the ventricular wall. Such a gross lesion usually produces coma and, whenever angiography, CT scan or MRI are performed on a seriously ill patient after a subarachnoid hemorrhage, evidence of ventricular enlargement should be sought. In some cases, unilateral dilatation can be observed, at other times the lateral ventricles may both be dilated but asymmetrical, whereas in still other cases symmetrical enlargement may be found. At times, a large third ventricle may be demonstrated.
In most cases the dilatation of the ventricular system develops gradually without dramatic symptoms. The changes often begin slowly after an interval of apparent clinical improvement. Patients who develop only mild ventricular enlargement may remain asymptomatic.

In most instances in which gradual hydrocephalus occurs, it begins within 1 month of the subarachnoid hemorrhage. In the patients who develop symptoms, the manifestations can be rather similar to normal pressure hydrocephalus; although there is great variability in the speed of development, the process is progressive when untreated and slow but steady dilation of the ventricles can be found over a period of time up to 3 years. The most prominent symptom of hydrocephalus is dementia, sometimes accompanied by gait disturbances and a spastic paraparesis. A surprisingly large number with more advanced hydrocephalus have epileptic seizures and develop hypertension when they had been normotensive before the subarachnoid hemorrhage. It is felt that arterial spasm and the occurrence of an intracerebral hematoma as well as the number of hemorrhages contributed significantly to the development of hydrocephalus.

It has been generally believed that the most important mechanism for the development of hydrocephalus is adhesions in the leptomeninges which cause an interference with the extracerebral circulation of cerebrospinal fluid. In some cases there may be arachnoiditis interfering with egress of fluid from the foramina of the fourth ventricle, but changes about these foramina more often result from infection. In some cases the subarachnoid blockage was not at the incisura but in other basal cisterns, the cisterns caudal to the block being irregularly dilated. It would also appear that mechanical blockage of cerebrospinal fluid circulation is not the sole cause of dilatation of the ventricular system but that cellular degenerative changes lead to a wasting of brain tissue because of anoxemic ischemia. Vasospasm is a prominent finding after subarachnoid hemorrhage in more than two-thirds of the patients who develop hydrocephalus. Such spasm may be prolonged and severe for
many days, as noted earlier, causing a reduction in cerebral blood flow. Once hydrocephalus has become established it may increase further owing to elongation and stretching of the intracranial vessels reducing blood flow and the mechanical production of periventricular demyelination.

**CAROTID-CAVERNOUS ANEURYSMS**

Almost all of the lesions in the extradural group are cavernous carotid aneurysms. The lesions are saccular in type and congenital in origin, presumably arising in connection with the numerous intracavernous minor branching of the internal carotid artery. In approximately one-fourth of the cases, cavernous carotid aneurysms are bilateral.

![Angiogram showing intracavernous carotid aneurysm](image)

Figure 26. **Angiogram showing intracavernous carotid aneurysm**

If such an aneurysm ruptures, a carotid-cavernous fistula results. In the absence of trauma, the spontaneous rupture of a saccular aneurysm is the most common cause of an arteriovenous fistula in this location. After a fistula has developed, it may be difficult or impossible to demonstrate the original sacculation by angiography because of surrounding dural sinus opacification, unless the arterial aneurysm had attained considerable size prior to rupture.

The second principal manifestation of a cavernous carotid aneurysm is its mass effect. Occasionally, symptoms may develop because of blockage of the cavernous sinuses. Some cavernous aneurysms become extremely large. This is possible because as they expand, usually upward, they are covered by the dural wall of the sinus which helps prevent early rupture. Rarely, they may act as an extracerebral subfrontal tumor in the anterior fossa. More often, they expand into the suprasellar cistern; an aneurysm must always be included in the differential diagnosis of suprasellar tumors. Less frequently, such a lesion may extend laterally and backward. Also, infrequently, the expansion of such aneurysms may so thin the overlying dura that they rupture intracranially to produce a subarachnoid hemorrhage or intracerebral hematoma. In many cases, a large portion of the aneurysmal lumen may be filled by organized thrombus, and a shell of calcium about its periphery may allow diagnosis from plain skull films. Inspite of the organized thrombus and calcification, many such lesions continue to enlarge slowly throughout life. Erosions of the superior
orbital fissure, the lateral aspect of the sella turcica, and of the clinoid processes are sometimes found.

Cranial nerves are often compressed because of the expanding mass of a cavernous-carotid aneurysm. The larger lesions extending into the suprasellar cistern may compress the optic nerves and chiasm producing visual impairment. These originate usually from the carotid system but may also arise from the basilar artery.

Within the cavernous sinus, the internal carotid artery lies chiefly below and medial to the oculomotor nerve. A rather similar relationship pertains to the trochlear nerve, whereas the abducent nerve is very close to the lateral wall of the carotid artery, along the transverse course of the vessel in the cavernous sinus. Extraocular movements and other functions may be impaired by compression of one or more of these cranial nerves by a cavernous aneurysm. A medially projecting aneurysm is occasionally seen to encroach upon the cavity of the sella turcica.

**VASCULAR ECTASIA (FUSIFORM ANEURYSMS)**

Fusiform lesions resulting from atherosclerosis were among the earliest intracranial aneurysms described and, although they are not nearly as common as congenital saccular lesions, they are occasionally encountered in the course of examination of older individuals. The major vessels at the base of the brain, particularly the basilar artery, are most commonly affected. The basilar artery is frequently found to be ectatic to a marked degree; the vessel is also usually elongated and tortuous.

As noted earlier, the increased mass of the artery may produce indentation of the floor of the third ventricle and interference with the circulation of cerebrospinal fluid. Occasionally, the vertebral artery may undergo aneurysmal atherosclerotic dilatation. A greatly elongated and ectatic vertebral artery may press upon cranial nerves and even simulate a cerebellopontine angle tumor clinically and at CT scan and MRI.

![Figure 27. Basilar ectasia with mural thrombosis](image)
Basilar and vertebral fusiform aneurysms may displace the brainstem backward and upward; it may also be displaced laterally by eccentric aneurysmal dilatation of an elongated S-shaped basilar artery and some lesions indent and compress the brain stem. They seldom rupture, but there are often symptoms of ischemia.

Apparently the orifices of branch vessels become occluded by the intimal disease. At times, the carotid siphon is grossly ectatic and tortuous. The enlargement may extend into the proximal segments of the main branches of the internal carotid and basilar arteries and elements of the circle of Willis may be involved.

Figure 28. A, The orifices of the branching vessels of the ectatic arteries are occluded by intramural thrombosis, B, Schematic representation of a thrombosed ectatic basilar artery

Occlusion of the orifices of branch vessels by thrombosis might induce brain stem infarction

At angiography, an estimation of the true size of the mass may be gained from the displacements of adjacent vessels and the circumferential course of the basilar arterial branches around the lesion and the displaced and deformed brainstem. Basilar artery fusiform aneurysms often imbed themselves deeply in the anterior or anterolateral aspect of the brainstem. Long tract signs are frequently produced. The aqueduct of Sylvius may be displaced far backward and narrowed, and the floor of the posterior part of the third ventricle may be invaginated. Narrowing of the aqueduct frequently produces hydrocephalus involving the lateral and third ventricles.
There also may be interference with cerebrospinal fluid circulation at the tentorial incisura. Such a large basilar artery fusiform aneurysm occasionally ruptures into the brainstem, even after having been present for very prolonged periods of time, during which it has acted as a slowly expanding anterior extra-axial mass. Rupture and haemorrhage is, however, extremely uncommon in fusiform aneurysms.

Some of the larger fusiform aneurysms can be identified by computerized tomography. With this technique, increased radiation absorption may be caused by a calcified shell, a densely organized mural thrombus, blood, or a blood clot in the lesion; or the density of an unclotted aneurysm may be enhanced by contrast enhancement techniques.

- **Neuroimaging of fusiform aneurysms**

Fusiform aneurysms also are known as atherosclerotic aneurysms. These lesions are exaggerated arterial ectasias that occur due to a severe and unusual form of atherosclerosis. Damage to the media results in arterial stretching and elongation that may
extend over a considerable length. These ectatic vessels may have more focal areas of fusiform or even saccular enlargement. Intraluminal clots are common, and perforating branches often arise from the entire length of the involved parent vessel. Fusiform aneurysms usually occur in older patients. The vertebrobasilar system commonly is affected. Fusiform aneurysms may thrombose, producing brainstem infarction. They also can compress the adjacent brain or cause cranial nerve palsies.

Fusiform atherosclerotic aneurysms usually arise from elongated, tortuous arteries. Patent aneurysms enhance strongly after contrast administration; thrombosed aneurysms are hyperdense on noncontrast CT scans. Tubular calcification with intraluminal and mural thrombi in the ectatic parent vessels and aneurysm wall is frequent. Occasionally, fusiform aneurysms cause erosion of the skull base.

At angiography, fusiform aneurysms often have bizarre shapes, with serpentine or giant configurations. Intraluminal flow is often slow and turbulent. These aneurysms typically do not have an identifiable neck. MRI is helpful in delineating the relationship between vessels and adjacent structures such as the brainstem and cranial nerves.

Figure 31. CT scan (upper left two images), MRI T2 image (upper right image) and MRA (lower two images) showing vertebrobasilar ectasia extending to the carotid system. Notice the arterial wall calcification and the brain stem lacunar infarctions.
• Differential diagnosis of fusiform aneurysms

True saccular aneurysms of principal arteries at the base of the brain produce mass effects, when they become large without rupturing, even more often than fusiform aneurysms, which may be silent. A large supraclinoid aneurysm of the carotid siphon frequently extends medially and upward to compress the optic chiasm and hypothalamus. There may even be obstruction at the foramen of Monro. In many instances, a large portion of the aneurysm is filled by mural thrombus so that there is much more vascular displacement than can be accounted for by the size of the opacified lumen at angiography.

![Figure 32. Calcified ectatic basilar artery](image)

Occasionally, an aneurysm arising at the origin of the ophthalmic artery may be encountered. Such a lesion may arise either intradurally or extradurally. Similarly, its expansion may occur within the subarachnoid space or extradurally along the course of the vessel toward the optic foramen. In the latter instance, erosion of the inner end of the optic canal may be visible on plain skull radiographs. Such an aneurysm can compress the optic nerve against the bony edge of its canal.

Surprisingly large aneurysms can develop along the course of the middle cerebral artery. Although many middle cerebral aneurysms bleed when they are relatively small, occasional aneurysms along the course of this vessel over the anterior perforated substance and between the temporal lobe and insula become sufficiently enlarged to act as tumors.

Saccular aneurysms of the basilar artery may become very large. Their massive proportions are probably related to the frequent development of a large organized thrombus about the periphery of the lumen. Circulation in the lumen of the lesion may constitute a relatively small part of its total volume.
**FUSIFORM ANEURYSMS**

- Commonly involve the vertebrobasilar system and might extend to involve other arteries around the circle of Willis
- Involved arteries are diffusely dilated, tortuous, kinked, abnormally prolonged with frequent mural thrombosis and occasional wall calcification.
- Fusiform aneurysms rarely rupture or produce subarachnoid haemorrhage
- Fusiform aneurysms are commonly associated with microvascular brain disease
- The clinical presentation of fusiform aneurysms includes
  - Ischemic manifestations
  - Pressure due to the mass effect of greatly dilated fusiform aneurysms

**References**

- Greenberg MS: Handbook of Neurosurgery. 4th ed 1997; Theme Medical Pub, Lakeland, FL.:.
Cerebrovascular disease is a leading contributor to dementia worldwide. In most populations which have been studied, only Alzheimer's disease (AD) is a more common cause of dementia (8). In 1974, Hachinski et al. (24) popularized the phrase "multi-infarct dementia" (MID) to represent the syndrome of dementia accompanied by focal neurologic signs or symptoms, characterized by stepwise deterioration, and frequently associated with hypertension. In some populations with a high prevalence of hypertension (such as African American men and the Japanese), MID is more common than AD (26, 56). The nomenclature of MID is complicated by several overlapping terms. Though criteria for the diagnosis of MID were published in DSM-III-R in 1987 (2) and have been widely adopted,
their reliability has been questioned and nonstandard alternatives have arisen (14). Furthermore, "vascular dementia" (VaD) has emerged as a diagnostic category that includes not only the multiple discrete infarcts of MID, but other dementing syndromes attributed to cerebrovascular origins. Among these is a dementia associated with diffuse subcortical white-matter disease putatively attributed to chronic subcortical ischemia. This state is commonly, but controversially, known as "Binswanger's disease" or "subcortical arteriosclerotic encephalopathy." In contrast, "Leuko-araiosis" was proposed by Hachinski et al. (25) as a description of radiologic and pathologic subcortical white-matter abnormalities such as those encountered in Binswanger's disease, but these changes are not obligately associated with dementia. Other less common causes of dementia, such as vasculitides, are also considered under the rubric of vascular dementia.

MID has been considered a "subcortical dementia" (10). The term "subcortical dementia" provides a clinical shorthand for dementia with prominent motor effects and relative rarity of the "cortical syndromes" of aphasia, agnosia, and apraxia. Erkinjuntti (13) reported, however, that 65 of 79 MID patients in his series had sustained a cortical stroke and that 56% of the subjects had evidence of cortical strokes alone. Mahler and Cummings (41) have subsequently considered large-vessel and small-vessel behavioral subtypes of vascular dementia. This distinction further clouds the concept of MID as a subcortical syndrome because the behavioral neurology of large-vessel infarctions typically involves "cortical" signs. The theoretical problems inherent in a cortical-subcortical dichotomy for the description of dementia have also been previously addressed (61). The interpretation of what constitutes MID is further complicated by a lack of specificity and uniform application of proposed criteria for diagnosis. Given the high prevalence of cerebrovascular disease, strokes frequently contribute to the cognitive morbidity of individuals with dementia of all types, including AD. Although antemortem clinical evaluations and imaging may confirm the presence of multiple strokes, those techniques cannot exclude the presence of AD pathology contributing to the overall condition. For instance, the presence of cerebral infarctions may allow the clinical expression of Alzheimer-type dementia even though the pathologic criteria for AD are not met. Consequently, the frequency of pure MID in autopsy studies is 10-23%, comparable to that of "mixed dementia" with changes of both MID and AD (35).

**CLINICAL FEATURES**

Recurrent cerebral infarctions are, by definition, the pathophysiologic basis of MID. The risk factors for MID are, not surprisingly, those for cerebrovascular disease, especially age and hypertension. There appear to be no risks specific for the development of MID within the context of cerebrovascular disease. In about 90% of pathologically verified cases of MID there is a history of acute unilateral motor or sensory dysfunction consistent with stroke (14). There may also be a history of acute impairment of "cortical" functions manifest as aphasia, apraxia, or agnosia. Urinary dysfunction and gait disturbance have been suggested as early markers for the development of MID (38). With accumulation of ischemic brain lesions there is typically incremental impairment of memory and behavioral initiation, along with extrapyramidal features such as facial masking and rigidity.
An "ischemic score" (IS) was proposed by Hachinski et al. (23) as a means of distinguishing MID from primary degenerative dementia. A number of variants have been employed since the introduction of the original IS; a typical example is shown in Table 1. These scales share the common weaknesses that they are sensitive but not specific indicators of MID and do not address the presence or absence of AD pathology (8). In the clinical setting, an IS is most useful as an instrument for suggesting the presence of cerebrovascular contributors to a dementia syndrome.

Table 1. Hachinski ischemia score

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrupt onset</td>
<td>2</td>
</tr>
<tr>
<td>Stepwise progression</td>
<td>1</td>
</tr>
<tr>
<td>Fluctuating course</td>
<td>2</td>
</tr>
<tr>
<td>Nocturnal confusion</td>
<td>1</td>
</tr>
<tr>
<td>Relative preservation of personality</td>
<td>1</td>
</tr>
<tr>
<td>Depression</td>
<td>1</td>
</tr>
<tr>
<td>Somatic complaints</td>
<td>1</td>
</tr>
<tr>
<td>Emotional incontinence</td>
<td>1</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>1</td>
</tr>
<tr>
<td>History of strokes</td>
<td>2</td>
</tr>
<tr>
<td>History of associated atherosclerosis</td>
<td>1</td>
</tr>
<tr>
<td>Focal neurologic symptoms</td>
<td>2</td>
</tr>
<tr>
<td>Focal neurologic signs</td>
<td>2</td>
</tr>
</tbody>
</table>

The diagnosis of MID depends on the establishment of dementia — that is, a sustained decrement from previously attained levels of cognitive ability, sufficient to interfere with everyday activities, without an associated impairment of consciousness. Dementia may be stable or progressive. If strokes are the cause of a dementia, it is conceivable that there might be an improvement in cognitive status as the deficits from an acute stroke resolve without returning to baseline. When dementia is accompanied by a history of strokes temporally linked to stepwise deterioration in intellectual abilities, the clinical diagnosis of MID is obvious, though mixed dementia is also a possibility. A more difficult diagnostic situation is the patient with a history of strokes not temporally associated with onset of worsening of cognitive impairment. Recently, Chui et al. (9) proposed criteria for the diagnosis of "ischemic vascular dementia," based on the model for diagnosis of AD (44). These criteria are summarized in Table 2. An even more broadly defined set of international diagnostic criteria for research studies of vascular dementia has been proposed (52), but these have been criticized for being overly inclusive and failing to address the importance of temporal association of vascular events with onset of intellectual impairment (12). Of particular note is the inability of any criteria, short of autopsy examination, to differentiate mixed dementia from MID. These factors have led to considerable controversy over the clinical usefulness of the "vascular dementia" concept (7, 49). Hachinski (22) has further argued that diagnostic criteria for vascular dementia fail to account for the fact that it is a syndromic diagnosis of multiple origins and outcomes.
**Table 2. Criteria for the diagnosis of ischemic vascular dementia (IVD)**

<table>
<thead>
<tr>
<th>I. Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia is a deterioration from a known or estimated prior level of intellectual function sufficient to interfere broadly with the conduct of the patient's customary affairs of life, which is not isolated to a single narrow category of intellectual performance and which is independent of level of consciousness.</td>
</tr>
<tr>
<td>This deterioration should be supported by historical evidence and documented either by bedside mental status testing or, ideally, by more detailed neuropsychological examination, using tests that are quantifiable and reproducible and for which normative data are available.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>II. Probable IVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. The criteria for the clinical diagnosis of probable IVD include <em>all</em> of the following:</td>
</tr>
<tr>
<td>1. Dementia</td>
</tr>
<tr>
<td>2. Evidence of two or more ischemic strokes by history, neurologic signs, and/or neuroimaging studies (CT of T1-weighted MRI)</td>
</tr>
<tr>
<td>B. The diagnosis of probable IVD is supported by:</td>
</tr>
<tr>
<td>1. Evidence of multiple infrared in brain regions known to affect cognition</td>
</tr>
<tr>
<td>2. A history of multiple transient ischemic attacks</td>
</tr>
<tr>
<td>3. History of vascular risk factors (e.g., hypertension, heart disease, diabetes mellitus)</td>
</tr>
<tr>
<td>4. Elevated Hachinski Ischemia Scale (original or modified version)</td>
</tr>
<tr>
<td>C. Clinical features that are thought to be associated with IVD but await further research include:</td>
</tr>
<tr>
<td>1. Relatively early appearance of gait disturbance</td>
</tr>
<tr>
<td>2. Periventricular and deep white-matter changes on T2-weighted MRI that are excessive for age</td>
</tr>
<tr>
<td>3. Focal changes in electrophysiologic studies (e.g., EEG, evoked potentials) or physiologic neuroimaging studies (e.g., SPECT-ET-NMR spectroscopy)</td>
</tr>
<tr>
<td>D. Other clinical features that do not constitute strong evidence either for or against a diagnosis of probable IVD include:</td>
</tr>
<tr>
<td>1. Periods of slowly progressive symptoms</td>
</tr>
<tr>
<td>2. Illusions, psychosis, hallucinations, delusions</td>
</tr>
<tr>
<td>3. Seizures</td>
</tr>
<tr>
<td>E. Clinical features that cast doubt on a diagnosis of probable IVD include:</td>
</tr>
</tbody>
</table>
1. Transcortical sensory aphasia in the absence of corresponding focal lesions on neuroimaging studies

2. Absence of central neurologic symptoms/signs, other than cognitive disturbance

### III. Possible IVD

A clinical diagnosis of possible IVD may be made when there is:

1. Dementia

   and one or more of the following:

2a. A history or evidence of a single stroke (but not multiple strokes) without a clearly documented temporal relationship to the onset of dementia or

2b. Binswanger's syndrome (without multiple strokes) which includes all of the following:

   i. Early-onset urinary incontinence not explained by urologic disease, or gait disturbance (e.g., parkinsonian, magnetic, apraxic, or "senile" gait) not explained by peripheral cause

   ii. Vascular risk factors

   iii. Extensive white-matter changes on neuroimaging

### IV. Definite IVD

Diagnosis of definite IVD requires histopathologic examination of the brain, as well as:

A. Chemical evidence of dementia

B. Pathologic confirmation of multiple infarcts, some outside of the cerebellum

### V. Mixed dementia

A diagnosis of mixed dementia should be made in the presence of one or more other systemic or brain disorders that are thought to be causally related to the dementia.

The degree of confidence in the diagnosis of IVD should be specified as possible, probably, or definite, and the other disorder(s) contributing to the dementia should be listed. For example: mixed dementia due to probable IVD and possible Alzheimer’s disease, or mixed dementia due to definite IVD and hypothyroidism.

**Note:** If there is evidence of Alzheimer’s disease or some other pathologic disorder that is thought to have contributed to the dementia, a diagnosis of mixed dementia should be made.

### NEUROPSYCHOLOGICAL FEATURES

Because they are sensitive to site of dysfunction as opposed to the mechanism causing it, neuropsychological tests have been incapable of consistently distinguishing between MID, AD, and mixed dementias (41). Gainotti et al. (19) reported that AD patients were more likely than those with MID to make "globalistic" or "odd" type errors on Raven's Colored Progressive Matrices task, and on a design copy task were more likely to demonstrate the "closing-in" phenomenon — that is, copying figures such that they overlap the model. Mendez and Ashla-Mendez (45) suggested that unstructured neuropsychological tasks,
such as the Tinker Toy test, may be able to distinguish between AD and MID, because of prominent aspontaneity in the latter. As with other neuropsychological measures, the ranges of performance of AD and MID patients overlap, which limits the diagnostic specificity in any individual patient. Furthermore, how well these results generalize to a populations not selected for the "classic" clinical courses of the syndromes is unknown. Rothlind and Brandt (53) have proposed the use of a Frontal/Subcortical Assessment Battery as a supplement to common bedside cognitive examinations for differentiating dementia types characterized by prominent subcortical pathology from AD.

**EPIDEMIOLOGY**

The reported frequency of MID in demented populations ranges from 4.5% to 39% (34). Karasawa and Homma (33) have suggested that the prevalence of MID, at least in Japan, has decreased since 1980 as the result of fewer strokes affecting the elderly.

Jorm et al.'s (29) extensive review of previous studies provides the basis for much of the current understanding of the demographics of MID. They calculated the prevalence of MID as doubling with every 5.3 years of age, which is in contrast to a popular perception that the prevalence of MID declines after age 75 because of mortality associated with recurrent strokes (43). Men are affected with MID more frequently — as opposed to AD, which is more common among women (29). In Europe, there is also a trend toward higher rates of MID in rural populations than in urban ones (34).

Meta-studies of the epidemiology of MID have been complicated by the lack of clear-cut and uniform diagnostic criteria. Another problem in the interpretation of MID epidemiology is that the illness is often defined on the basis of its risk factors regardless of temporal course. As pointed out by Kase (34), in the presence of dementia, the IS items of (a) history of hypertension, (b) history of stroke, (c) evidence of associated atherosclerosis, and (d) focal findings on neurologic exam are considered sufficient to diagnose MID. Prospective studies, using uniform diagnostic criteria and paying careful attention to the timing and character of stroke and dementia, will be required to more fully understand the epidemiology and natural history of MID.

**PATHOLOGY**

Tomlinson, Blessed, and Roth's landmark article (59) on the neuropathology of demented older individuals clarified the importance of AD pathology in senile dementia. It also reported a 20% frequency of multiple, discrete infarcts. These findings, along with Hachinski et al.'s (24) popularization of the term MID, defined the role of focal infarctions as a cause of dementia. **Lacunar infarctions**, also known as **lacunes**, are commonly implicated as a major contributor to MID because of the "subcortical" features often prominent in the clinical presentation of the illness. **Lacunes** are small cavitary lesions attributed to the occlusion of deep penetrating arteries. There is no uniform definition based on size, but most lacunes are less than 2 cm in diameter. Lacunar infarctions are almost invariably associated with lipohyalinosis of the brain microvasculature.
Lacunar infarctions are strongly associated with a history of hypertension. In Fisher's (16) report, 97% of 114 autopsy cases of lacunar infarction had a diagnosis of hypertension, though more recent studies with stricter criteria for hypertension suggest rates ranging from 60% to 75% (47). The importance of lacunes per se as contributors to the dementia has been questioned. Both Tomlinson et al. (59) and Fisher (17) minimized the role of these lesions in cognitive deficits. Cases of MID with lacunes also typically show myelin-stain evidence for extensive white-matter degeneration (leukoaraiosis) (27, 48). Whether an accumulation of lacunes themselves is able to produce dementia in the absence of associated noncavitary white-matter damage is unknown. Though frequently referred to as demyelination, electron microscopy (EM) indicates that axons within the myelin-stain lesions are lost as well (63). Because the diffuse white-matter changes and the cavitary lesions almost always co-occur and share a common pathophysiology, it is unlikely that their differential effects will be elucidated from human clinical material. The problem in differentiating "pure" MID pathologically is one factor contributing to the evolution of the
more inclusive concept of ischemic vascular dementia. Pathologically multi-infarct dementia, in ischemic microvascular brain disease, often contains a mix of lacunar infarctions, leukoaraiosis, central and cortical atrophy, granular atrophy and basal ganglionic calcification in various combinations. History and or radiological / pathological studies often show evidence of hypertensive hemorrhagic changes in MID patients.

Two other types of discrete infarctions contribute to many cases of MID. Large-vessel infarctions are usually identifiable by history with features of hemiparesis, hemianopia, aphasia, and so on. These are also unequivocally evident on CT or MRI. The volume of tissue loss from such lesions is an important factor in the development of dementia. Tomlinson et al. (59) reported that all their autopsy subjects with greater than 100 ml of tissue loss were demented. However, it is clear that dementia can follow much smaller losses of brain tissue if these are strategically located (11). The second type of cortical lesion contributing to MID is the micro-infarct. These have been reported as the sole basis of dementia (32, 59) and consist of 0.5-to 2-mm-diameter lesions within the cortical ribbon. They are associated with a history of transient ischemic attacks (48).
Other factors which predispose to the development of multiple cerebral infarctions are associated with MID or vascular dementia. Conditions leading to thromboembolic showers, such as endocarditis or atrial myxoma, can lead to the rapid development of a demented state often after a period of acute encephalopathy or coma. Autoimmune vasculitides, such as in systemic lupus erythematosus or granulomatous angiitis of the central nervous system, contribute to areas of cerebral ischemia and infarction. They can be associated with long-term cognitive impairments. Tertiary Lyme disease and syphilis can also cause dementia on the basis of vasculitic thromboses. Cerebral amyloid angiopathy, though often linked to AD, may lead to multiple intracerebral hemorrhages and play a significant role in the development of vascular dementia (28). One other lesion of vascular origin which can present as dementia is chronic subdural hematoma. These intracranial fluid collections can mimic the fluctuating, stepwise cognitive deterioration and prominent motor symptoms characteristic of MID, and they are largely reversible with surgical drainage of fluid and relief of mass effect.
Figure 5. A case of multi-infarct dementia. There are multiple cystic spaces consistent with small remote infarcts. These are predominantly in the subcortical white matter (black arrows) and basal ganglia (red arrow). In other sections more could be seen in the thalamus too. Note how small the basal ganglia are on the right vs. the left. There is also a dilatation of the lateral ventricles. In this case it is probably due to loss of tissue rather than increase in CSF, hence it is called hydrocephalus ex vacuo. Finally there is moderate atherosclerosis of the middle cerebral artery on the right (yellow arrows).

PATHOGENESIS

To date, there remains no concise explanation for the pathogenesis of MID except for infarctions causing loss of brain volume or loss of strategic, localized, areas integral to normal cognition, or a combination of these two factors.

Although CBF is diminished in MID, this is a feature common to most dementia and probably represents a response to reduced cerebral metabolism, rather than the cause of the cognitive impairment. Some MID patients show foci of elevated regional oxygen extraction fraction (rOEF) suggestive of areas of chronic compensated ischemia (21).
Rogers et al. argued (51) that a state of insufficient blood flow to the brain precedes the onset of dementia in MID patients by up to 2 years. Brown and Frackowiak (6) have cautioned, however, that such rOEF changes are not common among MID patients and therefore cannot be the major factor in the development of most MID. Two conditions associated with global diminution in CBF — cardiac disease (58) and hypertension (3) — have nonetheless been long recognized as contributors to impairment on neuropsychological testing. Meyer et al. (46), for example, reported that careful control of blood pressure improved cognition in some in MID patients, but overcontrol (with presumed diminution of CBF) worsened cognitive performance. Increased whole blood viscosity often contributes to diminished brain perfusion in MID patients. Increased whole blood viscosity is very common in essential hypertension.

MID and, more inclusively, vascular dementia are associated with changes in the blood-brain barrier (BBB). Elevated cerebrospinal fluid (CSF) concentrations of albumin and immunoglobulin G (IgG) have been reported for MID patients (40), though other studies have found no difference for albumin (1) or IgG (5). Interestingly, Blennow et al. (5) also reported increased CSF/serum ratios for albumin in AD patients with white-matter lesions or vascular risk factors. This indicates that BBB dysfunction in vascular dementia may result from risk factors for cerebrovascular disease rather than represent a unique contributor to MID. Wallin and Blennow (60) have argued that, because myelin lipids are significantly reduced in vascular dementia, the myelin sheath is a primary lesion site. They further hypothesize that the high metabolic demands of the oligodendrocytes render them prone to ischemic damage. These views are at odds with (a) the PET data, which suggest that chronic ischemia is not a contributor to MID (6), and (b) the EM studies, which show axonal loss in areas of noncavitary demyelination (63). Although myelin loss and BBB dysfunction may contribute to some vascular dementia syndromes, their causative role in MID is questionable. One of the difficulties in assessing the pathophysiology of vascular dementia is the considerable frequency of dementia with findings of both vascular disease and AD. Although this may simply represent the co-occurrence of two common illnesses, there is evidence that links cerebrovascular disease and AD pathology. Kalaria et al. (31), for instance, found that cerebral ischemia promotes deposition of potentially neurotoxic amyloid in the brain. Sofroniew et al. (57) reported that focal cerebral damage causes neuronal loss in the nucleus basalis of Meynert similar to that observed in AD. Furthermore, such changes in the basal forebrain, when associated with AD, have been linked to alterations of cerebral vascular regulation and diminution of CBF (54). The synthetic sites for the biogenic amines are also affected in AD (42, 50). Degeneration in these sites, the locus coerulesus and dorsal raphe nuclei, may adversely affect cerebrovascular function, because norepinephrine and serotonin also influence vascular autoregulation (53). The distinction between causes of vascular and "primary degenerative" dementias may therefore be more difficult than is commonly accepted.
Table 3. Pathological /clinical associates of multi-infarct dementia

<table>
<thead>
<tr>
<th>Vascular risk factors</th>
<th>Hypertension, NIDDM, type IV hyperglycaemia, old age, and LVH are common in MID patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive vascular pathology</td>
<td>Lipohyalinosis and arteriolar wall fibrosis are common in MID patients</td>
</tr>
<tr>
<td>Pathological findings</td>
<td>Neuronal degeneration, ischaemic demyelination, diffuse lacunar state, and leukoaraiosis are common in MID patients</td>
</tr>
<tr>
<td>Haemorheological profile</td>
<td>Increased whole blood viscosity and increased thrombotic tendency are common in MID patients</td>
</tr>
</tbody>
</table>

**ANIMAL MODELS**

Although a number of animal models for the development of MID have been employed, none have been satisfactory. Rodents tend not to have profound long-lasting behavioral effects from cerebral infarctions, and the multiple or diffuse, gradually acquired lesions characteristic of MID in humans have not been reproduced. The promising technique of inducing embolic ischemia in rats by injecting 35-μm-diameter microspheres into rat carotid arteries produced effects on memory, but these were not sustained (37).

**IMAGING**

As with most central nervous system diseases, imaging studies have an important role in the diagnosis of MID. In contrast to the diagnosis of AD, in which cerebral images are used to "rule out" structural changes contributing to the dementia, the images in MID can clearly identify significant pathology. In the neuropathologically verified series of Erkinjuntti's group (14), 74% of MID patients had cortical infarcts and 13% had deep infarcts on x-ray computed tomography (CT). Magnetic resonance imaging (MRI) is more sensitive to lesions in the brain than CT, but this is not necessarily an advantage in the diagnosis of MID. Cavities present on T1-weighted images are consistent with cerebral infarction, but many of the changes observed on MRI may represent the effects of healthy aging, such as dilated perivascular spaces. The typical changes include small, focal areas of increased signal as well as patchy or confluent periventricular white-matter hyperintensity on T2-weighted images. These nonspecific changes are the basis of the term "leukoaraiosis" (LA). It is important to recognize that a large volume of diffuse signal change may be present on CT or MRI without meaningful impairment of cognition. Nonetheless, LA is a frequent correlate of MID. In Erkinjuntti et al.'s (15) clinical series, 72% of MID patients had LA, as opposed to 19% of AD patients.
For many years, "cerebral arteriosclerosis" was considered an important component of most senile dementia — hence the popular use of the phrase "hardening of the arteries" as a synonym for dementia. This perception understandably led to extensive study of cerebral blood flow and metabolism, but with little concern over clinical differentiation of dementia types. The earliest studies employed inert gas measures of global cerebral metabolic rate.
for O2 (CMRO2). Such studies demonstrated diminished cerebral metabolism in demented subjects, both with and without known cerebrovascular disease (39).

![CT scan images showing periventricular diffuse hypodensity](image)

**Figure 8.** Leukoaraiosis, CT scan images showing periventricular diffuse hypodensity, which is mainly due to astrogliosis and interstitial edema. Notice central and/or cortical atrophy.

Developing technology subsequently allowed regional cerebral blood flow (CBF) measurements using the gamma-emitter 133Xe and multiple extracranial radiation detectors for planar or tomographic imaging. Simultaneously, a greater understanding of dementia subtypes improved the discriminative abilities of the techniques. Patients with vascular dementia, including MID, demonstrate patchy, irregular areas of decreased CBF consistent with areas of infarction or ischemia, whereas AD patients have more uniform frontal, parietal, and temporal decreases in CBF (36, 62). There is no general agreement that diminished CBF by 133Xe methods correlates with dementia severity. Some studies have found good correlation in MID only (23), and others have reported it in AD only (62); however most studies have found it in both (6).
Figure 9. leukoaraiosis, MRI T2 image. The MRI T2 periventricular hyperintensities are mainly due to astrogliosis and interstitial edema. Notice central and/or cortical atrophy.

Positron emission tomography (PET) using 15O allows detailed mapping of O2 metabolism. Neither AD nor MID patients typically demonstrate chronic ischemia by this method (18). Despite early enthusiasm for [18F]fluorodeoxyglucose (FDG) PET as a useful technique for the differentiation of MID and AD (4), subsequent investigations have not been as conclusive (6).

Single photon emission computed tomography (SPECT) is more widely available than PET and has been used clinically to differentiate MID from AD, though the validity of SPECT for this purpose is not known. Neither of the two isotopes in general use, 123I-labeled amphetamine (IMP) and 99mTc-labeled hexamethylpropylene amine oxime (HMPAO), has been shown to be superior in the differential diagnosis of dementia (20). As with other imaging modalities, MID patients tend to show patchy or multifocal hypoperfusion whereas AD patients show more diffuse changes, but there is sufficient overlap to prevent diagnostic surety in any individual patient (55).
Table 4. Pathological / radiological findings in multi -infarct dementia

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central and cortical atrophy</td>
<td>This is secondary to chronic global reduction of brain perfusion.</td>
</tr>
<tr>
<td>Leukoaraiosis</td>
<td>Leukoaraiosis is an ischaemic demyelination of the immediate periventricular white matter with axonal loss, astrogliosis and interstitial edema. It is secondary to chronic global reduction of brain perfusion.</td>
</tr>
<tr>
<td>Lacunar infarctions</td>
<td>Lacunar infarctions are secondary to the micro vascular thrombo-occlusive episodes. They are most numerous in the periventricular gray matter (thalamus and basal ganglia) and the immediate periventricular white matter. Spasm of the fine penetrating arterioles (secondary to increased VSMCs sensitivity) -can also result in Lacunar infarctions. It is commonly associated with lipohyalinosis of the microvascular brain bed.</td>
</tr>
<tr>
<td>Granular atrophy</td>
<td>Granular atrophy is defined pathologically as infarctions localized to the cerebral cortex and not extending to the subcortical white matter.</td>
</tr>
<tr>
<td>Basal ganglionic calcifications</td>
<td>These are calcification of the the arteriolar wall of the microcirculation within the basal ganglia .</td>
</tr>
</tbody>
</table>

**TREATMENT**

Drugs of many classes and presumed mechanisms of action have been tried in the treatment of the cognitive symptoms in MID, but none have consistently been demonstrated to be effective. No agent has been approved for such use in the United States. There are, however, potential means of symptomatic treatment. Improvement among selected MID patients on a screening instrument for cognition, the Cognitive Capacity Screening Exam (CCSE), was reported with treatment of vascular risk factors such as hypertension and smoking. Similar treatments did not affect the cognition of AD patients in the same paradigm (46). In systemic conditions that decrease CBF, such as valvular heart disease and hypertension, neuropsychological test performance can improve with treatment of the causative factor(s) (30).

Alteration of the course of the illness may also be accomplished. Reduction of blood pressure is a primary goal of treatment in order to diminish the risk for recurrent stroke (43). Other risk factors, such as smoking and diabetes mellitus, can be addressed to reverse or slow the progression of vascular pathology. Any treatment approach that reduces the likelihood of stroke, such as carotid endarterectomy in moderate stenoses or the use of aspirin or ticlopidine in primary and secondary prevention, is likely to alter the course of MID, but no definitive analyses have been reported. It is important, however, to emphasize that many of the vascular changes contributing to strokes are the result of long-term pathologic processes which are not reversed with treatment. As Meyer et al. (46) found,
overreduction in blood pressure can actually worsen cognition. That risk factor modification can affect the course of MID after diagnosis has not been conclusively demonstrated, but a reduction in vascular dementia prevalence has been attributed to attention to risk factors (26).

CONCLUSIONS

Multi-infarct dementia is a syndrome which varies according to the site, size, nature, number, and timing of the lesions. Although criteria for the diagnosis of vascular dementia as a whole have been proposed, the long-term utility of such criteria has been questioned (22). No specific risk factors beyond those for cerebral ischemia have been identified, but it is likely that with control of the risk factors, progression of the illness, and perhaps current function, can be affected. The challenge lies in the early identification of those at risk for subsequent development of cognitive impairments and intervention. Prevention of vascular dementia through risk factor management may have further impact because of potential interactions between cerebral ischemia and the expression of AD.

FUTURE DIRECTIONS

Hachinski (22) has claimed that "Few areas in medicine are as ripe for action as the vascular dementias." The success of further efforts to understand vascular dementia depends on several factors. Included among them are (a) a commonly accepted definition of what constitutes vascular dementia and (b) the recognition that multiple, potentially treatable causes contribute to a final common clinical state of dementia. Early recognition of risk, and subsequent intervention, are then possible before the evolution of the dementia. The development of more useful animal models and new techniques of functional imaging to understand the pathogenesis of dementia in the face of vascular compromise will be vital in settling many of the controversies surrounding the field today. Despite those controversies, and the impediments to progress engendered by them, it is apparent that prevention and treatment of vascular dementia is an achievable goal

REFERENCES


The author: Professor Yasser Metwally

Professor Yasser Metwally, Ain Shams university, Cairo, Egypt

[www.yassermetwally.com](http://www.yassermetwally.com)  February 26, 2012
In the last 30 years, the introduction and widespread use of cerebral angiography, CT of the brain, and MRI have allowed early diagnosis of CVT, completely modifying our knowledge of this condition.

More common than previously thought, CVT is remarkable by its large spectrum of clinical presentation, its highly variable mode of onset, its numerous causes, and its...
unpredictable but usually favorable outcome. CVT does remain a diagnostic and therapeutic challenge for the clinician, however, because of its often misleading presentation and sometimes difficult treatment.

Dural sinus thrombosis accounts for approximately 1% to 2% of acute strokes in young adults. Dural sinus thrombosis is associated with local and systemic diseases. Local diseases include infectious processes, such as mastoiditis, sinusitis, osteomyelitis, and meningitis; trauma involving a dural sinus; neoplasms such as meningioma and calvarial and meningeal metastases; and subarachnoid hemorrhage. Systemic processes include pregnancy, puerperium, and oral contraceptives; collagen vascular diseases such as systemic lupus erythematosus; and hematologic disorders, such as polycythemia, leukemia/lymphoma, sickle cell anemia, and other coagulopathies. Systemic diseases that cause a hypercoagulable state are among the most common causes of dural sinus thrombosis. At least one third of cases are associated with pregnancy.

Depending on the degree and rate of the involvement of the cerebral veins, degree of recanalization, and collateral venous formation, the presentation can vary from a slow process to an acute episode. Signs and symptoms are nonspecific. Headache is the most common presenting symptom and is seen in about 75% of patients. Other symptoms include nausea and vomiting, papilledema, and decreased level of consciousness. Involvement of the cerebral veins may cause hemorrhagic infarction, hemiplegia, and seizures. Rarely, patients may present with symptoms simulating transient ischemic attacks or subarachnoid hemorrhage.

Dural sinuses are formed by dural duplications and are fixed to the osseous skull. Because of absence of valves, blood can flow in different directions. The superior sagittal sinus joins the straight and lateral sinuses posteriorly forming the confluence of the sinuses. Lateral sinuses drain blood from the cerebellum, brain stem, and posterior parts of the hemispheres. The basal vein of Rosenthal drains both cortical and deep territories. The cortical territory includes the posterior part of the frontal lobe, parahippocampal gyrus, anterior part of the cingulate gyrus, and part of the temporoooccipital cortex. The deep territory includes the thalamus, basal nuclei, and deep brain structures. The basal vein of Rosenthal and internal cerebral veins join and form the vein of Galen, which drains into the straight sinus.

**RELEVANT VENOUS ANATOMY**

Blood from the brain is drained by cerebral veins which empty into dural sinuses, themselves drained mostly by internal jugular veins.
**Dural Sinuses**

The most commonly affected by thrombosis are the superior sagittal sinus, lateral sinuses, cavernous sinuses, and straight sinus.

- **Superior Sagittal Sinus (SSS).**

  The SSS, triangular in cross-section, lies in the attached border of the falx cerebri. It starts at the foramen cecum and runs backward toward the internal occipital protuberance, where it joins with the straight sinus (SS) and lateral sinuses (LS) to form the torcular Herophili. Its anterior part is narrow or sometimes absent, replaced by two superior cerebral veins that join behind the coronal suture. This is why the anterior part of the sinus is often poorly visualized at angiography and its isolated lack of filling is not sufficient to indicate thrombosis.

The SSS receives superficial cerebral veins and drains the major part of the cortex. It also receives diploic veins, themselves connected to scalp veins by emissary veins, which explains some cases of SSS thrombosis after cutaneous infections or contusions. SSS and other sinuses play a major role in CSF circulation because they contain most of the arachnoid villi and granulations (Pacchionian bodies) in which CSF absorption takes place. The clear-cut consequence is a direct dependency of CSF pressure upon the intracranial venous pressure, accounting for the frequently raised intracranial pressure in SSS thrombosis.
o Lateral Sinuses (LS)

These extend from the torcular Herophili to jugular bulbs and consist of two portions: the transverse portion, which lies in the attached border of the tentorium, and the sigmoid portion, which runs on the inner aspect of the mastoid process and is thus susceptible to infectious thrombosis in patients with mastoiditis or otitis media. LS drains blood from the cerebellum, brain stem, and posterior part of the cerebral hemispheres. They also receive some of the diploic veins and some small veins from the middle ear, another possible source of septic thrombosis.

There are numerous LS anatomic variations that may be misinterpreted as sinus occlusion at angiography. In particular, the right LS is frequently larger than the left, which receives most of its supply from the straight sinus. An isolated lack of filling of the transverse portion of left LS is thus more suggestive of hypoplasia than thrombosis.

o Cavernous Sinuses

Cavernous sinuses consist of trabeculated cavities formed by the separation of the layers of the dura and located on each side of sella turcica, superolaterally to the sphenoid air sinuses. The oculomotor and trochlear cranial nerves, along with the ophthalmic and maxillary branches of the trigeminal nerve, course along the lateral wall of the cavernous sinuses, whereas the abducent nerve and the carotid artery with its surrounding sympathetic plexus are located within the center of the sinus itself.

Cavernous sinuses drain the blood from the orbits through the ophthalmic veins and from the anterior part of the base of the brain by the sphenoparietal sinus and the middle cerebral veins. They empty into both the superior and inferior petrosal sinuses and ultimately into the internal jugular veins. Because of their situation, cavernous sinuses are often thrombosed in relation to infections of the face or sphenoid sinusitis and, by contrast to other varieties of sinus thrombosis, infection is still the leading cause. Rarely injected on carotid angiograms, cavernous sinuses are now well visualized on CT scans and MRI.

o Straight Sinus

Formed by the union of the inferior sagittal sinus and the great vein of Galen, it has a triangular lumen and runs caudally in the junction between the falx cerebri and the tentorium cerebella to join the torcular at the internal occipital protuberance.
Figure 2. Sagittal contrast-enhanced MR venogram MIP image of the deep cerebral veins and dural sinuses in a normal patient. SSS = superior sagittal sinus; To = torcular herophili or confluence of sinuses; S = straight sinus; G = great vein of Galen; I = inferior sagittal sinus; TH = thalamostriate veins; ICV = internal cerebral veins; R = basal vein of Rosenthal; L = vein of Labbe; TS transverse sinus; SG = sigmoid sinus; SP superior petrosal sinus; IP = inferior petrosal sinus; CS = cavernous sinus; sps = sphenoparietal sinus; PP = pterygoid plexus of veins; J = internal jugular vein; sov superior ophthalmic vein; C = internal carotid artery; and B = basilar artery,
Cerebral Veins

Three groups of veins drain the blood supply from the brain:

- **Superficial Cerebral Veins (or cortical veins)**

Some of these - the frontal, parietal, and occipital superior cerebral veins - drain the cortex upward into the SSS, whereas others, mainly the middle cerebral veins, drain downward into the cavernous sinuses. These veins are linked by the great anastomotic vein of Trolard, which connects the SSS to the middle cerebral veins, which are themselves connected to the LS by the vein of Labbe. These cortical veins have thin walls, no muscle fibers, and no valves, thereby permitting both dilation and reversal of the direction of blood flow when the sinus in which they drain is occluded. They are linked by numerous anastomoses, allowing the development of a collateral circulation (angiographically visible as "cork-screw" vessels) and probably explaining the good prognosis of some CVT. Since the number and location of cortical veins are inconstant, the angiographic diagnosis of isolated cortical vein thrombosis is extremely difficult and sometimes impossible.

- **Deep Cerebral Veins**

Blood from the deep white matter of the cerebral hemispheres and from the basal ganglia is drained by internal cerebral and basal veins, which join to form the great vein of Galen that drains into the straight sinus. By contrast to the superficial veins, the deep system is constant and always visualized at angiography, so its thrombosis is easily recognized.
Posterior Fossa Veins

The veins of the posterior fossa may be divided into three groups, superior draining into the galenic system, anterior draining into petrosal sinus, and posterior draining into the torcular and neighboring straight and lateral sinuses. They are variable in course, and angiographic diagnosis of their occlusion is extremely difficult.

- Pathophysiology of cerebral sinus thrombosis and its parenchymal changes

The pathophysiology of brain parenchymal involvement in venous occlusion differs from that in arterial occlusion. Parenchymal changes may be secondary to cytotoxic edema, vasogenic edema, or intracranial hemorrhage. The primary underlying mechanism is likely to be increased venous pressure. If collateral pathways of venous drainage are insufficient, especially in the presence of cortical venous involvement, subsequent parenchymal changes may occur. If venous pressure continues to increase, with a consequent diminishment in arterial perfusion pressure, cell death may ensue. If adequate collateral pathways develop or recanalization occurs before cell death or intracranial hemorrhage, the parenchymal changes may resolve partly or completely. Vasogenic and cytotoxic edema patterns may coexist.

Table 1. Effect of increased intracranial venous pressure due to sinovenous thrombosis.

<table>
<thead>
<tr>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous thrombosis produce effects on the vein that include increase in diameter and length of the thin walled vein, kinking, folding, stenosis, and sometimes occlusion. This has been described as a hemodynamic effect caused by pressure and flow of arterial blood in a vein.</td>
</tr>
</tbody>
</table>

In the presence of venous thrombosis, a subpial or cortical vein dilates, lengthens, and may kink at the junction with the sinus. It may also balloon to the point of rupture or thromboses. The deep venous collector in the galenic malformations (the embryonic precursor to the vein of Galen) typically shows a dilatation and focal stenosis at the outlet to the straight sinus or a falcine sinus. Occasionally, this structure spontaneously thromboses.

Under normal conditions, there is negative venous pressure in the dural sinuses relative to the heart. There are no valves and pulsatile flow in the sinuses. Blood is effectively sucked through the shunt rather than pushed. An increased resistance to flow occurs when the venous pressure rises. This may occur transiently during a Valsalva maneuver or chronically in severe right heart failure or when there is a stenosis in the venous sinuses due to sinus thrombosis. When there is increased venous pressure, there is a corresponding decrease in water resorption by the arachnoid granulations, which is reflected in an increased amount of water in the ventricles and subarachnoid spaces. The third and lateral ventricles become prominent, and the cerebral sulci enlarge. If the fontanelles are open, the head enlarges (macrocrania). Normally, the posterior fossa drainage relies on the petrosal sinuses draining anteriorly to the cavernous sinus and caudally to the jugular bulb. In the absence of anterior drainage and restricted caudal
drainage, there is an increase in cerebellar water, which results in a small fourth ventricle and tonsillar herniation.

With persistent increase of the venous pressure due to venous thrombosis, there will be reduction of the venous return, stasis of blood, or even reversal of flow of blood (cerebral venous reflux) depending on the degree of venous pressure rise. Stasis of blood in the venous sinuses predisposes to further thrombosis. Cerebral venous reflux predisposes to dilatation of superficial, deep venous system, transcerebral vein, white matter congestive encephalopathy with edema, petechial haemorrhages and mass effect. Increase of intravenous pressure often results in venous wall remodelling with increase in diameter and length of the thin walled vein, kinking, folding, stenosis, and sometimes occlusion of thrombosis.

Venous infarction or ischemic cerebral changes can occur due to increased venous pressure -secondary to venous thrombosis, the mechanism for venous infarction is obstruction of venous drainage with increasing venous pressure in the affected region of the brain. The venous congestion results in significant extravasation of fluid into the brain, producing focal cerebral edema and hemorrhage. The edema may be transient, if venous flow is re-established, or be associated with permanent tissue infarction if the increased venous blood pressure eventually exceeds the arterial blood pressure. In the latter situation, there is insufficient delivery of arterial blood and regional ischemic infarction. MR imaging studies utilizing diffusion-weighted imaging (DWI) have demonstrated cytotoxic edema early in acute venous thrombosis, preceding the onset of vasogenic edema. These findings support the presence of primary neuronal injury early in venous infarction.

Under normal conditions, there is negative venous pressure in the dural sinuses relative to the heart. There are no valves and pulsatile flow in the sinuses. Blood is effectively sucked through the shunt rather than pushed. An increased resistance to flow occurs when the venous pressure rises. This may occur transiently during a Valsalva maneuver or chronically in severe right heart failure or when there is a stenosis in the venous sinuses due to sinus thrombosis. Venous hypertension probably passes into three stages depending upon the degree of venous hypertension and the chronicity of the condition.
Table 2. Stages of cerebral venous hypertension

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Absence of any parenchymal changes. When there is increased venous pressure, there is a corresponding decrease in water resorption by the arachnoid granulations, which is reflected in an increased amount of water in the ventricles and subarachnoid spaces. The third and lateral ventricles become prominent, and the cerebral sulci enlarge. If the fontanelles are open, the head enlarges (macrocrania). Normally, the posterior fossa drainage relies on the petrosal sinuses draining anteriorly to the cavernous sinus and caudally to the jugular bulb. In the absence of anterior drainage and restricted caudal drainage, there is an increase in cerebellar water, which results in a small fourth ventricle and tonsillar herniation. At this stage the thrombosed sinus will show the characteristic MRI signal changes but without any parenchymal changes.</td>
</tr>
<tr>
<td>II</td>
<td>Early cerebral congestive encephalopathy with reversible parenchymal changes. With persistent increase of the venous pressure due to venous thrombosis, there will be reduction of the venous return, stasis of blood, or even reversal of flow of blood (cerebral venous reflux) depending on the degree of venous pressure rise. Stasis of blood in the venous sinuses predisposes to further thrombosis. Cerebral venous reflux predisposes to dilatation of superficial, deep venous system, transcerebral vein, white matter congestive encephalopathy with edema, petechial haemorrhages and mass effect. Increase of intravenous pressure often results in venous wall remodelling with increase in diameter and length of the thin walled vein, kinking, folding, stenosis, and sometimes occlusion of thrombosis. Parenchymal changes in this stage are due to reversible edema edema and petechial hemorrhage once venous flow is restored.</td>
</tr>
<tr>
<td>III</td>
<td>Late cerebral congestive encephalopathy with irreversible parenchymal changes. Venous infarction or ischemic cerebral changes can occur due to increased venous pressure -secondary to venous thrombosis, the mechanism for venous infarction is obstruction of venous drainage with increasing venous pressure in the affected region of the brain. The venous congestion results in significant extravasation of fluid into the brain, producing focal cerebral edema and hemorrhage. The edema may be transient, if venous flow is re-established, or be associated with permanent tissue infarction if the increased venous blood pressure eventually exceeds the arterial blood pressure. In the latter situation, there is insufficient delivery of arterial blood and regional ischemic infarction. MR imaging studies utilizing diffusion-weighted imaging (DWI) have demonstrated cytotoxic edema early in acute venous thrombosis, preceding the onset of vasogenic edema. These findings support the presence of primary neuronal injury early in venous infarction.</td>
</tr>
</tbody>
</table>

Acute dural sinus thrombosis leads to distinct stages of parenchymal changes, the severity of which depends on the degree of venous congestion, which, in turn, is closely related to intradural sinus pressure. As intradural sinus pressure increases, progression from mild...
Parenchymal change to severe cerebral edema and/or hematoma may occur if thrombolysis is delayed.

In the analysis of 29 patients with dural sinus thrombosis (by MRI, and dural sinus pressure measurement using a Tracker 18 end-hole catheter proximal to the thrombus and connected to a pressure transducer at ear level with the waveform displayed on either an Alpha 9 pressure monitor), Fong, et al. [30] could identify five stages of brain parenchymal changes secondary of sinus thrombosis, each stage relates to the dural intrasinus pressure. See table (3)

Table 3. Parenchymal changes, and intrasinus pressure in dural sinus thrombosis [30]

<table>
<thead>
<tr>
<th>Stage</th>
<th>Parenchymal Changes</th>
<th>Symptoms</th>
<th>One patient only</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No parenchymal change</td>
<td>Severe headache, papilledema, weakness, changed mentation, drowsiness, right hemiparesis (one patient only)</td>
<td>Taken: 4 mm Hg; 17 mm</td>
</tr>
<tr>
<td>II</td>
<td>Brain swelling, sulcal effacement and mass effect, no signal change</td>
<td>Increased headache, double vision, seizure, decreased mentation, extreme drowsiness, difficulty rousing, right lower extremity weakness (one patient)</td>
<td>Taken: 2mm Hg</td>
</tr>
<tr>
<td>III</td>
<td>Increased intensity of signal change as mild to moderate edema</td>
<td>Inability to rouse, obtundation, hemiparesis, seizure</td>
<td>Taken: 3mm Hg</td>
</tr>
<tr>
<td>IV</td>
<td>Severe edema, with or without hemorrhage</td>
<td>Hemiparesis, seizure, loss of consciousness, coma</td>
<td>Taken: 4mm Hg</td>
</tr>
<tr>
<td>V</td>
<td>Massive edema and/or hemorrhage</td>
<td>Coma, response to deep pain only</td>
<td>No measurement</td>
</tr>
</tbody>
</table>

Acute dural sinus and cerebral venous thrombosis may lead to various stages of parenchymal changes of venous infarction, with the degree of severity depending on the degree of venous congestion and elevated dural sinus pressure. The prognosis of venous thrombosis depends to a significant extent on the use of thrombolytics. Severe neurologic symptoms, including coma, may be reversible if treatment with thrombolytics is started before massive cerebral edema or hemorrhage has developed. Stage I may be treated with anticoagulants alone; however, if the patient deteriorates clinically, prompt thrombolysis is probably needed. All other stages should be treated with thrombolysis. A progression from mild brain swelling to severe cerebral edema and/or hemorrhage from increasing dural sinus pressure may occur if treatment with thrombolysis is delayed. [30]
## Table 4. Biochemical stages of sinus thromboses

<table>
<thead>
<tr>
<th>STAGE</th>
<th>MRI PICTURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>The acute deoxyhemoglobin stage of blood products (days 1 through 5)</td>
<td>In the acute stage of thrombus formation (0–5 days), the signal is predominantly isointense on T1-weighted images and hypointense on T2-weighted images because of deoxyhemoglobin in red blood cells trapped in the thrombus. A venous thrombus in the acute stage may have a signal intensity that mimics a normal flow state, and such a finding may lead to diagnostic error. The signal may be very hypointense on T2-weighted images and may be mistakenly thought to indicate a flow void. According to some estimates, in 10%–30% of cases of sinus thrombosis, the thrombus at initial presentation or imaging examination is in the acute stage of formation. Contrast-enhanced MR venography or CT venography is usually necessary to achieve a definitive diagnosis at this stage.</td>
</tr>
<tr>
<td>The subacute extracellular methemoglobin stage of blood products (from day 5 through day 15)</td>
<td>In the subacute stage of thrombus development (6–15 days), the signal is predominantly hyperintense on both T1-weighted images and T2-weighted images because of methemoglobin in the thrombus. Subacute-stage thrombus has been found in 55% of patients at clinical presentation with cerebral venous thrombosis. This stage of formation is the easiest stage at which to detect a thrombus on MR images, as the signal intensity of the sinus is most different from that in normal flow states. The finding of increased signal intensity on both T1-weighted images and T2-weighted images is almost always abnormal.</td>
</tr>
<tr>
<td>Chronic dural sinus thrombosis</td>
<td>The thrombus becomes hypointense and heterogeneous because of partial resolution and recanalization and might enhance after gadolinium administration. Enhancement within the occluded dural sinus is due to organization of the thrombus. Chronic thrombosis with incomplete recanalization of the sinus may present a diagnostic challenge at MR imaging. As many as 15% of patients in whom sinus thrombosis is diagnosed at MR imaging may have a chronic (&gt;15-day-old) thrombus. Compared with the MR signal in normal brain parenchyma, the signal in a chronic thrombus is typically isointense or hyperintense on T2-weighted images and isointense on T1-weighted images; however, significant variability in thrombus signal intensity exists. The signal intensity may be similar to that of very slowly moving oxygenated blood. Sinus enhancement in sinus thrombosis is presumably secondary to an organized thrombus with intrinsic vascularization as well as to slow flow in dural and intrathrombus collateral channels.</td>
</tr>
</tbody>
</table>
Parenchymal changes secondary to congestive encephalopathy are shown by MRI as subcortical white matter precontrast T1 hypointensity, with patchy, irregular and linear enhancement and T2 hyperintensity mixed with linear and patchy hypointensity and signal void structures. Changes are due to edema, petechial hemorrhages and dilated veins. Parenchymal changes commonly show positive mass effect and are usually focal rather than diffuse. Bilateral parenchymal changes are not uncommon. Although parenchymal changes may occur in areas of the brain that are directly drained by the occluded venous sinus, in some patients the parenchymal changes may not closely correlate with the location of venous occlusion.

Parenchymal swelling without abnormalities in attenuation or signal intensity on images may occur in as many as 42% of patients with cerebral venous thrombosis. Sulcal effacement, diminished cistern visibility, and a reduction in ventricular size may occur. Patients with brain swelling and without parenchymal signal intensity changes tend to have intrasinus pressures in the intermediate range (20–25 mm Hg); however, intrasinus pressures also may be markedly elevated. Such patients typically have more prominent clinical symptoms than would be expected on the basis of imaging findings.

In view of the variable nature of the parenchymal abnormalities that may occur in cerebral venous thrombosis, the use of the term venous infarct in reference to these lesions should be discouraged because that term implies irreversibility. In contrast with arterial ischemic states, many parenchymal abnormalities secondary to venous occlusion are reversible. It is much better to refer to these parenchymal changes secondary to cerebral sinus thrombosis as cerebral venous encephalopathy. Persistence of parenchymal MRI signal changes over a long time might warrant the usage of the terminology venous infarction.

- **Parenchymal hemorrhage in cerebral sinus thrombosis**

Parenchymal hemorrhage can be seen in one-third of cases of cerebral venous thrombosis. Flame-shaped irregular zones of lobar hemorrhage in the parasagittal frontal and parietal lobes are typical findings in patients with superior sagittal sinus thrombosis and should prompt additional imaging evaluations (eg, with MR venography or CT venography). Hemorrhage in the temporal or occipital lobes is more typical of transverse sinus occlusion. Hemorrhage in cerebral venous thrombosis is typically cortical with subcortical extension. Smaller zones of isolated subcortical hemorrhage also may be seen and may be accompanied by minimal edema. MR imaging with GRE sequences is sensitive in the depiction of these zones of parenchymal hemorrhage.

The mechanism of hemorrhage in cerebral venous thrombosis is multifactorial. Hemorrhage may be precipitated by continued arterial perfusion in areas of cell death, as can be seen at reperfusion in arterial ischemia. Elevation of venous pressure beyond the limit of the venous wall also is likely operative. Hemorrhage was noted in patients with intrasinus pressures higher than 42 mm Hg but not in those with lower pressures.
• **Contrast Enhancement**

Parenchymal enhancement in 1%–29% of cases of cerebral venous thrombosis has been reported. The enhancement is typically gyral in location and may extend into the white matter. Parenchymal enhancement, which indicates disruption of the blood-brain barrier, may be seen in areas of cytotoxic or vasogenic edema and in the presence of either irreversible or reversible brain abnormalities. Increased tentorial enhancement (likely related to dural venous collaterals), adjacent leptomeningeal enhancement, and prominent cortical venous enhancement (secondary to venous congestion) also may be visible after the administration of contrast material.

![Axial MR image series with a color overlay represents the major superficial cortical venous drainage territories. Most of the superior cerebrum (green) is drained primarily into the superior sagittal sinus, which also receives drainage from the parasagittal cortical regions at lower levels. The sylvian veins drain blood from the peri-insular region (yellow) into the basal dural sinuses. The transverse sinuses receive blood from the temporal, parietal, and occipital lobes (blue). The Labbé vein, if dominant, may drain much of this territory. Parenchymal abnormalities such as hemorrhage or edema in this territory may be indicative of thrombosis of the transverse sinus or Labbé vein.](image)
Figure 5. Axial MR image with color overlay shows the drainage territory of the deep cerebral veins (internal cerebral vein, vein of Galen) (pink), in which parenchymal abnormalities due to deep venous occlusion typically are found. The deep white matter (medullary) venous drainage territory (blue) also is shown.

PATHOLOGY

Pathologic findings have been extensively described in the past. They vary with the site of thrombosis and the interval between the onset of symptoms and death.

The thrombus itself is like other venous thrombi elsewhere in the body. When it is fresh, it is a red thrombus rich in red blood cells and fibrin and poor in platelets; when it is old, it is replaced by fibrous tissue sometimes showing recanalization. Its formation is due to the usual pathogenetic factors: venous stasis, increased clotting tendency, changes in the vessel wall, and, less frequently, embolization. Its location and extension are variable. In autopsy series, extensive thrombosis of SSS and tributary veins is the most frequent finding, but this pattern of involvement no longer reflects the real distribution of CVT.
Figure 6. Bilateral hemorrhagic venous infarction (A) due to superior sagittal thromboses (B)

The consequences of CVT on the brain are again highly variable. The classic picture is that of SSS thrombosis with extensive bilateral hemorrhagic infarcts affecting the cortex and adjacent white matter. CT scan and MRI studies have now convincingly shown, however, that sinus thrombosis can induce varying degrees of edema without infarction and can even have no detectable effect on the brain.

Figure 7. Superior sagittal sinus thromboses (A), with dilated thrombosed cortical veins radiating to the thrombosed sinus and forming what is termed radiologically the "cord sign".
INCIDENCE

The true incidence of CVT is totally unknown in the absence of specific epidemiologic studies. In most autopsy series, the incidence was found to be extremely low. It has been suggested that the incidence of CVT is higher in females and in the aged, reflecting the overall greater incidence of thromboembolic diseases in these categories. The age distribution is uniform in men, whereas in women it frequently occurred between 20 and 35. This probably reflects the frequency of specific causes such as pregnancy and oral contraceptive use in young women.

ETIOLOGY

Numerous conditions can cause or predispose to CVT. They include all surgical, gyneco-obstetric, and medical causes of deep vein thrombosis as well as a number of local or regional causes, either infective or noninfective, such as head trauma, brain tumors, and arterial infarcts. Although infection still constituted the major identifiable cause, the incidence of septic CVT has greatly diminished in developed countries since the introduction of antibiotics. Cavernous sinus thrombosis remains the most common form of septic thrombosis, usually following an infection of the middle third of the face due to Staphylococcus aureus. Other sites of infection include sphenoid or ethmoid sinusitis, dental abscess, and, less often, otitis media. In chronic forms, gram-negative rods and fungi such as Aspergillus species are more commonly isolated. Among general causes, parasitic infections such as trichinosis and more recently HIV and CMV infections have been added to the long list of infective conditions possibly leading to CVT.

In young women, CVT occurs more frequently during puerperium than pregnancy and remains very common in developing countries, whereas in developed countries the role of oral contraceptives is more important.

Among the numerous noninfective medical causes of CVT, malignancies, and inflammatory diseases such as Behcet's disease and connective tissue diseases are the most frequent. Although rare, hereditary antithrombin III, protein C, and protein deficiencies should be systematically looked for in the absence of obvious cause because they imply a family study and a long-term treatment.

In neonates and children, the etiology of CVT is characterized by the frequency of regional infections (otitis, mastoiditis), neonatal asphyxia, severe dehydration, and congenital heart disease.

Despite the continuous description of new causes, the proportion of cases of unknown etiology constitute about one third of cerebral venous thrombosis.
TOPOGRAPHIC DIAGNOSIS

Thrombosis most frequently affects (in order of decreasing frequency) SSS, LS, and cavernous sinus. In most cases, thrombosis affects several sinuses or sinuses and cerebral veins. Thrombosis of the galenic system is rare.

The frequent association of sinus and cerebral vein thrombosis explains the lack of well-defined topographic clinical syndromes, similar to those described in arterial occlusions. Thus, SSS thrombosis can present with any of the above described patterns; this also applies to LS thrombosis, in which isolated intracranial hypertension is probably even more frequent and, among focal signs, dysphasia is not unusual. Thrombosis of the petrosal sinuses was described in the old literature and was characterized mainly by a fifth nerve palsy for the superior sinus and by a sixth nerve palsy for the inferior one.

As already stressed, angiographic diagnosis of isolated cortical vein thrombosis is extremely difficult, but there are old reports of anatomic or surgical cases in patients presenting with an acute or rapid onset of focal deficits, seizures, or both. The classic picture of deep cerebral venous thrombosis is that of an acute coma with decerebration or extrapyramidal hypertonia leading to death in a few days or resolving, but with heavy sequelae such as akinetic mutism, dementia, bilateral athetoid movements, vertical gaze palsy, and dystonia. Recent reports have illustrated benign forms presenting mainly with confusion. The few reported cases of cerebellar vein thrombosis are mainly anatomic but we reported a patient presenting with a 3-month history of cranial nerve palsies, cerebellar incoordination, and papilledema simulating a posterior fossa tumor.

MR IMAGING OF SINUS THROMBOSIS

<table>
<thead>
<tr>
<th>Empty delta sign</th>
<th>21%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrast enhancement of falx or tentorium</td>
<td>19%</td>
</tr>
<tr>
<td>Small ventricles</td>
<td>52%</td>
</tr>
<tr>
<td>Enlarged ventricles</td>
<td>3%</td>
</tr>
<tr>
<td>Spontaneous hyperintensity</td>
<td>20%</td>
</tr>
<tr>
<td>Hypointensity</td>
<td>33%</td>
</tr>
<tr>
<td>Gyral enhancement</td>
<td>25%</td>
</tr>
</tbody>
</table>

On contrast-enhanced computed tomography (CT) and MR imaging dural sinus thrombosis typically appears as a filling defect in the dural sinus, also known as empty delta sign. The empty delta sign is due to enhancement of the surrounding falx with the hypodense central clot. A similar findings can be observed in MR imaging.

The empty delta sign has high specificity but low sensitivity. It is seen in only 30% of cases of sagittal sinus thrombosis. Hyperdense cortical veins (cord sign) may also be present. CT and MR imaging may also detect causes such as infection, trauma, or neoplasm. Imaging studies can also be helpful in the detection of complications such as diffuse edema or venous infarctions, which are often hemorrhagic. On MR imaging, dural sinus thrombosis is most commonly manifested as lack of the normal flow void within the dural sinuses. Affected dural sinuses demonstrate abnormal intraluminal signal, which varies depending
on the stage of the thrombus. In the acute stage (days 1 through 5), the thrombus is isointense to the brain on T1-weighted images and strongly hypointense on T2-weighted images because of the deoxyhemoglobin stage of blood products. Because of the low signal of acute thrombus on T2-weighted images, acquisition of only T2-weighted images may give a false impression of normal flow void.

**Figure 8.** Coronal contrast-enhanced T1-weighted images show isointense thrombus (arrow) within the superior sagittal sinus with increased enhancement of the superior sagittal sinus leaves indicating increased vascularization without evidence of recanalization. There is also enhancement of the left transverse sinus reflecting partial thrombosis. There is peripheral enhancement of the right parietal infarct (open arrows). The dura, falx cerebri, and tentorium cerebella show irregular enhancement.
Figure 9. MRI T1 postcontrast study showing widespread enhancement of the dural sinuses and cortical veins. Intra-sinuses hypointense filling defects are due to nonenhancement of the thrombus. Signal changes in the upper brain stem is probably due to ischemia.
In the subacute stage (from day 5 through day 15), the thrombus is hyperintense on both T1-weighted and T2-weighted images because of the extracellular methemoglobin stage of blood products. Signal changes evolve from the periphery to the central portion of the thrombus. By the third week, signal changes of the thrombus are different from an intracranial bleed. The thrombus becomes hypointense and heterogeneous because of partial resolution and recanalization.

Figure 10. A, Sagittal T1-weighted images show increased signal intensity in the superior sagittal sinus (arrowheads), anterior portion of the straight sinus (small arrow), and vein of Galen (big arrow), consistent with subacute thrombosis, B MRI T1 precontrast and , C, MRI T2 image showing right parasagittal subcortical hemorrhagic infarct in the parietal lobe. The superior sagittal sinus shows isointense signal intensity consistent with thrombus in methemoglobin stage a case of dural sinus thrombosis with subcortical hemorrhagic infarct of the right parietal region

Infarctions resulting from thrombosis of the internal cerebral vein or straight sinus are usually deep within the brain, such as the thalami. Dural sinus thrombosis may be associated with venous infarctions, which are frequently hemorrhagic. Venous infarctions characteristically have a subcortical location and do not follow a major arterial vascular territory. Infarctions resulting from thrombosis of the internal cerebral vein or straight sinus are usually deep within the brain, such as the thalami. Dilated collateral cortical and medullary veins may be visible as prominent signal voids. On contrast-enhanced MR imaging, the empty delta sign representing the intraluminal clot may be seen. With organization and recanalization of the thrombus, enhancement of the thrombus may be seen. The tentorium and falx may also show enhancement resulting from vascular congestion in the collateral venous channels. With obstruction of the venous system, cerebral edema and infarction may develop. It can be manifested as increased signal intensity on T2-weighted images. It may be associated with hemorrhage, which is most commonly seen in the parietal and parieto-occipital areas. The underlying venous stasis can lead to abnormal enhancement of the cortical or deep venous structures.
Flow in the dural sinuses may be depicted with MR venography using different techniques, such as time-of-flight, phase-contrast, or gradient-echo imaging sensitive to flow. Intraluminal hyperintensity seen with subacute thrombus cannot be distinguished from
flow hyperintensity on time-of-flight images; therefore this technique should be used cautiously when there is intraluminal increased signal intensity on T1-weighted images. To avoid saturation of the venous structures, contrast-enhanced three-dimensional time-of-flight MR angiography may improve the visibility of the venous structures.

**Table 5. Biochemical stages of sinus thromboses**

<table>
<thead>
<tr>
<th>STAGE</th>
<th>MRI PICTURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>The acute deoxyhemoglobin stage of blood products (days 1 through 5)</td>
<td>The thrombus is isointense to the brain on T1-weighted images and strongly hypointense on T2-weighted images because of the deoxyhemoglobin stage of blood products. Because of the low signal of acute thrombus on T2-weighted images, acquisition of only T2-weighted images may give a false impression of normal flow void.</td>
</tr>
<tr>
<td>The subacute extracellular methemoglobin stage of blood products (from day 5 through day 15)</td>
<td>The thrombus is hyperintense on both T1-weighted and T2-weighted images because of the extracellular methemoglobin stage of blood products. Signal changes evolve from the periphery to the central portion of the thrombus. By the third week, signal changes of the thrombus are different from an intracranial bleed. The thrombus becomes hypointense and heterogeneous because of partial resolution and recanalization.</td>
</tr>
<tr>
<td>Chronic dural sinus thrombosis</td>
<td>The thrombus becomes hypointense and heterogeneous because of partial resolution and recanalization and might enhance after gadolinium administration. Enhancement within the occluded dural sinus is due to organization of the thrombus.</td>
</tr>
</tbody>
</table>

Figure 12. MRI FLAIR study (A) showing bilateral deep cerebral, paraventricular signal changes representing subacute venous infarctions due to thrombosis of the deep venous systems. B, MRI T1 postcontrast showing the empty delta sign.
There are a number of pitfalls in the diagnosis of dural sinus thrombosis that should be considered. Flow-related enhancement occurs when unsaturated protons enter the imaging plane and produce increased signal intensity relative to the more saturated protons in the adjacent soft tissues. It is identified on T1-weighted images within dural venous structures oriented perpendicular to the scanning plane. It is more commonly seen in the sigmoid sinus and jugular bulb. The same findings may be seen in the cortical veins near the superior sagittal sinus on sagittal images. Changing of slice orientation with constant sequence parameters resolves the flow artifact. With normal flow, the signal intensity within the dural sinus changes. Extremely slow flow can also produce an intraluminal signal.

Figure 13. MRI T1 postcontrast study showing dural sinus, cortical venous dilations and enhancement due to widespread dural sinus & cerebral venous thrombosis. The enhanced cortical veins are seen forming the hyperdense cord signs which are seen radiating to the dilated and thrombosed dural sinuses. Also notice parenchymal subcortical hypointensities and patchy, irregular enhancement which could be due to edema, infarction or ischemia.
Increasing TR and TE diminishes this artifact. The anterior portion of the superior sagittal sinus may be hypoplastic or completely absent. The transverse sinuses are typically asymmetric, with the right usually larger than the left. One of the transverse sinuses may be completely absent. Hypoplasia or absence of a dural venous structure may result in a false positive result.

Figure 14. MRI T1 postcontrast study showing enhancement and dilation of the thrombosed superior sagittal sinus with central hypointense filling defects which could be due to the intraluminal thrombi. Dilated enhanced cortical veins are seen pouring in the thrombosed sinus, subcortical parenchymal hypointensity could be due to edema or infarction

In patients with chronic dural sinus thrombosis, the thrombus enhances after gadolinium administration. Enhancement within the occluded dural sinus is due to organization of the thrombus. The thrombus is vascularized as a result of invasion by fibroblasts and capillaries. This vascularization could lead to false negative results in patients with chronic dural sinus thrombosis using contrast-enhanced MR and time-of-flight MR Angiography techniques. Phase-contrast (with or without contrast) and time-of-flight (without contrast) MR angiography are preferred methods for evaluation of patients with dural sinus thrombosis.
Figure 15. MRI T2 images (A,B) and FLAIR (c) showing diffuse left hemispherical cortical/subcortical hyperintensities and mass effect due to widespread dural sinuses & cortical veins thromboses. Signal changes are due to edema, ischemia and infraction. Most of the parenchymal signal changes are due to edema in the acute stage of sinus thromboses.

SUMMARY

<table>
<thead>
<tr>
<th>Radiological sign</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empty delta sign</td>
<td>Thrombosis typically appears as a filling defect in the dural sinus, also known as empty delta sign. The empty delta sign is due to enhancement of the surrounding falx with the hypodense central clot left unenhanced.</td>
</tr>
<tr>
<td>Hyperintense (precontrast MRI T1) cortical veins (cord sign)</td>
<td>Dilated collateral cortical and medullary veins may be visible as prominent signal voids when not thrombosed. However when these veins are thrombosed they follow the same time-sensitive signal changes of the thrombosed dural sinuses. In the subacute stage of extracellular methemoglobin these veins are dilated and hyperintense on noncontrast MRI T1 studies. Enhancement of the cortical veins may also form the cord sign.</td>
</tr>
<tr>
<td>Edema</td>
<td>With obstruction of the venous system, cerebral edema may develop. It can be manifested as increased signal intensity on T2-weighted images and can result in herniations.</td>
</tr>
<tr>
<td>Venous infarctions</td>
<td>Hemorrhagic venous infarctions characteristically have a subcortical location and do not follow a major arterial vascular territory. Infarctions resulting from thrombosis of the internal cerebral vein or straight sinus are usually deep within the brain, such as the thalami, the basal ganglia or the paraventricular regions.</td>
</tr>
<tr>
<td>Affected dural sinuses</td>
<td>1. In the acute stage (days 1 through 5), the thrombus is</td>
</tr>
</tbody>
</table>
demonstrate abnormal intraluminal signal, which varies depending on the stage of the thrombus.

<table>
<thead>
<tr>
<th>Dural enhancement</th>
<th>The tentorium and falx may show enhancement resulting from vascular congestion in the collateral venous channels.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous stasis</td>
<td>The underlying venous stasis can lead to abnormal enhancement of the cortical or deep venous structures. It can also result in edema, ischemia of cerebral infarctions.</td>
</tr>
<tr>
<td>Thrombus enhancement</td>
<td>Enhancement within the occluded dural sinus is due to organization of the thrombus. The thrombus is vascularized as a result of invasion by fibroblasts and capillaries.</td>
</tr>
<tr>
<td>Parenchymal enhancement</td>
<td>Could be due to cerebral ischemic changes, or frank cerebral venous infarction (it occurs due to vascular endothelial damage)</td>
</tr>
<tr>
<td>Parenchymal hyperintensities, precontrast hypointensities</td>
<td>T2 Could be due to cerebral edema, ischemia or cerebral venous infarctions. Parenchymal signal changes in the acute stage of sinus thromboses (especially when associated with mass effect) are mainly due to cerebral edema and might completely disappear later on.</td>
</tr>
</tbody>
</table>

**MEDICATION**

Heparin should be considered seriously in the management of CVT. Conversion to warfarin as maintenance therapy is then suggested. Subcutaneous low-molecular-weight heparin (Lovenox) also has been used in patients with venous sinus thrombosis.

Thrombolytic therapy may be useful, but all studies so far describe its use only with local instillation by microcatheter or direct instillation at the time of surgical thrombectomy.

**Drug Category: Anticoagulants** - These medications are used to prevent propagation of the clot to more extensive areas of the cerebral venous system. Studies indicate a tendency toward better outcome in patients treated with anticoagulant therapy than in those who are not treated with anticoagulants. In Einhaupl's study, even patients with cerebral hemorrhage appeared to benefit from anticoagulation.
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Heparin (Hep-Lock)- Increases the action of antithrombin III, leading to inactivation of coagulation enzymes thrombin, factor Xa, and factor IXa. Thrombin is the most sensitive to inactivation by heparin. Because heparin is not absorbed from the GI tract, it must be given parenterally. When given IV, effect is immediate. Metabolism of heparin is complex; rapid zero-order metabolism is followed by slower first-order renal clearance. Zero-order process is saturable, leading to an increase in half-life from 30-150 min as dose increased. Weight-based protocol now often used for dosing. When choosing this therapy, risks of its contraindications must be weighed against potential benefits.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Dose</td>
<td>Loading dose: 80 U/kg IV bolus followed by infusion Initial infusion: 18 U/kg/h IV; aPTT checked in 6 h and q6h after any dosage change, as well as qam; adjust dose according to following parameters aPTT = &lt;1.2 times control: 80 U/kg bolus with increase of 4 U/kg/h aPTT = 1.2-1.5 times control: 40 U/kg bolus with increase of 2 U/kg/h aPTT = 1.5-2.3 times control: No change in infusion rate needed aPTT = 2.3-3 times control: Decrease infusion rate by 2 U/kg/h aPTT &gt;3 times control: Hold infusion for 1 h and decrease rate by 3 U/kg/h</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>Loading dose: 50 U/kg IV; increase by 15-25 U/kg/h to maintain aPTT at 1.5-2.5 times baseline</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity, aneurysm, active or recent bleeding, coagulopathy, endocarditis, hemophilia, hepatic disease, hypertension, inflammatory bowel disease, lumbar puncture/spinal anesthesia, sulfite hypersensitivity, surgery, thrombocytopenia</td>
</tr>
<tr>
<td>Interactions</td>
<td>Digoxin, nicotine, tetracycline, and antihistamines may decrease effects; NSAIDs, aspirin, dextran, dipyridamole, and hydroxychloroquine may increase toxicity</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>C - Safety for use during pregnancy has not been confirmed.</td>
</tr>
<tr>
<td>Precautions</td>
<td>Monitor platelet count for development of thrombocytopenia; severe hyperkalemia may occur with concomitant use of ACE inhibitors; increased bleeding risk occurs with many drugs, including platelet inhibitors, NSAIDs, valproic acid, Ginkgo biloba, and probenecid</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Warfarin (Coumadin)- Interferes with action of vitamin K, a cofactor essential for converting precursor proteins into factors II, VII, IX, and X. Does not affect activity of coagulation factors synthesized prior to exposure to warfarin. Depletion of these mature factors by normal metabolism must occur before therapeutic effects of newly synthesized factors can be seen, thus may take several days to become effective. Dose influenced by differences in absorption, metabolism, and hemostatic responses to given concentrations; dose must be monitored closely by following PT and INR. Higher initial doses do not appear to improve time required to achieve therapeutic levels but do increase bleeding risk.</td>
</tr>
<tr>
<td>Adult Dose</td>
<td>Initial: 5 mg PO qd; adjust dose by monitoring INR (target, 2.5)</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>Initial: 0.2 mg/kg PO up to 10 mg Maintenance: 0.1 mg/kg/d; INR must be monitored to determine maintenance dose</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity, alcoholism, aneurysm, bleeding, breastfeeding, endocarditis, pregnancy, hemophilia, lumbar puncture, thrombocytopenia, hypertension, leukemia, polycythemia vera, intracranial bleeding, vitamin C deficiency, vitamin K deficiency</td>
</tr>
<tr>
<td>Interactions</td>
<td>Monitor INR whenever a medication is added or discontinued; drugs that may decrease anticoagulant effects include griseofulvin, carbamazepine, glutethimide, estrogens, nafcillin, phenytoin, rifampin, barbiturates, cholestyramine, colestipol, vitamin K, spironolactone, oral contraceptives, and sucralfate; medications that may increase anticoagulant effects include oral antibiotics, phenylbutazone, salicylates, sulfonamides, chloral hydrate, clofibrate,</td>
</tr>
</tbody>
</table>
Diazoxide, anabolic steroids, ketoconazole, ethacrynic acid, miconazole, nalidixic acid, sulfonyleureas, allopurinol, chloramphenicol, cimetidine, disulfiram, metronidazole, phenylbutazone, phenytoin, propoxyphene, sulfonamides, gemfibrozil, acetaminophen, and sulindac; supplements such as ginger and Ginkgo biloba should be avoided; green leafy vegetables have high levels of vitamin K, which may decrease INR

<table>
<thead>
<tr>
<th>Pregnancy</th>
<th>X - Contraindicated in pregnancy</th>
</tr>
</thead>
</table>

**Precautions**

May cause uncontrolled bleeding and should not be used in conditions in which bleeding would be difficult to control, leading to a more catastrophic outcome; medications that inhibit platelet function should be avoided, including aspirin, NSAIDs, and valproic acid; patients with protein S or C deficiency may become transiently hypercoagulable (anticoagulate patient with heparin and then convert to warfarin); do not switch brands after achieving therapeutic response; caution in active tuberculosis or diabetes; patients with protein C or S deficiency are at risk of developing skin necrosis

**Drug Category: Thrombolytics** - These agents cause lysis of the clot. All studies concerning the use of these agents in CVT involve either direct instillation into the sinus at the time of surgery or the use of microcatheters to reach the venous sinus.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Alteplase (Activase)- Biosynthetic form of human tissue plasminogen activator. Tissue plasminogen activator exerts effect on fibrinolytic system to convert plasminogen to plasmin. Plasmin degrades fibrin, fibrinogen, and procoagulant factors V and VIII. Not given as IV infusion to treat CVT. Refer patient to facility with expertise to perform venous sinus catheterization.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Dose</td>
<td>1 mg/cm infused via venous sinus catheter throughout clot, then 1-2 mg/h</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>Not established</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity, aneurysm, arteriovenous malformation, bleeding, coagulopathy, endocarditis, diabetic retinopathy, mitral stenosis, recent surgery, pregnancy,</td>
</tr>
</tbody>
</table>
breastfeeding

**Interactions**

Drugs that alter platelet function (e.g., aspirin, dipyridamole, abciximab) may increase risk of bleeding prior to, during, or after alteplase therapy; may give heparin with and after alteplase infusions to reduce risk of rethrombosis; either heparin or alteplase may cause bleeding complications

**Pregnancy**

C - Safety for use during pregnancy has not been established.

**Precautions**

Monitor for bleeding, especially at arterial puncture sites, with coadministration of vitamin K antagonists; control and monitor BP frequently during and following alteplase administration (when managing acute ischemic stroke); do not use >0.9 mg/kg to manage acute ischemic stroke; doses >0.9 mg/kg may cause intracranial hemorrhage

---

**Drug Name**

Urokinase (Abbokinase)- Produced by kidney, converts plasminogen to plasmin by cleaving arginine-valine bond in plasminogen. Degradation products of fibrin and fibrinogen exert clinically significant anticoagulant effect. Erythrocyte aggregation and plasma viscosity also are reported to decrease.

Given in CVT by catheterization of venous sinus or by direct instillation at surgery during thrombectomy. Not currently available in US.

**Adult Dose**

250,000 U/h instilled directly or via venous sinus catheter; additional doses of 50,000 U; total dose 1,000,000 U over 2 h

Not currently available in the US

**Pediatric Dose**

Not established

**Contraindications**

Documented hypersensitivity, aneurysm, arteriovenous malformation, bleeding, coagulopathy, endocarditis, diabetic retinopathy, mitral stenosis, recent surgery, pregnancy, breastfeeding

**Interactions**

Effects increased with coadministration of aminocaproic acid, anticoagulants, antineoplastic
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Streptokinase (Kabikinase, Streptase)- Facilitates thrombolysis through formation of an activator complex with plasminogen. Indirectly cleaves arginine-valine bond in plasminogen, forming plasmin. Plasmin degrades fibrin, fibrinogen, and procoagulant factors V and VIII. Degradation products of fibrin and fibrinogen have significant anticoagulant effect.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>B - Usually safe but benefits must outweigh the risks.</td>
</tr>
<tr>
<td>Precautions</td>
<td>Caution in patients receiving IM administration of medications or with severe hypertension or trauma or surgery in previous 10 d; do not measure BP in lower extremities, because may dislodge DVT; monitor therapy by performing PT, aPTT, TT, or fibrinogen approximately 4 h after initiation of therapy</td>
</tr>
<tr>
<td>Adult Dose</td>
<td>Instilled directly or via venous sinus catheter</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>Only anecdotal reports describe use in children, and that in arterial occlusion; doses used were as follows Loading dose: 1000-3000 IU/kg; followed by infusion of 1000-1500 IU/kg/h; in CVT, administered by direct infusion via catheter</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity, aneurysm, arteriovenous malformation, bleeding, coagulopathy, endocarditis, diabetic retinopathy, mitral stenosis, recent surgery, pregnancy, breastfeeding</td>
</tr>
<tr>
<td>Interactions</td>
<td>Effects are increased with coadministration of aminocaproic acid, anticoagulants, antineoplastic agents, antithymocyte globulin, cefamandole, cefoperazone, Ginkgo biloba, NSAIDs, platelet inhibitors, porfimer, strontium-89 chloride, sulfipyrazone, tranexamic acid, valproic acid</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>C - Safety for use during pregnancy has not been established.</td>
</tr>
<tr>
<td>Precautions</td>
<td>Caution in severe hypertension, IM administration of medications, trauma or surgery in previous 10 d; do not measure BP in lower extremities, because may dislodge DVT; monitor therapy by performing PT, aPTT, TT, or fibrinogen approximately 4 h after initiation of therapy</td>
</tr>
</tbody>
</table>
d; measure hematocrit, platelet count, aPTT, TT, PT, or fibrinogen levels before therapy is implemented; either TT or aPTT should be <2 times the normal control value following infusion of streptokinase and before (re)instituting heparin; do not take BP in lower extremities, as possible DVT may be dislodged; PT, aPTT, TT, or fibrinogen should be monitored 4 h after initiation of therapy; in addition to bleeding complications inherent in thrombolytic agents, repeated administration of streptokinase can result in tolerance as well as hypersensitivity

References

Astrocytomas are tumors predominantly composed of astrocytes. Unless otherwise indicated, the term usually applies to diffusely infiltrating neoplasms (WHO grades II through IV). The pilocytic astrocytoma (WHO grade I), pleomorphic xanthoastrocytoma, and giant cell astrocytomas (commonly seen in tuberous sclerosis) have distinctly different biological, genetic, and phenotypic features. This distinction should be kept in mind during the discussion of astrocytomas.
### Table 1. Comparison between focal (grade 1) and diffuse (grade II,III,IV) astrocytomas

<table>
<thead>
<tr>
<th>Focal (grade I) astrocytomas ( pilocytic astrocytoma, pleomorphic xanthoastrocytoma, and giant cell astrocytomas)</th>
<th>Diffuse (grade II,III,IV) astrocytomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are benign tumours, well circumscribed</td>
<td>Are a single spectrum of malignant neoplasms</td>
</tr>
<tr>
<td>Grow by expansion of neural tissues</td>
<td>Grow by infiltration. Microscopically, tumor cells infiltrate between myelinated fibers in a nondestructive manner.</td>
</tr>
<tr>
<td>Never change its grade over time</td>
<td>Invariably change their grade of malignancy, over time, to the next higher grade</td>
</tr>
<tr>
<td>Can be completely removed surgically</td>
<td>Are never removed completely surgically</td>
</tr>
<tr>
<td>No postoperative radiotherapy or chemotherapy is required</td>
<td>Postoperative radiotherapy or chemotherapy are required</td>
</tr>
<tr>
<td>No postoperative recurrence if completely removed surgically</td>
<td>Postoperative recurrence is almost invariable</td>
</tr>
<tr>
<td>Better prognosis</td>
<td>Poor prognosis</td>
</tr>
<tr>
<td>Edema is not a feature</td>
<td>Edema is common in grade III,IV astrocytomas</td>
</tr>
<tr>
<td>Necrosis, vascular endothelial hyperplasia, and tumours hemorrhage are never seen</td>
<td>Necrosis, vascular endothelial hyperplasia, and tumours hemorrhage are very common in grade III,IV astrocytomas</td>
</tr>
<tr>
<td>Patchy, irregular or ring enhancement are not seen</td>
<td>Patchy, irregular or ring enhancement are very common in grade III,IV astrocytomas</td>
</tr>
<tr>
<td>Seen in younger age group</td>
<td>Seen in older age group</td>
</tr>
</tbody>
</table>

Of the estimated 17,000 primary brain tumors diagnosed in the United States each year, approximately 60% are gliomas. Gliomas comprise a heterogeneous group of neoplasms that differ in location within the central nervous system (CNS), age and sex distribution, growth potential, extent of invasiveness, morphological features, tendency for progression, and response to treatments.

Although there are only three major tumor types recognized, corresponding to the three types of glial cells (astrocytes, oligodendrocytes, and ependymal cells), gliomas encompass a broad spectrum of histopathologic and imaging findings. The variation in the phenotype and biological behavior of gliomas likely reflects the nature of the transformation-associated genes involved in the development of neoplasia. There have been numerous classification schemes and staging criteria proposed for glial neoplasms. The WHO classification is generally used as a reference.
Primary cerebral gliomas account for up to 45% of intracranial tumors, with peak incidence in the seventh decade of life. In children, most (70% to 80%) of gliomas are infratentorial. In the adult, GBM accounts for more than half (55%) of all gliomas. The remaining subtypes in decreasing order of frequency include astrocytoma (20.5%), ependymoma (6%), medulloblastoma (6%), oligodendroglioma (5%), and choroid plexus papilloma (2% to 3%). Histopathology may range from benign or "low-grade" tumors to the highly malignant anaplastic astrocytoma and GBM. Glial neoplasms can be heterogeneous, with anaplasia developing focally. This can limit the diagnostic accuracy of small surgical biopsies. Furthermore, there can be significant change in the degree of malignancy over time. Morbidity and mortality of these lesions can also be significantly influenced by the location of the lesion, which may limit surgical accessibility.

All gliomas, particularly the diffusely infiltrating variety, have a tendency toward progression to more malignant forms. Genetic alterations that appear to be common across low-grade to higher-grade astrocytomas include p53 mutations. Mutations in p16 and CDK4 gene amplification are present in both anaplastic astrocytomas and glioblastomas, whereas loss of heterozygosity of chromosome 10 and EGF-R gene amplification are almost exclusively found in glioblastomas.

Clinical presentation includes focal neurological signs or symptoms related to increased intracranial pressure (ICP). Signs and symptoms of increased ICP include headache (typically more severe in the morning), nausea, vomiting, and visual disturbances. In GBMs and anaplastic astrocytomas, these signs can develop rapidly and are progressive. Because many of these neoplasms tend to develop and grow in the deep white matter, they can be clinically silent until achieving relatively large sizes. Patients who present with focal neurological signs or seizures tend to have a more optimistic prognosis due to an earlier presentation.

In the absence of contraindications such as pacemakers, ferromagnetic aneurysm clips, metallic foreign bodies in the eye, or cochlear implants, contrast-enhanced MR imaging is the modality of choice for the diagnosis and follow-up of brain neoplasms. MR imaging is more sensitive than CT in the detection of gliomas, in the assessment of tumor extent, and for identification of potential complications (ie, herniation syndromes, venous thrombosis, leptomeningeal and ependymal spread). Functional MR imaging can be added to the preoperative assessment of patients for identification of critical motor and language areas. This assessment is facilitated by the use of high field strength units (1.5 T) with echoplanar imaging capabilities. In addition, intraoperative interactive navigational workstations can be used to review combined functional and anatomic information during biopsy and surgical resection of tumors.

Despite the exquisite sensitivity of MR imaging for identifying alterations in water content, it lacks specificity in the determination of histological grade. In general, the presence of contrast enhancement and hemorrhage correlate with increasing grade of tumor. However, the presence or pattern of contrast enhancement or degree of T2-prolongation cannot be used to grade these lesions. In addition, it has been well recognized that regions
of "normal-appearing brain" in patients with infiltrative or anaplastic astrocytomas and GBMs can harbor malignancy.\textsuperscript{1,15}

MR spectroscopy has long held the promise of in vivo histopathologic specificity. Preliminary work indicates that N-acetylaspartate (NAA) and gamma-amino butyric acid are decreased in brain tumors, whereas choline is elevated. Lactate levels may correlate with histologic grade, and alanine may be associated with benign tumors.\textsuperscript{16-18} NAA is found primarily in neuronal cells. Any process that either replaces normal neurons, or causes neuronal loss, can be expected to decrease the NAA level. For example, meningiomas are reported to have low NAA, low creatine, a prominent choline peak, and a mild elevation in lactate.\textsuperscript{20} The H spectrum of gliomas appears to be dependent on the grade of the tumor, with higher grade lesions having lower levels of creatine and more significant elevations of lactate and choline.\textsuperscript{19,20} Currently, MR spectroscopy may be useful in distinguishing tumor from other lesions that may mimic a neoplasm, such as encephalitis. However, the histopathologic specificity has been predominantly anecdotal, and its clinical usefulness has been limited by long imaging times and limited voxel resolutions. This may change with improvements in imaging hardware and novel imaging pulse sequences.

Common pathological characteristics of diffuse astrocytomas

- Diffuse astrocytomas are tumors predominantly composed of astrocytes. Unless otherwise indicated, the term usually applies to diffusely infiltrating neoplasms (WHO grades II through IV).
- Diffuse astrocytoma is unusual in the first decade of life and most commonly presents in older children or young adults up to the age of 40 to 45.
- All diffuse astrocytomas, particularly the diffusely infiltrating variety, have a tendency toward progression to more malignant forms. Diffuse astrocytomas have a peculiar tendency to change its grade over time into the next higher grade of malignancy and the condition is age dependant. A change in the grade of diffuse astrocytoma is more likely to occur in the older age group.
- Diffuse astrocytomas commonly start as grade II at a younger age group then gradually change its grade over time into the next higher grade until they ultimately dedifferentiate into glioblastomas (secondary glioblastoma multiforme), on the other hand, glioblastoma multiforme in older patients are usually primary-that is, they occur as glioblastoma multiforme from their inception, without progression from a lower-grade tumor.\textsuperscript{35,33,34,35,36}
- Diffuse astrocytomas appear to form a continuum of both biological and histological aggression. They vary from lesions with almost normal cytology (grade I and grade II astrocytomas) through intermediate stages (grade III, anaplastic astrocytomas) and up to the most aggressive of all human brain tumours (grade IV astrocytomas or glioblastoma multiforme).
- Diffuse astrocytoma often spreads widely through the brain but without destruction and also without interruption of normal function. Microscopically, tumor cells infiltrate between myelinated fibers in a nondestructive manner (perineuronal satellitosis). The local spread of diffuse astrocytomas (forming gliomatosis cerebri and butterfly gliomas)
does not mean that the tumour grade is grade IV (glioblastoma multiforme), local spread can occur in grade II and grade III and in the author experience gliomatoses cerebri and butterfly gliomas are much more commonly seen in grade II astrocytomas and has not been encountered in grade III (anaplastic astrocytomas) and grade IV (glioblastoma multiforme). It takes a long time for a diffuse astrocytoma to cross the corpus callosum to the opposite hemisphere to form a butterfly glioma. Patients harbouring glioblastomas have a much shorter life span for their tumours to form butterfly gliomas, however cases were reported for glioblastomas forming butterfly tumours.

- These glioma cells migrate through the normal parenchyma, collect just below the pial margin (subpial spread), surround neurons and vessels (perineuronal and perivascular satellitosis), and migrate through the white matter tracks (intrafacicular spread). This invasive behavior of the individual cells may correspond to the neoplastic cell's reacquisition of primitive migratory behavior during central nervous system development. The ultimate result of this behavior is the spread of individual tumor cells diffusely over long distances and into regions of brain essential for survival of the patient. The extreme example of this behavior is a condition referred to as gliomatoses cerebri, in which the entire brain is diffusely infiltrated by neoplastic cells with minimal or no central focal area of tumor per se. Furthermore, 25% of patients with GBM have multiple or multicentric GBMs at autopsy. Although GBMs can be visualized on MRI scans as mass lesions that enhance with contrast, the neoplastic cells extend far beyond the area of enhancement. Fig. 2 illustrates a typical result of "gross total resection" of a temporal lobe GBM followed 6 months later by recurrence at the surgical margin and elsewhere. Even with repeat surgeries for tumor recurrences, the patients die from tumor spread into vital regions of the brain.

- In practice considerable histological heterogeneity in astrocytic tumours is found (i.e., low grade areas with Rosenthal fibers and calcification can be intermixed with frankly malignant ones).

- The differences in histologic features, potential for invasiveness, and extent of progression likely reflect genetic differences acquired during astrocytoma growth.

- Grade IV astrocytomas (glioblastoma multiforme) differ from diffuse astrocytoma grade II and grade III (anaplastic astrocytomas) in the presence of gross necrosis, and microscopically in the presence of vascular endothelial hyperplasia and tumour hemorrhage.

RADIOLOGICAL PATHOLOGY OF LOW GRADE ASTROCYTOMAS (WHO GRADE II)

The name astrocytoma, without the use of any qualifiers, represents the most benign category of diffusely infiltrating tumors of astrocytic origin. These are grade II tumors in the WHO system. In most of the older classification systems, these low-grade diffuse astrocytomas are assigned to a grade of I, I-II, or II. This variability in the older grading schemes makes comparison of reports from the literature extremely difficult to interpret. These neoplasms may be composed of fibrillar, protoplasmic, or gemistocytic astrocytes. Diffuse astrocytoma is unusual in the first decade of life and most commonly presents in older children or young adults up to the age of 40 to 45. Ten percent of all
intracranial neoplasms are diffuse astrocytoma, and they represent one third of all CNS primary tumors. Most series show a slight male predilection. They are relatively uncommon in people older than age 65.

Astrocytomas account for 25% to 30% of all hemispheric gliomas with a peak incidence between 20 and 50 years of age. Low-grade astrocytomas (WHO grade II) are slow-growing tumors without significant necrosis or vascular proliferation. Most of these lesions will progress to a higher pathological grade. Fibrillary astrocytoma is the most frequent variant of astrocytoma with low to moderate cell density and consistent expression of glial fibrillary acidic protein (GFAP). Gemistocytic astrocytomas are predominantly composed of gemistocytic astrocytes, which have plump, glassy, eosinophilic cell bodies. This variant has a propensity for progression to anaplastic astrocytoma.

The brain can be extensively infiltrated before any symptoms occur. The low-grade diffuse astrocytoma often spreads widely through the brain but without destruction and also without interruption of normal function. In addition, the slow rate of growth may allow the brain to move functionality from one region into another. This process of remapping the brain, often considered as a property only seen in the immature and young brain, has been shown to occur at all ages. Because of these two features of slow growth and nondestructive invasion, the astrocytoma may occupy large volumes of brain and may extend not only from one lobe to another, but also from one hemisphere to the other, by spreading through the corpus callosum.

Grossly the brain that is infiltrated by a low-grade diffuse astrocytoma is expanded. The expanded brain is hypercellular compared with normal brain. Vascular changes and interstitial (vasogenic) edema are absent, however. There is no necrosis, and macrocysts are only rarely noted in this type of glioma. Microscopically the brain may merely seem more cellular than normal. Mitosis, necrosis, hemorrhage, vascular proliferation, endothelial change, and anaplasia are not present. If these features are visible, the pathologic grading is advanced to either grade III (anaplastic astrocytoma) or grade IV (GBM).

On gross examination, the infiltrated region of the brain is larger or bulkier than normal. For example, one cerebellar peduncle may be increased in size compared with normal or compared with the other side. They may appear on gross inspection to be circumscribed. They may be firm or gelatinous. These lesions are most frequent in the cerebral hemispheres. They may present in any part of the brain, however, including the cerebellum and brain stem. The diffuse nature of these low-grade infiltrating astrocytomas created the notion of gliomatosis cerebri as a hamartomatous or developmental process. In reality, most neuropathologists now consider that most cases of gliomatosis actually represent infiltration of brain by an extensive diffuse astrocytoma.
Low grade brain astrocytomas consist of relatively normal-appearing astrocytes, but there are just too many of them. In the past, this appearance created the impression of some type of developmental or hamartomatous change. They are not characterized by any significant vascular changes, and those that occur are limited to the capillaries. The tumors derive their nutrition from the preexisting normal vessels. Because the vessels are normal, the blood-brain barrier is intact. Mitosis, hemorrhage, vascular proliferation, endothelial changes, anaplasia and necrosis are notably absent in these neoplasms. The lesion infiltrates through the brain, usually by following the path of white matter tracts and the infiltrated brain is diffusely expanded and hypercellular. These tumors often may spread through the brain without causing destruction or functionally significant damage, so that symptoms are not an early feature.

From the pathological point of view diffuse astrocytomas (grade II) are neoplasms of widely varying potential that are unencapsulated, poorly marginated and diffusely infiltrate into the surrounding brain. These diffuse astrocytomas appear to form a...
continuum of both biological and histological aggression. They vary from lesions with almost normal cytology (grade I and grade II astrocytomas) through intermediate stages (grade III, anaplastic astrocytomas) and up to the most aggressive of all human brain tumours (grade IV astrocytomas or glioblastoma multiforme). The word diffuse astrocytoma is not synonymous with glioblastoma and is not against the pathological diagnosis of low grade glioma. A low grade glioma (grade II astrocytoma according to the WHO) has a tendency to diffusely infiltrate the nearby neural tissues, however at a much slower rate (compared with glioblastomas) and with a little tendency to induce extensive structural damage or profound functional disturbance.

**Histologic Findings:** Four histological variants of low-grade astrocytomas are recognized—protoplasmic, gemistocytic, fibrillary, and mixed.

1. Protoplasmic astrocytomas generally are cortically based, with cells containing prominent cytoplasm. Protoplasmic astrocytomas constitute approximately 28% of infiltrating astrocytomas.

![Figure 3. Grade II astrocytoma with cystic changes](image)

Figure 3. Grade II astrocytoma with cystic changes

![Figure 4. Low-grade fibrillary astrocytoma and low cellularity with minimal nuclear atypia, Fibrillar astrocytoma with microcyst formation, Gemistocytic astrocytoma. Tumor cells have eosinophilic cytoplasm with nuclei displaced to the periphery.](image)

Figure 4. Low-grade fibrillary astrocytoma and low cellularity with minimal nuclear atypia, Fibrillar astrocytoma with microcyst formation, Gemistocytic astrocytoma. Tumor cells have eosinophilic cytoplasm with nuclei displaced to the periphery.

1. Gemistocytic astrocytomas generally are found in the cerebral hemispheres in adults and are composed of large round cells with eosinophilic cytoplasm and eccentric cytoplasm. Gemistocytic astrocytomas constitute 5-10% of hemispheric gliomas.
Figure 5. Characteristic pilocytic astrocytoma, long bipolar tumor cells, and Rosenthal fibers, Anaplastic astrocytoma with high cellularity with marked nuclear atypia, Gross specimen of a low-grade astrocytoma

1. Fibrillary astrocytomas, the most frequent histological variant, resemble cells from the cerebral white matter and are composed of small, oval, well-differentiated cells. The tumors are identified by a mild increase in cellularity and fibrillary background. Markers for glial fibrillary acidic protein (GFAP) are used to identify fibrillary astrocytomas.

2. Compared to low-grade lesions, anaplastic astrocytomas show a marked tendency for regional or diffuse hypercellularity. Furthermore, anaplastic astrocytomas show increased anaplasia, demonstrated by increased nuclear complexity, the presence of mitoses, increased cytoplasmic variability, and increased endothelial cell proliferation.
Figure 6. A, Atypical nuclear changes (arrow), B, Another indication of malignancy is vascular proliferation. Endothelial proliferation of a vessel in a glioblastoma multiform is seen in the B (arrow). The hyperplastic vessels are very often simply very minute lumens embedded in a thick collar of fibroblasts and vascular smooth muscle. C, necrosis which is characteristic of grade 4 astrocytomas [glioblastomas] illustrated in C.

Figure 7. Mitosis, hemorrhage, vascular proliferation, endothelial changes, anaplasia, necrosis, hyperchromatic nuclei, pleomorphism are all characteristic of glioblastoma multiforme.
Now we will discuss the features which indicate rapid growth potential in astrocytomas, grade III-IV, respectively named by most neuropathologists as anaplastic astrocytoma and glioblastoma multiforme. The most important criterion will be the appearance of the nucleus. Atypical nuclear changes are shown in the anaplastic astrocytoma in Figure 6 A.

- There is extreme pleomorphism of these large, irregular, dark, bizarre nuclei. Often, this pleomorphism is so extreme that giant cells are seen Figure 6 A. However, these cells resemble both the other neoplastic astrocytes in this image and also non-neoplastic reactive astrocytes. The points of resemblance are the homogeneous eosinophilic cytoplasm and the formation of processes--i.e., extensions of the cytoplasm. The degree of cellularity is also important in determining the high grade of malignancy.

- Another indication of malignancy is vascular proliferation. Endothelial proliferation of a vessel in a glioblastoma multiform is seen in Figure 6B.

- The hyperplastic vessels are very often simply very minute lumens embedded in a thick collar of fibroblasts and vascular smooth muscle. The source of the proliferating vessels or their connective tissue matrix has been much debated. There has even been at least one study claiming genetic relationship between the apparent connective tissue/smooth muscle and the malignant astrocytes themselves. In addition the sarcomatous portion of the tumor known as gliosarcoma has been thought to arise from the supposed connective tissue surrounding the proliferating or "hyperplastic" vessels. However recent studies state that the apparent sarcoma is really just a phenotypic change of malignant astrocytes!!!

- One might think that vascular hyperplasia improves the nutrition of the tumor. But, in fact, the lumens are so small that this contributes, along with the increase in total vascular length, to an increase in vascular resistance and probably to decreased blood flow in the tumor. One might even speculate that this contributes to the necrosis which is characteristic of grade 4 astrocytomas [glioblastomas] illustrated IN Figure 6C.

- Note the irregular, necrotic, central area surrounded by a palisade of tumor cells. This is called pseudopallisading. Much of the necrosis [ which denotes the highest degree of malignancy (grade IV) ] is presumed to be due to the fact that the tumor is growing so rapidly that it has outstripped its blood supply. There may also be a role for apoptosis. Figure 6C

In practice considerable histological heterogeneity in astrocytic tumours is found (i.e., low grade areas with Rosenthal fibers and calcification can be intermixed with with frankly malignant ones). Biopsy specimen, either stereotaxic or open, is usually too small and might miss the tumour regions that contain the most malignant part and subsequently biopsy is useless in so far as tumours grading is concerned. Tomita et al, 1981 review of autopsy and
biopsy data gathered from multiple large series of brain gliomas demonstrated significant discrepancies between surgical and autopsy pathology.

Radiologically the tumor is usually identified by a combination of brain asymmetry, enlargement of a portion of the brain, or abnormal signal intensity on MR or abnormal attenuation on CT. The lesions typically have precontrast CT attenuation and MRI signal changes suggesting increased water content and lower than normal specific gravity (diffuse low CT scan densities with MRI T1 hypointensities and diffuse MRI T2 hyperintensities).

Figure 8. MRI T2, FLAIR, and T1 postcontrast images showing a well circumscribed lesion in the left frontal lobe, the lesion is hyperintense in T2 and FLAIR images, hypointense on T1 image with no postcontrast enhancement. The lesion is much better delineated on FLAIR image. The lesion is not surrounded by edema, with very mild mass effect (if any). Low grade astrocytomas are sometimes mistaken with old infarction.

It is tempting to consider that these changes represent edema. The question then arises: Is this vasogenic edema or cytotoxic edema? Because the blood-brain barrier is intact in these tumors, vasogenic edema is unlikely. The cells are not dead or dying, so that cytotoxic edema is also unlikely. Perhaps the edema results from the increased number of astrocite cells that spread apart the normal myelinated axons of the white matter. The presence of significant amount of normal appearing astrocytes (hyperplasia), with marked cytoplasmic hypertrophy and low nuclear to cytoplasm ratio result in total increase in the water content of the brain. These cells may merely have different physical and chemical properties than the normal tightly packed bundles of axons that traverse through the brain. 

Diffuse astrocytomas (grade II, III or grade IV astrocytomas) grow by infiltration of the nearby neural tissues (commonly in the form of remote neoplastic cells radiating from the mother tumour) and so they are poorly marginated and, practically, complete surgical resection is not possible and some neoplastic cells are almost invariably left behind after surgical resection.

Astrogliosis is commonly associated with widened fluid filled extracellular spaces (microcavitations) which definitely increase tissues water content resulting in the characteristic CT scan/MRI...
picture. Absence of significant edema coupled with the very slow growth rate of these tumours result in minimal mass effect.

Figure 9. Astrocytes have extensive vascular foots, Astrogliosis (astrocytic hyperplasia) commonly results in the formation of a mesh with enlargement of extracellular spaces and extensive fluid-filled microcavitations. This, coupled with marked cytoplasmic hypertrophy of astrocytes-that results in low nuclear to cytoplasm ratio- are responsible for the neuroimaging picture of low grade astrocytomas.

Figure 10. Diffuse astrocytoma. A, This T2-weighted MR image demonstrates a well-demarcated mass in the right temporal lobe. The expanded lobe is herniated over the edge of the tentorium and into the suprasellar and ambient cisterns. This lesion did not show any enhancement or necrosis. However, the biopsy showed a largely low-grade (WHO Grade II) diffuse astrocytoma-with foci of anaplasia. Thus, the overall lesion diagnosis was anaplastic astrocytoma (WHO Grade III) B, Gross specimen showing left hemispherical...
astrocytoma grade II. The tumour has markedly expanded the left hemisphere and distorted the normal anatomy with absence of the normal gray/white matter junction, notice absence of a definite mass

These tumors are classically described as either well-demarcated (MR) or poorly marginated (CT) regions of expanded tissue, with an altered brain composition. Typical presentation includes asymmetric thickening of a cerebral or cerebellar peduncle or the corpus callosum. The lesions are characterized by an increase in tissue water (edema) that lowers the specific gravity and CT attenuation. There is a corresponding decrease in attenuation on CT and lower signal intensity on T1-weighted MR imaging. The lesions are brighter than cerebrospinal fluid on proton-density MR imaging. These low-grade diffuse astrocytomas do not enhance on either MR with gadolinium contrast administration or on CT with iodine contrast administration. 

Figure 11. World Health Organization (WHO) Grade II infiltrating astrocytoma. Axial T2-weighted, FLAIR, and enhanced T1-weighted images. There is a high signal intensity mass in the left frontal lobe. No significant edema or enhancement is identified.
The absence of contrast enhancement is consistent with the absence of any vascular changes histologically. Only half of the lesions with these typical imaging findings actually prove to be low-grade astrocytoma. Anaplastic astrocytoma is notorious for its variable enhancement characteristics. Anaplastic astrocytoma may have faint enhancement, patchy enhancement, or no enhancement at all. Encephalitis and infarction may also present as regions of altered brain composition without enhancement. For these reasons, other diagnostic tests and clinical correlation are needed to confirm an imaging diagnosis of a low-grade diffuse astrocytoma. Tissue histology from biopsy or open resection is the only proven means of obtaining a diagnosis. MR spectroscopy has become increasingly useful in selecting patients for biopsy.

On imaging, the expansion of the infiltrated brain may be subtle or gross. Small lesions and subtle expansions may be difficult to recognize. Even large and extensive regions of expansile infiltration may be missed when the tumor is bilateral and causes symmetric involvement of the corpus callosum or both sides of the brain stem.

The prognosis in diffuse astrocytoma is variable. There is frequent transformation of diffuse astrocytomas into higher-grade lesions. Grade II lesions transform into anaplastic astrocytoma (grade III). Grade III lesions transform into GBM (grade IV). Because the lesions are infiltrating at the microscopic level, the tumor cannot be easily separated from the normal tissues. Residual tumor left behind is at risk for recurrence not only at the same grade, but also for transformation into a more aggressive lesion. In addition, in
consideration of treatment categories, sampling errors are relatively frequent when limited amounts of tissue (e.g., needle biopsy material) are used for diagnosis.

Figure 13. Pontine astrocytoma. A, This axial T1-weighted gadolinium-enhanced MR image shows an expanded pons, with abnormally decreased signal intensity. The lesion has grown ventrally to partially surround the flow-void for the basilar artery. The lesion does not enhance. B, Gross specimen of the brain stem showing diffuse infiltrating astrocytoma grade II of the brain stem. The infiltrated brain stem is larger or bulkier than normal without a definite focal mass. Notice posterior exophytosis into the 4th ventricle. The lesion has grown ventrally to partially surround the basilar artery.

As the blood brain barrier is intact in low grade brain astrocytomas (grade II astrocytomas according to the WHO), no significant enhancement or perilesional edema occur, either on MRI or CT scan. Enhancement is characteristic of the more aggressive anaplastic astrocytomas (grade III) or glioblastoma multiforme.
Table 2 Diagnostic criteria of low grade (grade II) astrocytoma

- Mild clinical disability (if any), with long history before clinical presentation
- The lesions are well defined, oval or rounded with minimal mass effect, and not surrounded by edema
- The lesions appear diffusely hypodense on CT scan, hypointense on precontrast T1 MRI images and hyperintense on T2 MRI images, with no postcontrast enhancement
- The lesions are better delineated by FLAIR imaging
- The lesions are frequently misinterpreted as old infarctions, however they can easily be differentiated from infarctions by the following criteria
  - The existence of definite, though subtle positive mass effect
  - The lesions are not in the distribution of a known blood vessel
  - The clinical picture of the patients is not consistent with cerebrovascular disorders
  - The lesions are oval or rounded in shape and purely subcortical while embolic infarctions are wedge shaped cortical and subcortical

In fact, the existence of such a lesion (hypodense of CT scan, hypointense on MRI T1 images and hyperintense on MRI T2 images with minimal mass effect and no postcontrast enhancement) in a patient presented clinically with fits (in any age and especially in adult age) should always warrant biopsy and the clinician should not jump to the diagnosis of old infarctions, encephalomalacia or similar useless terminologies. Diagnosis of low grade astrocytomas at a younger age is very important because with the passage of time diffuse low grade astrocytomas (grade II) have a peculiar tendency to change its grade into a higher grade (grade III, IV or anaplastic astrocytomas and glioblastomas). Diffuse astrocytoma is a pathological spectrum that starts at a younger age as grade II and with time it changes its grade to grade III and IV astrocytoma. Chance for survival is undoubtedly greater when the neoplasm is diagnosed when at grade II.

Genetically primary glioblastomas (those that start as glioblastomas from the very beginning) are different from secondary glioblastomas (those that start as astrocytomas grade II at a younger age and change to glioblastomas at an older age).

Genetic lesions associated with the development and malignant transformation of diffuse astrocytomas have been well described in the cytogenetic literature. To date, three distinct clinical, histologic, and genetic patterns of glioblastoma multiforme have been characterized. In younger patients, most diffuse astrocytomas are believed to begin as low-grade astrocytoma, with progression to glioblastoma multiforme through a stepwise acquisition of genetic lesions. These secondary glioblastoma multiforme often contain areas of well-differentiated residual tumor. The most frequent chromosomal abnormality identified in diffuse astrocytomas is the abnormal gain of chromosome 7 with an associated loss of one of the sex chromosomes. Additionally, allelic loss or mutation of 17p, resulting in...
critical alterations of the TP53 gene, has been targeted as an essential step in the early development of glioma. Mutant TP53, identified in at least one third of all astrocytomas, may contribute to the formation of these tumors by inhibiting programmed cell death. Glioblastoma multiforme in older patients are usually primary-that is, they occur as glioblastoma multiforme from their inception, without progression from a lower-grade tumor. In this group, the development of glioblastoma multiforme involves a parallel sequence of genetic alterations, including amplifications and deletions, that up-regulate growth factor receptors and drive cell proliferation.

RADIOLOGICAL PATHOLOGY OF ANAPLASTIC ASTROCYTOMAS (WHO GRADE III)

Anaplastic astrocytoma (WHO grade III) is a lesion of intermediate aggression, between simple astrocytoma (WHO grade II) and GBM (WHO grade IV, astrocytoma grade IV). This subtype appears to be less frequent than either GBM or simple astrocytoma. The difficulty with this diagnostic category is related to both variable pathology and variable imaging characteristics. Anaplastic astrocytoma has histologic and imaging characteristics that are along a spectrum between grade II and grade IV. Anaplastic astrocytomas (WHO grade III) demonstrate focal or diffuse areas of anaplasia with mitotic activity. They may arise from low-grade astrocytomas, but are also frequently found at initial presentation. These tumors have a rapid tendency to progress toward GBM.

Grossly, anaplastic astrocytoma is similar to astrocytoma. The brain may appear expanded but is not characterized by necrosis or hemorrhage. Histologically, as the name implies, there is considerable variation (anaplasia) in the cellular morphology. Mitoses are present but infrequent. Vascular proliferation is limited. Necrosis is not allowed as a feature of anaplastic astrocytoma in most classification schemes, including the WHO formulation.

![Figure 14. Anaplastic astrocytoma. Axial T2-weighted and enhanced T1-weighted images demonstrate a large right temporal mass with prominent enhancement and extensive surrounding infiltration. Differential diagnosis includes lymphoma.](image-url)
Figure 15. Anaplastic astrocytoma. Axial T2-weighted, FLAIR, and gradient echo images demonstrate a left frontal opercular mass with a minimal amount of edema. Appearance might suggest low-grade glioma; however, the presence of hemorrhage (white arrow) suggests higher grade.

On imaging studies, anaplastic astrocytoma tends to mimic the appearance of low-grade astrocytoma. They may present as a non-enhancing, relatively homogeneous region of abnormal signal intensity or expanded brain. In some cases, there may be patchy contrast enhancement. Because of the pathologic definition of anaplastic astrocytoma, heterogeneous ringlike enhancement should not occur. Anaplastic astrocytoma may arise out of a preexisting grade II tumor. Because these lesions are graded based on the most aggressive component, it is common for an anaplastic astrocytoma lesion to be largely grade II and only focally grade III. The natural history of many residual or recurrent anaplastic astrocytomas includes a rapid transformation into the next level of lesion, the astrocytoma grade IV, or GBM.

RADIOLOGICAL PATHOLOGY OF GLIOMATOSIS CEREBRI

Gliomatosis cerebra is an uncommon pattern of glial neoplasia. It is most common in the middle adult years but may occur at any age. Gliomatosis is defined by extensive multilobar and, often, bihemispheric neoplastic infiltration. Despite the extent of tumor, neural connections are preserved, resulting in a paucity of symptoms even at diagnosis. The diagnosis requires a combination of histologic and imaging findings. Before the modern imaging era, the diagnosis was made exclusively at autopsy. Today, survival ranges from weeks to many years postdiagnosis.
Figure 16. Gliomatosis cerebri, notice bihemispheric tumour spread with contrast enhancement.

Gross examination demonstrates diffusely expanded and distorted parenchyma without a destructive mass. White matter involvement predominates, with tumor often following anatomical pathways. Blurring of the gray-white junction and expansion are seen.

Figure 17. Gross specimen showing gliomatosis cerebri, notice bihemispheric tumour spread and distortion of normal anatomy with blurring of the gray-white junction.

Figure 18. Gliomatosis cerebri. Coronal FLAIR images show diffuse infiltration of the left temporal lobe with gray and white matter involvement (arrowhead). Note the relative lack of mass effect for the degree of infiltration. The white matter infiltration extends across the corpus callosum (white arrow) and involves bilateral deep white matter tracts (double arrow).
Figure 19. Gliomatosis cerebri in a 74-year-old woman. A, Axial T2-weighted, FLAIR, and enhanced T1-weighted images demonstrate high signal intensity in the right temporal lobe involving white matter and cortex. The acute clinical presentation suggested infarct. B, Diffusion weighted image and TRACE apparent diffusion coefficient (ADC) map demonstrate increased water diffusion in the lesion (slightly higher values on ADC map, outlined by arrowheads), excluding acute infarction. Note that encephalitis may have a similar MR appearance and diffusion characteristics.

Microscopically, tumor cells infiltrate between myelinated fibers in the nondestructive manner of low-grade gliomas. The cytologic features are usually those of a fibrillary astrocytoma, but there are case reports of gliomatosis cerebri with the features of oligodendroglioma. Areas with significant atypia, mitotic figures, and even necrosis are sometimes observed. With tumor progression, expansive tumor foci of high-grade tumor may result.
Figure 20. MRI T1 pre and post contrast A,B and T2 images C,D and FLAIR images E,F,G showing a case of gliomatosis cerebri in a 40 years old female patient. Notice the biparietal, the medial temporal lobe, orbital frontal, and brain stem involvement, the condition started by temporal lobe epilepsy followed by bilateral pyramidal manifestations and ended in unilateral third nerve involvement. The pathology is more evident in FLAIR images. Also notice the necrotic foci (D,E images) and the postcontrast enhancement (B). Clinically the condition was characterized by paucity of clinical signs and symptoms despite extensive brain involvement.

The CT characteristics of gliomatosis can be subtle, reflecting only mild hypodensity or mass effect. MR imaging typically demonstrates a large area of hemispheric T2 signal abnormality involving white and gray matter, reflecting the infiltrative nature of this lesion.
with mild mass effect. Enhancement in gliomatosis may be subtle or absent. The lesion can radiographically resemble infarct and cerebritis. Diffusion imaging can be helpful in distinguishing tumor from an acute infarct as there will be no corresponding decrease in apparent diffusion coefficient (ADC), which is diagnostic for acute infarction.

**RADIOLOGICAL PATHOLOGY OF GLIOBLASTOMA MULTIFORME (WHO GRADE IV)**

Glioblastoma multiforme is the most common and the most malignant adult supratentorial glial neoplasm. It is the most malignant of the glial tumors with a median survival of 6 months. It represents the bulk of brain gliomas and up to 20% of all intracranial neoplasms. GBM is rare in patients less than 30 years old, with most presenting between 45 and 55 years of age. There is a slight male predominance of 3:2. This tumor has a peak incidence in adults, however, and represents only 6% of primary tumors in patients 20 years old and younger. Most lesions occur in the frontal lobe (which is statistically the favored site of many neoplasms because of lobar volume considerations). These lesions characteristically cross the corpus callosum resulting in a butterfly distribution with bihemispheric involvement. Tumor can spread along the leptomeningeal and dura, the subarachnoid space, across white matter pathways, and along the ependyma. These neoplasms rarely metastasize beyond the CNS.

Glioblastoma multiforme (GBM) is composed of poorly differentiated neoplastic astrocytes, glioblastomas primarily affect adults, and they are located preferentially in the cerebral hemispheres. Much less commonly, GBMs can affect the brain stem in children and the spinal cord. These tumors may develop from lower-grade astrocytomas (World Health Organization [WHO] grade II) or anaplastic astrocytomas (WHO grade III), but, more frequently, they manifest de novo, without any evidence of a less malignant precursor lesion. The treatment of glioblastomas is palliative and includes surgery, radiotherapy, and chemotherapy.

GBM, although originally considered to be a tumor of immature precursor cells (glioblasts), is now generally recognized as a poorly differentiated neoplasm arising from transformation of previously normal adult cells. Approximately one half of GBM probably represent the end stage of a series of genetic changes occurring in astrocytes. The earliest genetic change transforms a resting, normal, adult astrocyte into an autonomously replicating cell. This early stage of dysautoregulation creates a clone of neoplastic cells that may appear histologically normal on routine hematoxylin and eosin light microscopic evaluation. These cells probably replicate slowly, and thus mitotic figures are only rarely, if ever, found. These neoplastic astrocytomas infiltrate into the surrounding normal brain by following the path of normal bands of white matter. This growth may represent the expression of a normal embryologic feature, in which precursor cells migrate from the periventricular region outward toward the cortex, by climbing along the radial glia.

As the name multiforme implies, these are variegated tumors. The hallmarks of GBM include both microscopic and gross necrosis as well as rich neovasculartiy. These lesions
may appear to be deceptively localized on gross inspection, but they are microscopically invasive. Microscopically, these tumors are extremely heterogeneous, often composed of several different cell populations. Mitoses are frequent. Necrosis is noted in its microscopic form-pseudopalisading necrosis. Endothelial proliferation and hypervascularity are common characteristics. The vessels have abnormal endothelium and often form glomeruloid balls. Two different scenarios account for the frequent finding of neoplastic cells remote from the main bulk of the tumor. First, many GBM arise within a preexisting lower-grade diffuse astrocytoma. This field of surrounding neoplastic cells continues to be at risk for transformation into the next highest grade of tumor. Second, even GBM that arise de novo are noted to send malignant cells streaming into the surrounding brain. This mode of spread is apparently facilitated by the widened extracellular spaces created through vasogenic edema.

GBM is the most aggressive and least differentiated type of glioma. The overwhelming majority of GBM are of astrocytic origin-and GBM has become synonymous with high-grade (malignant) astrocytoma. Uncommonly poorly differentiated ependymomas and oligodendrogliomas are described as glioblastoma, however. These are grade IV lesions in the WHO classification. Many of them appear to arise through a progressive transformation from a preexisting lower-grade lesion. (See earlier discussion of astrocytoma.) Thus, their appearance may be complex because the lesion may be composed of mixtures of different grades of astrocytoma, including grade III, grade II, or both.

Gliosarcoma is a variant of GBM containing a neoplastic mesenchymal (sarcomatous) component. Immunohistochemical and genetic analyses suggest a common origin from neoplastic glial cells. Gliosarcomas have a greater tendency toward dural invasion, cerebrospinal fluid (CSF) seeding, and distant metastases.

Figure 21. Glioblastoma multiforme. This coronal gross brain section shows a large mass extending from the corpus callosum into both hemispheres. There is gross bleeding from the cut surface due to the exuberant neovascularity typical of these lesions.
Pathophysiology: Glioblastomas can be classified as primary or secondary.

<table>
<thead>
<tr>
<th>Type</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary GBMs</td>
<td>Account for the vast majority of cases (60%) in adults older than 50 years. After a short clinical history, usually less than 3 months, they manifest de novo (ie, without clinical or histopathological evidence of a preexisting less malignant precursor lesion).</td>
</tr>
<tr>
<td>Secondary GBMs</td>
<td>Account for 40% of cases. Typically develop in younger patients (&lt;45 y) through malignant progression from a low-grade astrocytoma (WHO grade II) or anaplastic astrocytoma (WHO grade III). The time required for this progression varies considerably, ranging from less than 1 year to more than 10 years, the mean interval being 4-5 years. Increasing evidence indicates that primary and secondary glioblastomas constitute distinct disease entities that evolve through different genetic pathways, affect patients at different ages, and likely differ in response to therapy. Of all the astrocytic neoplasms, glioblastomas contain the greatest number of genetic changes.</td>
</tr>
</tbody>
</table>

Over the past 5 years, the concept of different genetic pathways leading to the common phenotypic endpoint (ie, GBM) has gained general acceptance. Genetically, primary and secondary glioblastomas show little overlap and constitute different disease entities. Some of the more common genetic abnormalities are described as follows:

**p53:** Mutations in p53, a tumor suppressor gene, were among the first genetic alterations identified in astrocytic brain tumors. While present in less than 10% of primary glioblastomas, more than 65% of secondary glioblastomas have p53 mutations.

**Epidermal growth factor receptor (EGFR) gene:** The EGFR gene is involved in the control of cell proliferation and is either amplified or overexpressed in more than one third of glioblastomas, sometimes in a truncated and rearranged form. EGFR amplification is much more common in primary glioblastomas. These tumors typically show a simultaneous loss of chromosome 10 but rarely a concurrent p53 mutation.

**MDM2:** Amplification or overexpression of MDM2 constitutes an alternative mechanism to escape from p53-regulated control of cell growth by binding to p53 and abolishing its activity. Overexpression of MDM2 is observed in more than 50% of primary GBMs but rarely in secondary glioblastomas.

**Platelet-derived growth factor (PDGF) gene:** The PDGF gene acts as a major mitogen for glial cells by binding to the PDGF receptor (PDGFR). Amplification or overexpression of PDGFR is typical (60%) in the pathway leading to secondary glioblastomas.

**PTEN:** PTEN (also known as MMAC and TEP1) encodes a tyrosine phosphatase located at 10q23.3. The function of PTEN as a cellular phosphatase is consistent with possible tumor
suppressor function. Phosphatases act by turning off signaling pathways dependent upon phosphorylation. When phosphatase activity is lost because of genetic mutation, signaling pathways can become activated constitutively, resulting in aberrant proliferation. PTEN mutations have been found in as many as 30% of glioblastomas.

Additional genetic alterations in primary glioblastomas include p16 deletions (30-40%), loss of heterozygosity (LOH) at 10p and 10q, and retinoblastoma gene (RB) protein alterations. Progression of secondary glioblastomas often includes LOH at chromosome 19q (50%), RB protein alterations (25%), PTEN mutations (5%), deleted-in-colorectal-carcinoma gene (DCC) loss of expression (50%), and LOH at 10q.

Figure 22. A, Glioblastoma multiforme with necrosis and haemorrhage, glioblastomas are often multicolored on cross section due to hemorrhage and necrosis.

Cardinal features of glioblastomas

<table>
<thead>
<tr>
<th>VASCULAR ENDOTHELIAL PROLIFERATION</th>
<th>NECROSIS</th>
<th>HAEMORRHAGE</th>
</tr>
</thead>
</table>

GBMs occur most often in the subcortical white matter of the cerebral hemispheres. In a series of 987 glioblastomas, the most frequently affected sites were the temporal (31%), parietal (24%), frontal (23%), and occipital (16%) lobes. Combined frontotemporal location is particularly typical. Tumor infiltration often extends into the adjacent cortex or the basal ganglia. When a tumor in the frontal cortex spreads across the corpus callosum into the contralateral hemisphere, it creates the appearance of a bilateral symmetrical lesion, hence the term "butterfly glioma." Sites for glioblastomas that are much less common are the brainstem (which often is affected children), the cerebellum, and the spinal cord.
Figure 23. Glioblastoma multiforme. A, Note moderate to marked hypercellularity and focus of necrosis with pseudopalisading. Glioblastoma multiforme. B, Central necrosis surrounded by viable tumor nuclei giving appearance of palisading which is called pseudopalisading. Necrosis is found in glioblastoma multiformed but not anaplastic astrocytoma.

In general three zones are identified in glioblastomas (1) A central zone (hypointense on the T1 images, hyperintense on the T2 images and hypodense on CT scan) (2) A peripheral enhanced rim with multiple enhanced mural nodules and (3) An ill-defined diffuse large zone surrounding the first two zones. (hypointense on the T1 images, hyperintense on the T2 images and hypodense on CT scan). The first zone corresponds to the necrotic tumour tissues, the second zone corresponds to the viable tumour tissues, while the third zone corresponds to edema, malignant glial cell infiltrations and reactive gliosis. The mere presence of a necrotic center in any glioma shifts the pathological grade from one with low grade malignancy to the highly malignant glioblastoma.

Histologic Findings: As its name suggests, the histopathology of GBM is extremely variable. GBMs are composed of poorly differentiated, often pleomorphic astrocytic cells with marked nuclear atypia and brisk mitotic activity. Necrosis is an essential diagnostic feature, and prominent microvascular proliferation is common. Macrosopically, glioblastomas are poorly delineated, with peripheral grayish tumor cells, central yellowish necrosis from myelin breakdown, and multiple areas of old and recent hemorrhages. Most glioblastomas of the cerebral hemispheres are clearly intraparenchymal with an epicenter.
in the white matter, but some extend superficially and contact the leptomeninges and dura.

Figure 24. Glioblastoma multiforme. Note moderate to marked hypercellularity, mitoses, and moderate pleomorphism (often even more pleomorphic).

Despite the short duration of symptoms, these tumors often are surprisingly large at the time of presentation, occupying much of a cerebral lobe. Undoubtedly, glial fibrillary acidic protein (GFAP) remains the most valuable marker for neoplastic astrocytes. Although immunostaining is variable and tends to decrease with progressive dedifferentiation, many cells remain immunopositive for GFAP even in the most aggressive glioblastomas. Vimentin and fibronectin expression are common but less specific.

The regional heterogeneity of glioblastomas is remarkable and makes histopathological diagnosis a serious challenge when it is based solely on stereotactic needle biopsies. Tumor heterogeneity also is likely to play a significant role in explaining the meager success of all treatment modalities, including radiation, chemotherapy, and immunotherapy.

Staging: Completely staging most glioblastomas is neither practical nor possible because these tumors do not have clearly defined margins. Rather, they exhibit well-known tendencies to invade locally and spread along compact white matter pathways, such as the corpus callosum, internal capsule, optic radiation, anterior commissure, fornix, and subependymal regions. Such spread may create the appearance of multiple glioblastomas or multicentric gliomas on imaging studies.
Careful histological analyses have indicated that only 2-7% of glioblastomas are truly multiple independent tumors rather than distant spread from a primary site. Despite its rapid infiltrative growth, the glioblastoma tends not to invade the subarachnoid space and, consequently, rarely metastasizes via CSF. Hematogenous spread to extraneural tissues is very rare in patients who have not had previous surgical intervention, and penetration of the dura, venous sinuses, and bone is exceptional.

The histopathology demonstrates diverse cell forms with areas of marked cellularity and necrosis. There is vascular endothelial proliferation within and adjacent to the tumor. Microscopically, no clear margin between normal brain and tumor cells, edema, or reactive gliosis is identified. GBM can develop de novo, or by progression from low-grade or anaplastic astrocytomas. These cannot be reliably distinguished histopathologically, although genetic distinctions have been suggested involving p53 mutations, EGF-R amplification, and loss of heterozygosity on chromosomes 10 and 17p.

CT and MR imaging of GBMs demonstrate heterogeneous masses, reflecting the presence of hemorrhage, necrosis, and varying cellularity. Flow voids may be identified indicating the hypervascular nature of these tumors, whereas calcification is rare. These tumors are associated with significant mass effect with extensive surrounding edema. Areas of abnormal signal on T2-weighted images may represent the presence of tumor or edema. In addition, regions of "normal-appearing brain" on MR images may be infiltrated by tumor cells on pathological evaluation. Thus, tumor margins cannot be accurately defined by imaging.
Glioblastomas are characterized by vascular endothelial hyperplasia with defective endothelial lining resulting in increased permeability of endothelial cells to macromolecules, such as the plasma proteins and various other molecules, whose entry is limited by the capillary endothelial cells (blood brain barrier). Increased permeability of the endothelial cells of the newly formed blood vessels results in vasogenic edema and contrast enhancement.

Enhancement patterns of GBMs are heterogeneous and can be nodular, ringlike, diffuse, or irregular with necrotic areas. The appearance can be similar to metastases, as well as radiation necrosis. GBMs are reported to be multifocal in 5% of cases. These likely represent diffuse infiltration by tumor rather than synchronous development of separate lesions. Contrast enhancement can be useful in guiding surgical biopsy, as well as identifying the presence of subependymal or subarachnoid seeding. Postoperative imaging is typically performed within 2 days to distinguish postsurgical change and scar from enhancing residual tumor. Necrosis can develop following radiotherapy, and the appearance may be difficult to distinguish from recurrent tumor. SPECT imaging and MR
cerebral perfusion imaging may be of value in this setting. Recurrent tumor should be hypervascular, whereas areas of radiation necrosis appear avascular.

Figure 27. Multifocal glioblastoma multiforme (GB). A, B,C,D Axial T2 and FLAIR images demonstrate multiple regions of increased signal abnormality including the right cerebellum, right temporal lobe, and left frontal lobe. Despite diffuse involvement, white matter signal abnormality cannot be traced to connect all the lesions. E,F, Axial enhanced T1-weighted images show multiple discrete ring-enhancing masses. Imaging findings are indistinguishable from metastatic disease.
Figure 28. GBM in a 49-year-old man. A, Axial T2-weighted image demonstrates a large right heterogeneous hemorrhagic mass with areas of necrosis (black arrow). B, Axial susceptibility gradient echo image demonstrates variable low signal intensity within the tumor, which confirms the presence of the blood products (white arrow) C, Axial enhanced T1-weighted image. Note second right frontal lobe-enhancing lesion representing multifocal involvement (open arrow).

On imaging studies, GBM usually presents with a fairly typical and characteristic appearance. There is usually a solitary, deep, heterogeneous, ring-enhancing lesion, with extensive surrounding vasogenic edema. Contrast enhancement is nearly universal, when the actual volume of GBM is macroscopic (>1 cm diameter). The central necrosis that is so common in these tumors does not enhance. It is surrounded by living tumor, with prominent bright enhancement on both MR and CT. The most common feature of the enhancing ring is irregularity, with a wide rind that varies in thickness and has an irregular or shaggy inner margin. These lesions extend into or through the commissure of the corpus callosum in almost three quarters of the cases. The nature of these tumors is to produce significant neovascularity, with vessels that are freely permeable, without a blood-brain barrier. In many cases, a major component of the tumor's mass effect is produced by the surrounding vasogenic edema that envelops the enhancing areas.
Figure 29. A, Glioblastoma multiforme. This axial contrast-enhanced CT image shows a multiloculated, heterogeneous ring-enhancing mass. The lesion is large enough to be both deep and superficial. The nonenhancing regions are cavitation from tumor necrosis. B, This axial T1-weighted gadolinium-enhanced MR image shows a typical appearance for a GBM. There is a solitary, deep, heterogeneous ring-enhancing mass. The irregular central cavity is due to necrosis.

The relationship between neuroimaging actual tumor extent is critical to the use of these studies in diagnosis and treatment design. In general three zones are identified in malignant brain tumours: (1) A central zone (hypointense on the MRI T1 images, hyperintense on the MRI T2 images and hypodense on CT scan) (2) A peripheral enhanced rim with multiple enhanced mural nodules and (3) An ill-defined diffuse large zone surrounding the first two zones.

**ZONE** | **DESCRIPTION**
---|---
**CENTRAL ZONE** | FORMED OF NECROTIC TUMOUR TISSUE
**INTERMEDIATE CONTRAST ENHANCING RIM** | FORMED OF VIVABLE TUMOUR TISSUE
**PERIPHERAL DIFFUSE ZONE** | FORMED OF OEDEMA, REACTIVE GLIOSIS AND MALIGNANT INFILTRATIONS

(hypointense on the T1 images, hyperintense on the T2 images and hypodense on CT scan). The first zone corresponds to the necrotic tumour tissues, the microscopic correlate of enhancement is hypercellularity, mitotic activity, and neovascularity with breakdown of blood brain barrier resulting in increased permeability of brain capillary endothelial cells to macromolecules, such as the plasma proteins and various other molecules, whose entry is limited by the capillary endothelial cells (blood brain barrier), while the third zone corresponds to edema, malignant glial cell infiltrations and reactive gliosis. The surrounding zone of edema demonstrates a decreasing gradient of infiltrating tumor cells. The infiltrating tumor cells primarily follow white matter tracts, accompanied by vasogenic edema that may facilitate migration.

Although tumor cells may spread a great distance, typically, most are within 2 cm of the enhancing margin.

Gliomas are graded and carry a final diagnosis based on the most aggressive components. Correlation of imaging with pathology can be lacking, however, when a tumor has foci of GBM but is largely composed of lower grade tissue, such as anaplastic astrocytoma or even grade II astrocytoma. Because microscopic infiltration is just that, microscopic, imaging fails to outline the true extent of the tumor. In fact, to date, no imaging technique can determine the true lesion boundary. Most imaging parameters (density, signal intensity, enhancement, MR spectroscopy, perfusion, and metabolism), however, identify and outline the main bulk of the tumor.
Table 3. Differences between grade II astrocytoma and glioblastomas (grade IV astrocytomas)

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Grade II astrocytoma</th>
<th>Glioblastoma multiforme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central necrosis</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Vascular proliferation*</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Vasogenic edema *</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Enhancement*</td>
<td>Absent, to mild/moderate</td>
<td>Usually marked</td>
</tr>
</tbody>
</table>

*Glioblastomas are characterized by vascular endothelial hyperplasia with defective endothelial lining resulting in increased permeability of endothelial cells to macromolecules, such as the plasma proteins and various other molecules, whose entry is limited by the capillary endothelial cells (blood brain barrier). Increased permeability of the endothelial cells of the newly formed blood vessels results in vasogenic edema and contrast enhancement.

Figure 30. A, Astrocytoma grade II and B, glioblastoma multiforme. Astrocytoma grade II is diffusely infiltrating and expanding the left hemisphere without a definite mass, Notice the subfalcine herniation (arrow), while glioblastoma is multicolored due to cystic necrosis and hemorrhagic spots.
Figure 31. Glioblastoma (A) compared with astrocytoma grade II (B) at surgery. Notice the multicolor appearance and the more vascular nature of glioblastomas.


42. Metwally, MYM: Textbook of neuroimaging, version 3.2 or later, Metwally, MYM (ed), webcd agency for electronic publishing, 2002


44. Dunn J, Kemohan JW: Gliomatosis cerebri. Hum Pathol 64:82-91, 1957

45. Malamud N, Wise BL, Jones OW Jr: Gliomatosis cerebri. Hum Pathol 64:82-91, 1957


64. Scherer Hj: The forms of growth in gliomas and their practical significance. Brain 63:1-35, 1940


INTRODUCTION

Astrocytomas are, by far, the largest category of primary neoplasms of the brain. There are two primary patterns of growth seen in astrocytomas: diffuse and circumscribed. The diffusely infiltrating astrocytomas have been known since the early days of brain surgery and neuropathology. The circumscribed group of astrocytomas has only recently received widespread acceptance, although one subtype—pilocytic astrocytoma (PA)—has been well described for decades. Several of the subtypes of astrocytoma more recently added to the WHO classification are characterized by a circumscribed pattern of growth.
- **Pilocytic Astrocytoma**

PA is the prototype for low-grade (benign) circumscribed astrocytoma. This tumor represents approximately 2% to 6% of all primary brain tumors. In some series, they are described as the most common tumor of the cerebellum in childhood. In other series, they are less frequent than medulloblastoma and account for little more than 7% of all neoplasms in patients younger than age 20. Patients with these tumors present primarily during childhood with the peak ages of presentation between 5 and 15 years old. Tumors of the chiasm and other locations of the diencephalon may present at younger ages. Within the diencephalon, PA may present in the orbital portions of the optic nerves, within the hypothalamus, and within the thalamus. Most of the optic nerve gliomas that occur in neurofibromatosis type 1 (von Recklinghausen type) are PA. Most series report an equal incidence in both sexes; others indicate a slight preponderance of female patients in a ratio less than 4:3.

<table>
<thead>
<tr>
<th>Common anatomical location</th>
<th>1,3,5,6,7,8,10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral hemisphere (18%)</td>
<td></td>
</tr>
<tr>
<td>Cerebellum (55%)</td>
<td></td>
</tr>
<tr>
<td>Brain stem (17%)</td>
<td></td>
</tr>
<tr>
<td>Hypothalamic, chiasmal (2%)</td>
<td></td>
</tr>
</tbody>
</table>

In the Egyptian study of Metwally most of the tumors occurred in the deep parietal region (64%) and the cerebellum was involved next in frequency. (see table 1) In all the reviewed literature the cerebellum was the primary site of involvement in patients younger than the age of ten while in older patients pilocytic astrocytomas occur more frequently supratentorially and this is consistent with the results of Metwally since patients in his study with supratentorial (parietal) tumors were older, and greater in number, than patients with cerebellar tumors and subsequently the percentage of tumor occurrence, anatomically, was higher in the supratentorial (deep parental) zone, compared with the cerebellar area in this series. All patients in the Egyptian study of Metwally were males and this is unlike most of the reviewed studies.
Figure 1. A pilocytic astrocytoma, notice the peripherally located hypercellular part (mural nodule [arrows]) and the multicystic appearance of the tumors.

It is interesting that the clinical picture, in pilocytic astrocytomas patients, is characterized by mild clinical disability and paucity of clinical signs despite the fact that tumors are frequently large enough. This can be explained by the benign nature of this neoplasm that apparently resulted in a very slow rate of growth. These tumors widely, and very slowly, expand neural tissues without neural destruction or interruption of normal function. The very slow rate of growth of these tumors allows the brain to move functionality from one region to another and this process of brain remapping, which has been shown to occur at all ages, is partially responsible for the relatively late appearance of symptoms and paucity of clinical signs on presentation in pilocytic astrocytomas patients.

Table 1. Distribution of pilocytic astrocytomas in Egypt

<table>
<thead>
<tr>
<th>Anatomical localization</th>
<th>%</th>
<th>Mean age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep frontoparietal</td>
<td>64%</td>
<td>13 years</td>
</tr>
<tr>
<td>Cerebellar hemispherical</td>
<td>18</td>
<td>6 years</td>
</tr>
<tr>
<td>Hypothalamus, 3rd ventricular</td>
<td>9</td>
<td>9 years</td>
</tr>
<tr>
<td>Brain stem, pontine</td>
<td>9</td>
<td>9 years</td>
</tr>
</tbody>
</table>
GROSSLY, PA IS A WELL-CIRCUMSCRIBED YET UNENCAPSULATED MASS. THE LESION GROWS PRIMARILY BY EXPANSION RATHER THAN THE INFILTRATION CHARACTERISTIC OF MOST ASTROCYTOMAS. IN MANY CASES, LESIONS ARE EASILY SEPARATED FROM THE ADJACENT UNINVOLVED CEREBELLAR FOLIA. MOST PA HAVE A SIGNIFICANT GROSSLY VISIBLY CYSTIC COMPONENT. IN MANY CASES, THE TUMOR HAS THE CLASSICALLY DESCRIBED CYST WITH NODULE MORPHOLOGY-IN WHICH NEOPLASM IS CONFINED TO A NUBBIN OF TISSUE EMBEDDED IN THE WALL OF A FLUID-FILLED CAVITY. IN THESE CASES, THE CYST FLUID IS SURROUNDED BY NONNEOPLASTIC COMPRESSED OR GLIOTIC TISSUE. CALCIFICATION CAN BE SEEN IN 25% OF CASES. MICROSCOPICALLY, THERE IS A BIPHASIC PATTERN OF DENSE AREAS WITH ELONGATED BIPOLAR HAIRLIKE (PILOCYTIC) ASTROCYTES ALTERNATING WITH LOOSER REGIONS THAT MAY HAVE MICROCYSTS. ONE DISTINCTIVE FEATURE IS THE PRESENCE OF EOSINOPHILIC CURVILINEAR ROSENTHAL FIBERS WITHIN THE DENSE REGIONS. THE CAPILLARIES MAY BE ABNORMAL AND CAN BE COILED (ANGIOMATOUS) AND THICK-WALLED. APPARENTLY THE BLOOD-BRAIN BARRIER IS NOT WELL FORMED IN THESE TUMORS. THE PROTEINACEOUS FLUID THAT ACCUMULATES AS BOTH MICROCYSTS AND MACROCYSTS PROBABLY LEAKS FROM THE ABNORMAL VESSELS. MITOSIS AND NECROSIS ARE DISTINCTLY UNCOMMON. DESPITE THIS, OCCASIONAL PA SHOW MICROSCOPIC HEMORRHAGES OR BROWNISH STAINING.

**Table 2. The mural nodule is composed of two main parts as follows**

<table>
<thead>
<tr>
<th>Part</th>
<th>Appearance</th>
<th>Histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part I</td>
<td>Dense compact appearance</td>
<td>Composed of elongated bipolar hairlike (pilocytic) astocytes with high nuclear to cytoplasmic ratio and with minimal extracellular fluid. This part is relatively vascular.</td>
</tr>
<tr>
<td>Part II</td>
<td>Loose appearance</td>
<td>Relatively acellular and composed mainly of microcysts and enlarged extracellular fluid filled spaces. This part is relatively avascular.</td>
</tr>
</tbody>
</table>

* The spatial distribution of each part within the mural nodule will determine the neuroimaging appearance of the mural nodule.
Many astrocytomas, particularly in the cerebellum, hypothalamus, and optic pathways of children, exhibit a typical histologic appearance previously termed polar spongioblastoma and now universally referred to as juvenile pilocytic astrocytoma. These tumors frequently contain both macrocysts (as in cystic cerebellar astrocytoma) or microcysts. Rosenthal fibers, strongly eosinophilic coalescences of neurofibrillary elements, are characteristic of juvenile pilocytic astrocytoma, but may be found in other forms of tumor, particularly as a glial reaction surrounding craniopharyngioma. Endothelial proliferation is common in these tumors and has none of the ominous connotations in this context that it implies in other forms of astrocytomas.

From the pathological point of view pilocytic (hair cells) astrocytomas are composed of two main parts, a fluid-filled large cyst and a projecting mural nodule. The neoplastic cells are confined to the mural nodule and the cyst walls are composed of non-neoplastic compressed or gliotic neural tissues. Pilocytic astrocytomas do not have true capsule, yet they can easily be separated from the surrounding tissues. Calcification can be seen in 25% of cases. These tumors frequently have microcysts and macrocysts. Microscopically, there is a biphasic pattern of dense areas with elongated bipolar hairlike (pilocytic) astrocytes alternating with looser regions that may have microcysts. One distinctive feature is the presence of eosinophilic curvilinear Rosenthal fibers and strongly eosinophilic coalescences of neurofibrillary elements within the dense regions.
capillaries may be abnormal and can be coiled (angiomatous) and thick-walled. Apparently the blood-brain barrier is not well formed in these tumors. The proteinaceous fluid that accumulates as both microcysts and macrocysts probably leaks from the abnormal vessels. Necrosis, mitotic activity, endothelial proliferation are selectively absent in pilocytic astrocytomas. Pilocytic astrocytomas are very slowly growing tumors, with long premonitory symptoms before clinical presentation, that selectively grow by expansion rather by infiltration of the surrounding neural tissues that is more characteristic of diffuse astrocytomas.

**Figure 4.** This figure shows a gross specimen of a pilocytic astrocytoma of the posterior fossa. Identify the cerebellar hemispheres, the pons and the fourth ventricle. The fourth ventricle is nearly obliterated due to the large cystic tumor in the midline. Note the white nodule to one side of the cyst. This is the actual tumor. Many pilocytic astrocytomas in the posterior fossa will have an associated cyst and a contrast enhancing "mural" nodule. Pilocytic astrocytomas are one of the most common pediatric brain tumors and most occur in the posterior fossa, but in children with Neurofibromatosis type I, they may occur in the optic tracts.

Juvenile pilocytic astrocytomas tend to be well circumscribed and to grow slowly with long periods of premonitory symptoms before presentation. This pattern is especially true of tumors that arise in the cerebellum. Tumors of the anterior third ventricle tend to be well-defined superiorly but diffusely infiltrating the optic mechanisms and hypothalamus inferiorly. The course of these tumors is normally benign but may be unpredictable thereby making treatment decisions extremely difficult. The presence of a juvenile pilocytic astrocytoma that extends into the subarachnoid space is common.

Pilocytic astrocytomas differ from the more common diffuse astrocytomas from the pathological, nosological, radiological, genetic and prognostic point of view. From the pathological point of view diffuse astrocytomas are neoplasms
of widely varying potential that are unencapsulated, poorly margined and diffusely infiltrate into the surrounding brain. These **diffuse astrocytomas** appear to form a continuum of both biological and histological aggression. They vary from lesions with almost normal cytology (grade II astrocytomas) through intermediate stages (grade III, anaplastic astrocytomas) and up to the most aggressive of all human brain tumors (grade IV astrocytomas or glioblastoma multiforme).

![Figure 5. This figure shows a gross specimen of a pilocytic astrocytoma of the posterior fossa. Identify the cerebellar hemispheres, the pons and the fourth ventricle. The fourth ventricle is nearly obliterated due to the large cystic tumor in the midline.](image)

**Figure 5.**

![Figure 6. Histopathological and gross pathological picture of the pilocytic astrocytoma with the characteristic microcysts and a large mural nodule](image)

**Figure 6.**

From the nosological point of view, and according to the **WHO** classification of brain tumors,** pilocytic astrocytomas are ranked as grade I benign gliomas while **diffuse astrocytomas** are ranked as grade II, grade III (anaplastic astrocytomas) and grade IV (glioblastoma multiforme). The following pathological differences are present between diffuse and pilocytic astrocytomas.

- **Diffuse astrocytomas**, unlike pilocytic astrocytomas, have a peculiar tendency to change its grade over time and the condition is age dependant. A change in the grade of diffuse astrocytoma is more likely to occur in the older age group. In older age group (over the age of 40 years) diffuse low grade astrocytomas (grade II astrocytoma according to **WHO**) have a bad prognosis because they have a great tendency for anaplastic transformation (to grade III or grade IV astrocytoma according to **WHO**), while at a younger age group anaplastic transformation
of diffuse low grade astrocytomas (grade II astrocytoma according to WHO) is extremely uncommon, also the probability for diffuse low grade astrocytomas to have a highly malignant component (i.e., grade III or IV mixed with grade II) is higher in the older age group. On the other hand pilocytic astrocytomas (grade I astrocytoma according to WHO) never change its grade over time.

- **Diffuse astrocytomas** (grade II, III or grade IV astrocytomas) grow by infiltration of the nearby neural tissues (commonly in the form of remote neoplastic cells radiating from the mother tumor) and so they are poorly marginated and, practically, complete surgical resection is not possible and some neoplastic cells are almost invariably left behind after surgical resection. On the other hand pilocytic astrocytomas grow by expansion and so they are well circumscribed and subsequently complete surgical resection is possible.

- **Diffuse astrocytomas**, unlike pilocytic astrocytomas, are highly cellular neoplasms with cells that range from normal appearing astrocytes (grade II) to cells with marked pleomorphism and hyperchromatic nuclei (grade III, and IV). On the other hand pilocytic astrocytomas are histopathologically composed of scanty elongated cells, Rosenthal fibers and microcysts and this combination constitutes the classic of pilocytic astrocytomas. Cells are only confined to the mural nodule in pilocytic astrocytomas and subsequently the mural nodule is the only neoplastic part of the tumor.

- Pilocytic astrocytomas are truly benign gliomas while **diffuse astrocytomas** are, at best, of low grade malignancy.

Radiologically pilocytic astrocytomas differ from diffuse astrocytomas in the following points

1. Pilocytic astrocytomas are typically "cystic tumors with a mural nodule" and with prominent mass effect, while diffuse astrocytomas with a lower grade (grade II) are typically solid tumors with minimal or no mass effect that appear homogeneously hypodense on CT scan, hyperintense on the MRI T2 images and hypointense on the T1 MRI images. The neuroimaging appearance of diffuse astrocytomas is due to increased cell count. The mural nodule of pilocytic astrocytomas might or might enhance while diffuse low grade astrocytomas usually do not enhance on postcontrast scan. Diffuse low grade astrocytomas (grade II) diffusely expand the affected part of the brain with poor margin, while pilocytic astrocytomas are well circumscribed rounded or oval tumors.

2. Although central necrosis in highly malignant glioblastoma multiforme might, morphologically, create the appearance of a cyst with a projecting mural nodule, however this can easily be differentiated from pilocytic astrocytomas by the fact that the walls of the cyst in pilocytic astrocytomas, being composed of non-neoplastic compressed neural tissues, never enhance while the walls of the cyst in glioblastomas with central necrosis invariably enhance because it is composed of viable tumor tissues. Wall enhancement is characteristic of glioblastomas with central necrosis and when it is observed radiologically should shift the tumor grade from...
the most benign pilocytic astrocytoma to the most malignant glioblastoma multiforme, see figure 8.\textsuperscript{11,12,13} The presence of significant edema and short history before clinical presentation favor the diagnosis of glioblastoma multiforme. In general glioblastoma multiforme occurs at an older age compared with pilocytic astrocytoma.\textsuperscript{11,12,13,27,28} The presence of blood products on CT scan or MRI is characteristic of the highly malignant glioblastoma multiforme.

Figure 7. Two CT scan studies showing juvenile pilocytic astrocytomas in left cerebral hemisphere, A and the cerebellum, B. Notice the wall calcification in (B). Notice that the mural nodule has a hypodense core and a hyperdense rim in A (pattern I), and is diffusely hyperdense in B (pattern II). The cystic component of the tumors is diffusely hypodense.

Figure 8. A,B Precontrast and postcontrast CT scan studies showing parietal pilocytic astrocytoma, notice that only the mural nodule was enhanced on postcontrast scan A, while the cyst wall remained unenhanced. For comparison a postcontrast CT scan study of a case with glioblastoma and with central necrosis is presented (C). Notice that in glioblastoma both the cyst wall and the mural nodule are enhanced.
On imaging studies, the presence of a cystic component in these lesions is suggestive of pilocytic astrocytomas. The lesions may appear on both CT and MR as a classic cyst with nodule mass. Purely solid masses are not common. Complex shapes (e.g., multiloculated) are frequent and may create a misleading appearance. With contrast infusion, both on CT and on MR, PA almost invariably demonstrate prominent enhancement. The pattern may be a classic cyst with nodule, (only the mural nodule enhances brightly while the cyst wall, being composed of nonneoplastic compressed neural tissues, usually does not enhance beyond the edge of nodule) although variable degrees of wall enhancement also occur. More complex patterns of enhancement may appear to suggest necrosis and a high-grade neoplasm. Although this is a low-grade (WHO grade I) tumor, in certain examples, especially those presenting in the cerebral hemispheres, the prominent surrounding vasogenic edema may create a disturbing appearance.

Figure 9. A. Precontrast MRI T1, and MRI T2 (B,C) showing cerebellar pilocytic astrocytoma, Notice that the mural nodule is isointense, relative to the normal cerebellar tissues, on the T1 image hypointense, relative to the cyst, on the T2 MRI images, (B,C). The cyst is hypointense on the T1 image and hyperintense on the T2 images.

In neuroimaging studies of juvenile pilocytic astrocytomas, the acellular cystic part generally appears as a low signal intensity on T1-weighted sequences, as a high signal intensity on T2-weighted sequences and diffusely hypodense on CT scan studies. The mural
nodule, which is the neoplastic part of the tumor, have four neuroimaging patterns of CT density and MRI T1, T2 signal intensities as follows:

Table 3. Neuroimaging patterns of the mural nodule \(^{30}\) (see Fig 16)

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pattern I</td>
<td>The mural nodule has a large central core and a peripheral thin rim. The core is hypointense on precontrast T1 MRI studies, hypodense on precontrast CT scan studies and hyperintense on the MRI T2 images. The peripheral rim is hyperintense on the precontrast MRI T1 images, and hyperdense on precontrast CT scan studies (even though not calcified) and hypointense on the MRI T2 studies. Because the peripheral thin rim has CT density/MRI signal intensity different from the central core of the mural nodule and from the tumor cystic cavity, it separates the mural nodule from the cystic cavity on neuroimaging studies making it easier to differentiate between the cystic component and the mural nodule. CT Density measurement reveals no evidence of calcification in all cases with this pattern. In this pattern the peripheral thin rim is hypercellular/vascular while the central core of the mural nodule is relatively acellular/avascular and composed of microcysts. After contrast enhancement only the hypercellular peripheral rim of the mural nodule enhances, while the acellular central core does not enhance. Mural nodule with this pattern is larger in size. See Fig 7A</td>
</tr>
<tr>
<td>Pattern II</td>
<td>The nodule appears diffusely hyperdense on precontrast CT scan and diffusely hypointense on MRI T2 images. CT Density measurement reveals no evidence of calcification in all cases with this pattern. In this pattern the mural nodule has a compact, dense appearance and is diffusely hypercellular/vascular and enhances diffusely and brightly after contrast injection. Mural nodule with this pattern is smaller in size. See Fig 7B and Fig 13</td>
</tr>
<tr>
<td>Pattern III</td>
<td>The nodule appears diffusely hypodense on precontrast CT scan, diffusely hypointense on precontrast MRI T1 images, and diffusely hyperintense on MRI T2 images. Differentiation between the mural nodule and the cystic part of the tumor might not be easy. The nodule in pattern III is relatively diffusely acellular and has a looser appearance. Contrast enhancement in this pattern is poor. See Fig 10b</td>
</tr>
<tr>
<td>Pattern IV</td>
<td>The nodule appears irregularly hyperdense on precontrast CT scan and hypointense on MRI T2 images. CT Density measurement reveals evidence of patchy calcification of the mural nodule in all cases with this pattern. See Fig. 14</td>
</tr>
</tbody>
</table>

In the author experience the prevailing radiological pattern of the mural nodule is pattern I.

Microscopically, the mural nodule is composed of a biphasic pattern of dense areas with elongated bipolar hairlike (pilocytic) astrocytes (with high nuclear to cytoplasmic ratio and
with minimal extracellular fluid), these astrocytes are arranged peripherally in most tumor nodules, and alternating with looser regions that are rich in fluid filled microcysts, these regions are arranged centrally in most tumor nodules. The hypercellular peripheral rim (with cells that have a high nuclear to cytoplasmic ratio with minimal extracellular fluid) appear hyperintense on the precontrast T1 images, hypointense on the MRI T2 studies and hyperdense on precontrast the CT scan studies, while the relatively acellular fluid filled microcystic core appear hypointense on the precontrast T1 studies, hyperintense on the MRI T2 studies and hypodense on the precontrast CT scan studies. The topographic distribution of the hypercellular part, peripherally, and the microcystic acellular part, centrally, within the mural nodule is responsible for the production of the patten I. Should the hypercellular part predominate the histopathological architecture of the mural nodule, pattern II is the expected result. Should the relatively acellular fluid filled microcystic part predominate the histopathological architecture of the mural nodule, pattern III is the expected result. Should the mural nodule become calcified, pattern IV is the expected result.

Figure 10. A, CT scan showing pattern I of the mural nodule, B, CT scan showing pattern II of the mural nodule, C, MRI T2 image showing pattern III of the mural nodule, the nodule is not showing because it is isointense to the cystic cavity. D,E MRI T1,T2 showing pattern I of the mural nodule. F, MRI T2 image showing pattern II of the mural nodule, the nodule is hypointense relative to the cystic cavity.
Pilocytic tumors are sometime wholly solid (noncystic) and composed of elongated bipolar hairlike (pilocytic) astrocytes (with high nuclear to cytoplasmic ratio and with minimal extracellular fluid). The tumor in this case appears hyperintense on the precontrast T1 images, hypointense to isointense on the MRI T2 studies and hyperdense on precontrast CT scan studies, with dense postcontrast enhancement. In the author experience perilesional edema is common in solid tumors.

Figure 11. A solid pilocytic astrocytoma, The tumor is hyperdense on noncontrast CT scan (A), with dense postcontrast enhancement. (B). The tumor contains some cystic spaces and is surrounded by edema. This is probably the initial stage in the natural evolution of the tumor.

After the infusion of an intravenous contrast agent, the solid hypercellular components of the mural nodule tend to enhance brightly and to appear as a distinct, well-defined mass. Contrast enhancement is prominent is mural nodule with pattern II tissue, while in mural nodule with pattern I tissues enhancement, though present in the hypercellular/vascular peripheral thin rim, might not be appreciated visually (enhancement can be appreciated if the CT density of the peripheral rim is taken before and after contrast injection). Enhancement is prominent in purely solid tumors. The cyst wall, being composed of nonneoplastic compressed neural tissues, usually does not enhance with contrast material.
In general pilocytic astrocytomas have heterogeneous histopathological composition (biphasic pattern of dense areas with elongated bipolar hairlike (pilocytic) astrocytes alternating with looser regions that may have microcysts) and subsequently the tumor might be completely solid and occasionally the tumor might be cystic with a small dense hypercellular peripheral mural nodule (pattern II). Sometimes the mural nodule itself might have a large cystic core with a peripheral hypercellular thin cover (pattern I). Although the share taken by the cystic (acellular/avascular) and the solid (hypercellular/vascular) in the histopathological composition of the pilocytic astrocytomas might vary (resulting in heterogeneous appearance of the tumors in neuroimaging study both in precontrast and in postcontrast studies), however the neuroimaging appearance of pilocytic astrocytomas simply reflects the natural evolution of the tumors.

A pilocytic astrocytoma usually starts as hypercellular solid tumor with elongated bipolar hairlike (pilocytic) astrocytes with high nuclear to cytoplasmic ratio and with minimal extracellular fluid (purely solid tumors). Solid tumors are vascular and their capillaries may be abnormal and can be coiled (angiomatous) and thick-walled. Apparently the blood-brain barrier is not well formed in these tumors and proteinaceous fluid probably leaks from the abnormal vessels and accumulates in the tumors as microcysts, first, and macrocysts later on. With progressive enlargement of the macrocysts (microcysts enlarge and coalesce forming a single large cyst), the viable tumor tissues are progressively compressed into a smaller, dense and hypercellular peripheral mural nodule (pattern II). Progressive leakage of proteinaceous fluid within the core of the mural nodule will result in progressive enlargement of the mural nodule, the core of which will be cystic with a thin
outer cover of viable tumor tissues (pattern I). Although the typical appearance of a pilocytic tumor is a large single cyst with a mural nodule, however the spatial distribution of the solid (hypercellular/vascular) and the cystic components within the tumors can vary, also the share taken by the solid the cystic parts in the histopathological make-up of the tumors might vary. These histopathological variations might result in tumors that have quite atypical appearance with irregular cystic and solid parts and with irregular or patchy contrast enhancement.

Color plate 1. A pilocytic astrocytoma commonly starts as a solid mas (1), however due to defective blood brain barrier in the newly formed blood vessels proteinaceous fluid probably leaks and accumulates inside the tumor as microcysts, first (2), and macrocysts later on (3). With progressive enlargement of the macrocysts (microcysts enlarge and coalesce forming a single large cyst), the viable tumor tissues are progressively compressed into a smaller, dense and hypercellular peripheral mural nodule (pattern II) against a large cyst (3). Progressive leakage of proteinaceous fluid within the core of the mural nodule will result in progressive enlargement of the mural nodule, the core of which will be cystic with a thin outer cover of viable tumor tissues (pattern I) (4,5,6). (Blue = cystic parts and brown = solid parts of the tumor)

If the CT scan discloses that both the wall of the cyst and the solid component of the neoplasm enhance with intravenous injection of contrast material, MRI scan commonly disclose that the tumor is more extensive than the CT scan suggested and the surgical specimens disclose highly malignant gliomas (anaplastic astrocytoma or glioblastoma).
In general calcification is commonly present in pilocytic astrocytomas (28%\textsuperscript{30}), calcification might be present in the mural nodule (see figure 14) or in the cyst wall (see figure 7).

The appearance of cystic astrocytomas of the brain stem is very similar to that of cystic astrocytomas of the cerebellum. The CT scans/MRI disclose only the mural nodule enhanced with contrast. Cystic astrocytomas are often associated with a large cyst that excavates much of the brain stem. These tumors are commonly found in the cerebral peduncle or pons, and both CT scan and MRI give satisfactory imaging.

Figure 13. Pilocytic astrocytoma. Axial and sagittal T\textsubscript{1}-weighted gadolinium-enhanced MR images show a classic cyst with nodule morphology (with pattern II tissues). Notice that the wall of the cyst does not enhance beyond the edge of nodule.

Figure 14. A, Precontrast CT scan showing frontal pilocytic tumor with a calcified mural nodule (pattern IV), and (B) cystic cerebellar pilocytic tumor with a large, calcified mural nodule (pattern IV).
After intravenous infusion of contrast material, the tumor will normally enhance brightly and thoroughly. Two patterns seem to exist in the primarily cystic varieties. Most commonly, the mural nodule enhances brightly and the cyst wall does not enhance. In this case, pathologic assessments show that the cyst wall is composed of compressed cerebellar tissue and that the tumor is confined to the mural nodule. In some tumors, the entire wall of the cyst enhances. This apparently means that there has been degeneration within the center of the tumor, and viable tumor completely surrounds the cyst. In this case, the pathological diagnosis is glioblastoma multiforme and the entire cyst wall must be resected.

Figure 15. A, postcontrast CT scan study showing a large parietal pilocytic astrocytoma. Neither the mural nodule nor the cyst wall was enhanced. B. postcontrast CT scan study showing a large hypothalamic pilocytic astrocytoma with wall enhancement.

Figure 16. The stages of the natural evolution of pilocytic astrocytoma. The initial solid stage with some microcysts is illustrated in (A). The second stage is illustrated in (B) where the tumor is composed of a large cyst with a single densely enhanced non-cystic small mural nodule (pattern II). The third stage is illustrated in (C) The mural nodule has enlarged and is composed or a cystic hypodense central core and a peripheral rim of viable tumor tissue (pattern I). The mural nodule ultimately becomes cystic.

From the genetic point of view pilocytic astrocytoma is different from diffuse astrocytomas in the following points

- The analyses of the genetic lesions of pilocytic astrocytoma have targeted the TP53 gene on chromosome 17. Investigations have not confirmed a critical role for
alterations of this gene in the development of these tumors, however. In one series, the cytogenetic analysis of 14 pilocytic tumor cultures did not identify a specific pattern of chromosomal aberration. (15) Patients with tumors characterized by normal stem line karyotypes had the most favorable outcomes. The presence of clonal structural abnormalities and the presence of markers were associated with a high risk of early recurrence. (15)

- On the other hand genetic lesions associated with the development and malignant transformation of diffuse astrocytomas have been well described in the cytogenetic literature. (16, 17, 18, 19) To date, three distinct clinical, histologic, and genetic patterns of glioblastoma multiforme have been characterized. In younger patients, most diffuse astrocytomas are believed to begin as low-grade astrocytoma, with progression to glioblastoma multiforme through a stepwise acquisition of genetic lesions. These secondary glioblastoma multiforme often contain areas of well-differentiated residual tumor. (20, 21) The most frequent chromosomal abnormality identified in diffuse astrocytomas is the abnormal gain of chromosome 7 with an associated loss of one of the sex chromosomes. Additionally, allelic loss or mutation of 17p, resulting in critical alterations of the TP53 gene, has been targeted as an essential step in the early development of glioma. (22, 23) Mutant TP53, identified in at least one third of all astrocytomas, may contribute to the formation of these tumors by inhibiting programmed cell death. Glioblastoma multiforme in older patients are usually primary-that is, they occur as glioblastoma multiforme from their inception, without progression from a lower-grade tumor. (16, 17, 18, 19) In this group, the development of glioblastoma multiforme involves a parallel sequence of genetic alterations, including amplifications and deletions, that up-regulate growth factor receptors and drive cell proliferation. (16, 17, 18, 19, 24, 25)
Management of juvenile pilocytic astrocytoma

Because pilocytic astrocytomas grow by expansion rather than infiltration of the nearby neural structure (infiltration results in tumor cells being found histologically radiating diffusely from the mother tumor to the surrounding normal neural structures), they remain circumscribed and can be separated from normal neural tissues, thus allowing complete surgical removal without leaving behind any residual tumor cells and it is because of this that postoperative radiotherapy or chemotherapy are not indicated and probably even contraindicated because Burger and Fuller reported a pilocytic astrocytoma recurring after 28 years as a glioblastoma multiforme in a child who received postoperative radiotherapy and they attributed this rare occurrence to the probable teratogenic effect of radiotherapy. The prognosis in pilocytic astrocytoma is good with a five year survival rate reaching up to 95% to 100% in many studies after complete surgical removal. Recurrence was attributed in most studies to incomplete surgical removal in technically difficult anatomical sites such as patients with hypothalamic neoplasm.

Because of the very good prognosis of this neoplasm it is important to be familiar with its clinical and neuroimaging pictures. The presence of a cystic component in these lesions is suggestive. The lesions may appear on both CT and MR as a classic cyst with a nodular mass. Purely solid masses are not common. Complex shapes (e.g., multiloculated) can occur and may create a misleading appearance. With contrast infusion, both on CT and on MR, the mural nodule might or might not enhance, however the cyst wall...
does not enhance. Histopathological confirmation is invariably needed for the ultimate diagnosis of this neoplasm. Although the word astrocytoma is typed in the name of this neoplasm, however it should not be equated with the more common diffuse astrocytoma. "Overgrading" occurs when the generic name "astrocytoma" is applied to pilocytic astrocytomas, so it is very important to distinguish between diffuse astrocytoma and pilocytic astrocytoma as there is a real chance that pilocytic astrocytomas are cured by surgery alone once the neoplasms are completely removed.

REFERENCES


Professor Yasser Metwally
Professor of neurology, Ain Shams University, Cairo, Egypt

http://yassermetwally.com
RADIOLOGICAL PATHOLOGY OF MENINGIOMAS

Meningioma is the most common nonglial primary intracranial tumor, with a female preponderance, occurring most commonly in the 40- to 60-year-old age range. Most arise from arachnoid cap cells in arachnoid granulations, and 90% are supratentorial. They are commonly located along meningeal surfaces in the parasagittal region, lateral convexity, falx, sphenoid ridge, olfactory groove, cerebellopontine angle, petrous ridge, and tentorium in descending order of frequency. In approximately 8% of cases meningiomas are multiple,
and the multiplicity is usually sporadic but may be familial or associated with [neurofibromatosis type II](https://en.wikipedia.org/wiki/Neurofibromatosis_type_II). Other causes of meningiomas include prior cranial irradiation and previous head trauma. There is an increased incidence of meningioma with breast carcinoma and pregnancy, suggesting a hormonal influence.

**Figure 1.** Common sites for meningiomas (A) and (B) The 10 most common locations in which meningiomas are found, in order of frequency, are: parasagittal (1), cerebral convexity (2), sphenoid ridge (3), olfactory groove (4), suprasellar (5), cerebellopontine angle (6), spinal (7), floor of middle fossa (8), torcular (9), and intraventricular (10).
Table 1. Common sites for meningiomas

<table>
<thead>
<tr>
<th>Location</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parasagittal</td>
<td>Monoparesis of the contralateral leg</td>
</tr>
<tr>
<td>Subfrontal</td>
<td>Change in mentation, apathy or disinhibited behavior, urinary incontinence</td>
</tr>
<tr>
<td>Olfactory groove</td>
<td>Anosmia with possible ipsilateral optic atrophy and contralateral papilledema. This triad is termed Kennedy-Foster syndrome.</td>
</tr>
<tr>
<td>Cavernous sinus</td>
<td>Multiple cranial deficits (II, III, IV, V and VI), leading to decreased vision and diplopia with associated to facial numbness</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>Contralateral hemianopsia</td>
</tr>
<tr>
<td>Cerebellopontine angle</td>
<td>Decreased hearing with possible facial weakness and facial numbness</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>Localized spinal pain, Brown-Sequard (hemi-spinal cord) syndrome</td>
</tr>
<tr>
<td>Optic nerve meningiomas</td>
<td>Exophthalmos, Monocular loss of vision or blindness; ipsilateral dilated pupil that does not react to direct light stimulation but might contract on consensual light stimulation. Often monocular optic nerve swelling with opto-ciliary shunt vessels.</td>
</tr>
<tr>
<td>Sphenoid wing meningiomas</td>
<td>Seizures; multiple cranial nerve palsies if the superior orbital fissure is involved.</td>
</tr>
<tr>
<td>Tentorial meningiomas</td>
<td>Tentorial meningiomas may protrude within the supratentorial and infratentorial compartments. Meningiomas in this location produce symptoms by compressing specific structures within these two compartments.</td>
</tr>
<tr>
<td>Foramen magnum meningiomas</td>
<td>Paraparesis; sphincteric troubles; tongue atrophy associated to fasciculation.</td>
</tr>
</tbody>
</table>
Meningiomas can be divided into three histological groups: (1) classic, (2) angioblastic, and (3) malignant. There are histological subtypes for each of these groupings as well. The classic type of meningioma includes syncytial, transitional, and fibroblastic subtypes. Most intracranial meningiomas are of the syncytial or transitional subtype. The angioblastic group includes hemangioblastic and hemangiopericytic subtypes. The angioblastic meningioma is a rapidly growing aggressive variant with extensive thin-walled vascular spaces. Although meningiomas tend to invade venous sinuses, distant metastasis is rare, with an incidence of 0.1%. The angioblastic type is the most frequent type to metastasize.

Figure 3. A, Meningioma. Whirls of cells and elongated cells. No psammoma bodies. B, Meningioma. Note whirling pattern of tumor cells and psammoma bodies (round dense purple structures). C, Multiple meningiomas in a case with neurofibromatosis type 2

Meningiomas are generally well-circumscribed, expansive tumors. They produce symptoms by external compression of the brain. Consequently, they usually are amenable to complete resection. The major exceptions are meningiomas of the skull base, particularly of the cavernous sinus, where the tumors disseminate around multiple vital structures, usually precluding extirpation. Meningiomas tend to be smooth and round or lobular. Their cut surfaces range from firm, white, and fibrous to soft and myxoid. Brain invasion is rare, but infiltration into and, if untreated, through the skull is not unusual. Most meningiomas are benign, WHO grade I tumors, but a spectrum of aggressive tumors occurs, including essentially sarcomatous grade IV tumors.
Figure 4. A, Meningioma. Whirls of cells and elongated cells. No psammoma bodies. B, Meningioma. Note whirling pattern of tumor cells and psammoma bodies (round dense purple structures).

Meningiomas have myriad microscopic appearances. Their defined subtypes are too numerous to list here. Befitting their heritage as tumors of cells with both structural and epithelial functions, the most common histologic types are fibrous, meningothelial, and transitional, which combines the features of the first two. The psammoma body, a lamellar calcospherite, is a pathognomonic feature that can dominate some tumors. Cytologic atypia, a high mitotic rate, and necrosis are all positively correlated with increased aggressiveness. For individual tumors, however, prognosis is determined primarily by the extent of resection. Although brain invasion is uncommon and usually associated with the other high-grade features, it also occurs in otherwise typically benign slow-growing tumors.
Figure 5. A, Meningioma. Note common parasagittal location. Note compression but not invasion of the brain. B, convexity meningioma.

The relationship between neurofibromatosis type 2 and meningioma development has been well established. The most common genetic abnormality associated with meningioma is the deletion of chromosome 22 and an associated tumor-suppressor gene specific to meningioma formation. Aggressive or invasive variants of this lesion have been associated with additional chromosomal aberrations involving chromosomes 1 and 14. ³
Table 2. Histological subtype of meningiomas

<table>
<thead>
<tr>
<th>Histological subtype</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibroblastic meningiomas</td>
<td>Composed of large, narrow spindle cells. The distinct feature is the presence of abundant reticulum and collagen fibers between individual cells. 21 On MR imaging, fibroblastic meningiomas with cells embedded in a dense collagenous matrix appear as low signal intensity in T1-weighted and T2-weighted pulse sequences. 10</td>
</tr>
<tr>
<td>Transitional meningiomas (psammomatous)</td>
<td>Characterized by whorl formations in which the cells are wrapped together resembling onion skins. 10 The whorls may degenerate and calcify, becoming psammoma bodies. Marked calcifications can be seen in this histologic type. MR imaging of transitional meningiomas thus also demonstrates low signal intensity on T1-weighted and T2-weighted images, with the calcifications contributing to the low signal intensity.</td>
</tr>
<tr>
<td>Syncytial (meningothelial, endotheliomatous) meningiomas</td>
<td>Contain polygonal cells, poorly defined and arranged in lobules. 28 Syncytial meningiomas composed of sheets of contiguous cells with sparse interstitium might account for higher signal intensity in T2-weighted images. Microcystic changes and nuclear vesicles can also contribute to increased signal intensity.</td>
</tr>
<tr>
<td>Angioblastic meningiomas</td>
<td>Highly cellular and vascular tumors with a spongy appearance. Increased signal in T2-weighted pulse sequence of these tumors is due to high cellularity with increase in water content of tumor. Thus based on the correlation between histology and MR imaging appearance of meningiomas.</td>
</tr>
</tbody>
</table>
CT SCAN IMAGING OF MENINGIOMAS

CT Scans. On noncontrast CT, typically the tumor appears dense with intrinsic calcification (seen in 20% to 25% \(^1\)) and induces hyperostosis, or less commonly osteolysis, of adjacent bone. Meningiomas can erode the base of the skull and project extracranially. The tumors intensely enhance with contrast material. Cystic meningiomas are uncommon, occurring in less than 10% of cases. Cysts may be intratumoral (mostly in syncytial and angioblastic meningiomas), intraparenchymal, or may represent trapped CSF. Hemorrhagic meningiomas are uncommon. There is a rare lipoblastic or xanthomatous type of meningioma, which can show negative CT numbers.

Syncytial meningiomas are commonly slightly hyperdense than the normal brain tissues (which correlates well with histopathologic findings of high degree of cellularity, with increased nuclear to cytoplasmic ratio) and cystic components are not infrequent. Skull bone hyperostosis and enlarged meningeal vascular marking are commonly reported in this histological subtype of meningiomas. Enlarged meningeal vascular marking occurs because syncytial meningiomas are vascular tumours which parasitize pial and meningeal blood vessel resulting in their enlargement. Hyperostosis is new bone formation occurring in the neighborhood of a meningioma and is regarded as a reactive change in the skull and not an integral part of the tumor. The exact mechanism of hyperostosis is not well understood, however it is necessary for tumor cells to invade the overlying bone to invoke hyperostosis, the density of the change found in some cases and the difficulty of identifying tumor cells in the densely hyperostotic area may denote a bone reaction out of proportion to the quantity of invading tumour cells. Hyperostosis can also result from...
hypervascularity of the periosteum overlying the meningiomas. Involvement of the outer table -by hyperostosis- makes tumor invasion more likely.

Edema and mass effect are common in syncytial and angioblastic meningiomas and contrast enhancement is intense and uniform. The existence of prominent edema and mass effect in syncytial and angioblastic meningiomas probably indicates the higher rate of growth of this neoplasm compared with that of the calcified transitional (psammomatous) meningiomas. Prominent clinical signs and symptoms on presentation definitely denotes the more aggressive biological behavior of syncytial meningiomas.

Vasogenic edema is characterized by increased permeability of brain capillary endothelial cells to macromolecules, such as the plasma proteins and various other molecules, whose entry is limited by the capillary endothelial cells (blood brain barrier). The high vascularity (with defective endothelial lining of the newly formed blood vessels) of the syncytial and angioblastic meningiomas probably accounts for the edema observed in these subtypes of meningiomas.

Figure 7. A, Plain x ray showing enlarged vascular markings ending in hyperostotic bone. B, Gross specimen showing bone hyperostosis, Meningiomas often evoke reactive changes in the adjacent bone to produce hyperostosis. This figure shows the inner aspect of the bone adjacent to a meningioma. The tumor cells have infiltrated the bone marrow spaces and induced the deposits of new bone.

Bone hyperostosis and enlarged meningeal vascular marking are almost invariably coupled in every patient, they occur almost exclusively in syncytial meningiomas.
Figure 8. Enlarged meningeal vascular marking. The enlarged channels are seen ending in a hyperostotic bony region.

Figure 9. Left frontal syncytial meningioma causing hyperostosis, notice the perilesional edema.
Figure 10. Syncytial meningioma, notice the mass effect, prominent edema. The meningioma is slightly hyperdense before contrast with intense and uniform enhancement, notice the hypodense cystic changes

Transitional meningiomas (psammomatous) are characterized by the existence of calcification which causes marked increase of CT density before contrast injection, postcontrast enhancement is common. Bone hyperostosis and enlarged meningeal vascular marking are very rare -if they ever occur- in transitional meningiomas and edema is not commonly encountered around this histological subtype of meningiomas. Mass effect is mild or absent despite the occasional large size of these tumours. Absence of prominent edema and mass effect in transitional meningiomas probably indicates the slower rate of growth of this neoplasm compared with that of the highly cellular syncytial type. Paucity of clinical signs and symptoms on presentation definitely denotes the less aggressive biological behavior of transitional meningiomas.
Figure 11. Bifrontal heavily calcified psammomatous meningioma with intense postcontrast enhancement, notice absence of edema

Table 3. Plain X ray and CT scan differences between Syncytial meningiomas and Transitional meningiomas (psammomatous)

<table>
<thead>
<tr>
<th>Finding</th>
<th>Syncytial meningiomas</th>
<th>Transitional meningiomas (psammomatous)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skull bone hyperostosis and enlarged vascular marking</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Perilesional edema</td>
<td>Present*</td>
<td>Absent</td>
</tr>
<tr>
<td>Tumour calcification</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Cystic changes</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Precontrast CT density</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>Contrast enhancement</td>
<td>Intense and uniform</td>
<td>Intense and uniform</td>
</tr>
<tr>
<td>Mass effect</td>
<td>Prominent</td>
<td>Mild or absent</td>
</tr>
<tr>
<td>Rate of growth</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>Biological behavior</td>
<td>More aggressive</td>
<td>Less aggressive</td>
</tr>
<tr>
<td>Vascularity</td>
<td>More vascular</td>
<td>Less vascular</td>
</tr>
</tbody>
</table>

*Syncytial meningiomas - compared with transitional meningiomas - are vascular tumours with defective endothelial lining of blood vessels resulting in increased permeability of endothelial cells to macromolecules, such as the plasma...
proteins and various other molecules, whose entry is limited by the capillary endothelial cells (blood brain barrier). Increased permeability of the endothelial cells of the newly formed blood vessels results in vasogenic edema.

Figure 12. Angioblastic meningioma. The lesion is markedly vascular and surrounded by prominent edema.

MR IMAGING OF MENINGIOMAS

Precontrast and postcontrast MR imaging studies can easily diagnose meningioma as well as CT. MR imaging can also predict histologic subtypes of meningioma.

Diagnosis of meningiomas using MR imaging is made by demonstrating the extra-axial nature of the mass. Several key MR imaging signs aid in this distinction including: (1) the CSF cleft sign (a cleft of CSF between the lesion and the brain); (2) direct visualization of displaced or involved dura; (3) demonstration of displaced pial vessels, which lie between the brain and the extra-axial mass; and (4) buckling of the gray-white matter junction. Meningiomas are thus characterized by the existence of a hypointense cleft between the tumour and the brain that probably represents blood vessels or a CSF interface.
Figure 13. MRI T1 pre and postcontrast showing a convexity syncytial meningioma. The tumour is hypointense on the precontrast scan (A), with an apparent CSF cleft, dense enhancement and a meningeal tail on the postcontrast scan.

Another characteristic feature is the existence meningeal tail on the enhanced T1 images. The tail extends to a variable degree away from the meningioma site. This tail does not represent neoplastic infiltration and may instead reflect fibrovascular proliferation in reaction to the tumour.

- **The dural tail or "dural flair"**

The dural tail is a curvilinear region of dural enhancement adjacent to the bulky hemispheric tumor. The finding was originally thought to represent dural infiltration by tumor, and resection of all enhancing dura mater was thought to be appropriate. However, later studies helped confirm that most of the linear dural enhancement, especially when it was more than a centimeter away from the tumor bulk, was probably caused by a reactive process. This reactive process includes both vasocongestion and accumulation of interstitial edema, both of which increase the thickness of the dura mater. Because the dural capillaries are "nonneural," they do not form a blood-brain barrier, and, with accumulation of water within the dura mater, contrast material enhancement occurs.
Figure 14. Dural tail enhancement with meningioma. (a) Diagram illustrates the thin, relatively curvilinear enhancement that extends from the edge of a meningioma. Most of this enhancement is caused by vasocongestion and edema, rather than neoplastic infiltration. The bulk of the neoplastic tissue is in the hemispheric extraaxial mass; nonetheless, the dural tail must be carefully evaluated at surgery to avoid leaving neoplastic tissue behind. (b) Photograph of a resected meningioma shows the dense, "meaty," well-vascularized neoplastic tissue. At the margin of the lesion, there is a "claw" of neoplastic tissue (arrowhead) overlying the dura mater (arrows) that is not directly involved with tumor.
Figure 15. Dural tail enhancement with meningioma. Sagittal gadolinium-enhanced T1-weighted MR image reveals a large extraaxial enhancing mass. The dural tail (arrows) extends several centimeters from the smooth edge of the densely enhancing hemispheric mass. Most of this dural tail enhancement is caused by reactive changes in the dura mater.

Figure 16. Dural tail tissue adjacent to meningioma. Lower portion of the photomicrograph (original magnification, x250; hematoxylin-eosin [H-E] stain) shows normal dura mater that is largely collagen. The upper region shows reactive changes characterized by vascular...
congestion and loosening of the connective tissue. Slow flow within these vessels and accumulation of edema in the dura mater allow enhancement to be visualized on gadolinium-enhanced T1-weighted MR images.

Grossly meningiomas are characterized, by the existence of a vascular rim that surrounds the meningioma and appears signal void on both T1,T2 MRI images, this finding is consistent with the overall blood supply of meningiomas (the peripheries of meningiomas are supplied by branches from the anterior or middle cerebral arteries that encircle the tumour and form the characteristic vascular rim). Meningiomas encase, narrow and parasitize pial and meningeal vessels. Vascular rim is common in syncytial and angioblastic types and much less commonly seen in transitional meningiomas.

Heterogeneous appearance of meningiomas in T2-weighted pulse sequence can be due to tumor vascularity, calcifications, and cystic foci. MR imaging has also been found to be superior to CT in evaluating meningiomas for venous sinus invasion or internal carotid artery encasement. Brain edema is observed in about 50% of meningiomas, with severe edema occurring with syncytial and angioblastic types. Elster et al reported a strong correlation between tumor histology and tumor intensity on T2-weighted images compared with those of the cortex. Meningiomas are classified into four basic subtypes: fibroblastic, transitional, syncytial, and angioblastic. Elster et al have stated that meningiomas significantly hyperintense to cortex tend to be primarily of syncytial or angioblastic type, whereas meningiomas hypointense to cortex tend to be primarily of fibrous or transitional type.

Table 4. MRI appearance of the various types of meningiomas

<table>
<thead>
<tr>
<th>Type</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibroblastic meningiomas</td>
<td>Fibroblastic meningiomas are composed of large, narrow spindle cells. The distinct feature is the presence of abundant reticulum and collagen fibers between individual cells. On MR imaging, fibroblastic meningiomas with cells embedded in a dense collagenous matrix appear as low signal intensity in T1-weighted and T2-weighted pulse sequences.</td>
</tr>
<tr>
<td>Transitional meningiomas</td>
<td>Transitional meningiomas are characterized by whorl formations in which the cells are wrapped together resembling onion skins. The whorls may degenerate and calcify, becoming psammoma bodies. Marked calcifications can be seen in this histologic type. MR imaging of transitional meningiomas thus also demonstrates low signal intensity on T1-weighted and T2-weighted images, with the calcifications contributing to the low signal intensity.</td>
</tr>
<tr>
<td>Syncytial meningiomas</td>
<td>Syncytial (meningothelial, endotheliomatous) meningiomas contain polygonal cells, poorly defined and arranged in lobules. Syncytial meningiomas composed of sheets of contiguous cells with sparse interstitium might account for higher signal intensity in T2-weighted images. Microcystic changes and nuclear vesicles can also contribute to increased signal intensity.</td>
</tr>
<tr>
<td>Angioblastic meningiomas</td>
<td>Angioblastic meningiomas are highly cellular and vascular tumors with a spongy appearance. Increased signal in T2-weighted pulse sequence of these tumors is due to high cellularity with increase in water content of tumor.</td>
</tr>
</tbody>
</table>
Figure 17. MRI T1 precontrast A,B and postcontrast C,D,E, and MRI T2 image F, showing two syncytial meningiomas in the same patient, notice the CSF cleft A,F, the cystic changes (both intratumoural and intraparenchymal) A,D, the intense postcontrast enhancement, D,E,F, the meningeal tail D,E. Also notice that the tumour is slightly hyperintense on the MRI T2 image F. There is also compression and displacement of the 4th ventricle.

Figure 18. The psammomatous meningioma is hypointense on the T2 images.
Thus based on the correlation between histology and MR imaging appearance of meningiomas, it has been concluded that meningiomas significantly hyperintense to cortex tend to be primarily of syncytial or angioblastic type, whereas meningiomas hypointense to cortex tend to be primarily of fibrous or transitional type. Heterogeneous appearance of meningiomas in T2-weighted pulse sequence can be due to tumor vascularity, calcifications, and cystic foci.

Table 5. MRI characteristics of meningiomas

<table>
<thead>
<tr>
<th>Pathological type</th>
<th>T2 MRI appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibroblastic</td>
<td>Hypointense on the T2 images because of the existence of dense collagen and fibrous tissue</td>
</tr>
<tr>
<td>Transitional</td>
<td>Hypointense on the T2 images because of the existence of densely calcified psammoma bodies</td>
</tr>
<tr>
<td>Syncytial</td>
<td>Hyperintense on the T2 images because of the existence of high cell count, microcysts or significant tissue oedema</td>
</tr>
<tr>
<td>Angioblastic</td>
<td>Same as the syncytial type. Blood vessels appear as signal void convoluted structures</td>
</tr>
</tbody>
</table>
Figure 20. MRI T1 pre, and postcontrast images showing the characteristic hypointense cleft.

Figure 21. The characteristic meningeal tail on the contrast enhanced T1 MRI images

Figure 22. The characteristic meningeal tail on the contrast enhanced T1 MRI images
Figure 23. A, Postmortem specimen, B,C MRI T1 postcontrast studies showing convexity meningioma with the characteristic meningeal tail.
Table 6. MRI CHARACTERISTICS OF MENINGIOMAS

<table>
<thead>
<tr>
<th>MRI feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular rim</td>
<td>The peripheries of meningiomas are supplied by branches from the anterior or middle cerebral arteries that encircle the tumour and form the characteristic vascular rim</td>
</tr>
<tr>
<td>Meningeal tail</td>
<td>The tail extends to a variable degree away from the meningioma site and probably represents a meningeal reaction to the tumour</td>
</tr>
<tr>
<td>Hypointense cleft</td>
<td>Hypointense cleft between the tumour and the brain that probably represents blood vessels or a CSF interface</td>
</tr>
</tbody>
</table>

Figure 24. MRI T1 postcontrast studies showing parasagittal meningioma (left two images) and retroclivus meningioma (right image), notice the characteristic meningeal tail, and the dense contrast enhancement.

Figure 25. MRI precontrast T1, proton density and T2, proton density images showing medial sphenoidal ridge syncytial meningioma, notice the vascular rim demonstrated as signal void linear structures surrounding the tumour (arrows). Also notice the surrounding edema.
Figure 26. Meningioma in a 27-year-old woman who presented with new-onset seizure. A, Axial unenhanced CT image demonstrates a large hyperdense extra-axial mass in the left temporal region with associated central calcification (black arrow) and surrounding edema. B, Axial enhanced CT demonstrates intense homogeneous enhancement. Distinction of intra- versus extra-axial mass by CT can be difficult. C, Axial T2-weighted MR image clearly demonstrates a CSF cleft around the circumference of the tumor (arrowhead) indicating this to be an extra-axial mass. D, Sagittal postcontrast T1-weighted image demonstrates a dural tail anteriorly and posteriorly along the tentorium (white arrows).

Figure 27. Cystic meningioma. A, Axial postcontrast T1-weighted image reveals a cystic mass lesion involving the left frontal lobe with peripheral enhancement, as well as enhancement around a trapped CSF intensity collection laterally (white arrow). B, Axial postcontrast T1-weighted image near vertex of the head demonstrates the extra-axial nature of the mass with associated dural attachment (white arrow).
UNUSUAL LOCATIONS OF MENINGIOMA

- **Cerebellopontine Angle Meningioma**

  The meningioma is the second most common mass lesion of the cerebellopontine angle, with 13%–18% of all neoplastic lesions in this location being meningioma. Less than 5% of all intracranial meningiomas occur in the cerebellopontine angle. The acoustic schwannoma, from which meningiomas must be distinguished, is by far the most common tumor in this region. Meningiomas, however, tend to be larger, more hemispheric in shape rather than spherical, and more homogeneously enhancing. Meningiomas may be associated with hyperostosis. They do not have a propensity to involve the internal auditory canal (which is a fairly constant feature of schwannomas).

- **Orbital Meningioma (optic sheath meningioma)**

  Orbital meningiomas account for less than 2% of cranial meningiomas but constitute 10% of all intraorbital neoplasms. Most of these tumors arise from the optic nerve sheath between the globe and the optic canal. They may produce diffuse thickening of the optic nerve, a well-defined and rounded mass, or even an eccentric lesion with an irregular border. Calcification along the optic nerve sheath is highly suggestive of meningioma.

- **Multiple Meningiomas**

  In one series, CT demonstrated multiple tumors in about 9% of patients with intracranial meningioma. This approaches the 16% frequency of multiplicity found in an autopsy series. As with solitary examples, multiple meningiomas are more commonly seen in women. Although multiple meningiomas are associated with neurofibromatosis type 2 ("central" neurofibromatosis), the majority of patients do not have other characteristic features such as multiple schwannomas. Further research with genetic testing is required to determine whether multiple meningiomas are inherited without neurofibromatosis type 2. Secondary spread of tumor via the subarachnoid space is a less well-accepted explanation for multiple meningiomas.

- **En Plaque Meningioma**

  En plaque meningiomas cloak the inner table of the skull, where they may infiltrate both the dura mater and underlying bone. On CT scans, especially those obtained without contrast material, it may be difficult to distinguish the tumor itself from the associated hyperostosis. The extent of radiographic hyperostosis has little relation to the degree or presence of bone invasion and may occur secondary to local hypervascularity. Peritumoral edema is less common with en plaque tumors. MR images obtained with gadolinium enhancement enable this type of meningioma to be easily distinguished from the associated bone changes.
Intraventricular Meningioma

Intraventricular meningiomas arise from the tela choroidea or the stroma of the choroid plexus itself. Approximately 80% arise in the lateral ventricles with a preference for the left trigone, 15% occur in the third ventricle, and about 5% within the fourth ventricle. Overall, intraventricular meningiomas account for approximately 2%-5% of intracranial meningiomas. Meningioma is the most common trigonal intraventricular mass in an adult.

Ectopic Meningioma

Less than 1% of meningiomas develop extradurally (this is exclusive of tumors that secondarily spread from intracranial sites).

These ectopic meningiomas may arise within the intradiploic space, from the outer table of the skull, in the overlying skin, inside the paranasal sinuses, in the parotid gland, and from the parapharyngeal space. Theories to explain these sites of origin include derivation from the arachnoid around the cranial nerve sheaths or from arachnoid cells disseminated during the formation of the skull (ie, ectopic inclusions). Destruction of the skull base with secondary intracranial extension is seen in over one-third of nasopharyngeal and paranasal sinus meningiomas. Meningiomas have also rarely been discovered in locations far removed from the neuraxis including the mediastinum, lung, and adrenal glands. Possible explanations include ectopic arachnoid cells and meningothelial differentiation from pluripotential mesenchymal cells.
Figure 29. Intradiploic meningioma. (A) Radiograph of a 34-year-old black man, who complained of a bump on his head and orbital pressure, reveals a central radiolucent lesion with partial loss of the outer table of the skull (arrows) and with extension into the frontal sinus. The tumor arose within bone but had extended through the dura mater and involved the frontal sinus. (B) Lateral image from an external carotid arteriogram of a 20-year old man with mild frontal headaches reveals marked hyperostosis of the frontal bone and anterior aspect of the parietal bone. There is marked widening of the diploic space with perpendicular spiculation (arrowhead). Radiolucent areas proved at microscopic examination to be medullary spaces of lamellar bone, filled with tumor cells, fibrous tissue, and a few osteoclasts. (C) CT scan of a 69-year old white man, who complained of a bump on his head for the past 10 years, demonstrates an osteoblastic area within the right parietal bone with mild expansion of the diploic space. A completely intraosseous meningioma with marked hyperostotic reaction was confirmed pathologically.
Figure 30. (A) Ethmoid meningioma. Contrast-enhanced CT scan of a 20-year-old black man with a 1-year history of decreased visual acuity and proptosis of the right eye demonstrates an enhancing paranasal sinus mass with infiltration and destruction of the ethmoid air cells. There is extension through the right medial orbital wall. The radiologic findings are nonspecific, and other neoplastic or inflammatory conditions might have a similar appearance. (B) Sphenoid and nasopharyngeal meningioma. Unenhanced CT scan obtained with bone windows of a 77-year-old white man with spontaneous epistaxis demonstrates a smooth lobulated and partially calcified mass within both sphenoid sinus compartments. No bone destruction and no intracranial component were found. Parapharyngeal meningioma. Axial (C) and coronal (D) contrast-enhanced CT scans of a young girl with a hearing loss in the left ear reveal a large tumor that involves the left nasopharyngeal space, infratemporal fossa, and pterygoid fossa. The tumor also extends intracranially through the sphenoid bone. Note the bone remodeling and hyperostosis of the maxillary sinus wall (arrows in C). At surgery, tumor was discovered in the left maxillary sinus, ethmoid air cells, and orbit.
ATYPICAL IMAGING FEATURES OF MENINGIOMA

In general, the various imaging features of meningiomas may not accurately reflect the specific histologic subtypes of this common neoplasm, and the biologic and clinical behavior of meningiomas does not always correlate with the different histologic variants. Therefore, from an imaging standpoint, it is important to recognize the variable and pleomorphic features exhibited by these neoplasms, so that an unusual appearing meningioma is not confused with other intracranial masses.

- **Cystic Meningioma**

The term cystic meningioma has been used to describe two different morphologies: intratumoral cavities and extratumoral or arachnoid cysts. Therefore, the cysts can be located within the tumor mass, either centrally or eccentrically; outside and adjacent to the edge of the tumor; and, occasionally, inside the adjacent brain parenchyma. True intratumoral cystic meningiomas, with large dominant fluid-filled cysts, are an uncommon variant. Benign meningiomas with heterogeneous enhancement that contain small nonenhancing areas of cystic change or necrosis occur much more frequently (up to 8%-23% of cases). A large cystic meningioma may have an atypical clinical presentation, in that they are more common in male and pediatric patients; these unusual clinical features often contribute to a misdiagnosis of a cystic or necrotic glioma.

**Figure 31.** Cystic meningioma. (a) Contrast-enhanced CT scan of a 72-year-old woman with headaches shows a right frontal meningioma and a large extratumoral cyst. Aside from the fluid-filled area, the lesion has characteristics of a meningioma: hemispheric, dural-based mass with prominent enhancement. (b) Contrast-enhanced CT scan of another patient shows similar findings. However, there is faint enhancement of the cyst rim (arrows), which may be either a meningeal reaction or neoplastic tissue.

Various explanations for cyst formation have been offered, including that intratumoral cysts are due to tumor necrosis or degeneration. A peripheral cyst, on the other hand, may
represent either peripheral degeneration or an arachnoid cyst. Although the imaging
differentiation between a peripheral (neoplastic) intratumoral cyst and an extratumoral
(reactive) arachnoid cyst may be suggested when ring enhancement is seen surrounding the
fluid collection, histologic analysis, demonstrating neoplastic cells in the cyst wall, may be
required for confirmation. In addition, cysts may result from direct secretion of fluid by
tumor cells, from absorption of internal hemorrhage, or from loculated cerebrospinal fluid
in tissues within or adjacent to the meningioma 51.

Figure 32. Cystic
meningioma. Axial
contrast-enhanced CT (A),
axial enhanced MR (B),
coronar enhanced MR (C),
and coronal enhanced CT
images of a 45-year-old
man demonstrate a
meningioma with what
appears to be an
extratumoral cyst (*) in a).
However, the curvilinear
enhancement (arrowhead) is
suspicious for neoplastic
involvement of the cyst
wall. Note the “dural tail”
sign (arrow in b),
suggestive of an extraaxial
mass such as meningioma.

- **Lipoblastic Meningioma**

Lipoblastic meningiomas represent a variant in which there is a metaplastic change
of meningotheial cells into adipocytes, through the accumulation of fat (mostly triglycerides)
within their cytoplasm 52. The evidence against the lipoblastic meningioma representing
either a true intracranial lipoma or a “collision” tumor (between fat and a meningioma)
lies in the recognition of a spectrum of cells, ranging from typical meningotheial cells,
through those containing various amounts of intracellular lipid, to cells that have been transformed into adipocytes 52. The lipoblastic meningioma may have an imaging
appearance of a fatty tumor, with low negative attenuation on CT scans and a short T1 relaxation time with high signal intensity on T1-weighted MR images. Xanthomatous change in meningioma can be differentiated histologically from the lipoblastic variant; however, since both contain excess lipid, the radiologic distinction may be difficult. However, the lipoblastic meningioma may be suggested when the fatty regions are larger, are more confluent, and do not have prominent enhancement.

Figure 33. Lipoblastic meningioma. (A) Contrast-enhanced CT scan of a 60-year-old white woman with a 2-week history of seeing flashing lights and difficulty in reading shows a well-circumscribed low-attenuation lesion. The rim of the lesion is enhanced, and faint intratumoral strands of enhancing tissue are seen. Sagittal T1-weighted (B) and axial T2-weighted (C) MR images demonstrate a signal intensity within the lesion that is similar to that of subcutaneous fat. (D) Gross specimen shows a well-circumscribed mass and the yellowish color of fatty metaplasia.
Figure 34. Lipoblastic meningioma. (A) Contrast-enhanced CT scan of a 36-year-old white woman with progressive gait difficulty demonstrates a left frontoparietal mass with an extremely low-attenuation (compatible with fat) center and a thick enhancing rind. Note the small mound of hyperostosis (*) underlying the central enhancing nodule of meningioma (arrow). (B) Right external carotid arteriogram shows enlargement of the middle meningeal artery that supplies the tumor. The spoke-wheel pattern of the fine radial arterioles is characteristic of meningioma. The ‘‘dimple’’ in the center of the neovascularity (arrow) corresponds to the mound of bone seen in a. (C) Photograph of the cut specimen shows the attachment of the tumor to the dura mater (arrows) and the yellow-white color typical of lipoblastic meningioma.

- **Meningeal Hemangiopericytoma**

Hemangiopericytoma of the meninges is an aggressive, highly vascular neoplasm that is commonly grouped with “angioblastic” or “malignant” meningiomas. However, hemangiopericytoma of the meninges is a distinct nosologic entity arising from the vascular pericytes rather than from meningothelial cells; thus, it is not a true meningioma at all. These tumors generally recur more frequently and earlier than meningiomas, and they have a greater propensity to develop distant metastases. The following features are suggestive (but not pathognomonic) of a meningeal hemangiopericytoma: a multilobulated contour, a narrow dural base or ‘‘mushroom’’ shape, large intratumoral vascular signal voids on MR images, multiple irregular feeding vessels on angiograms, and bone erosion rather than hyperostosis. It has also been reported that prominent peritumoral edema and increased signal on T2-weighted MR images are more common in the syncytial and angioblastic meningiomas (a category that includes hemangiopericytoma) than in other types.
• **Peritumoral Edema**

Vasogenic edema within the white matter of the brain is a common feature of intraaxial masses like glioma, metastatic disease, and abscess. However, mild to moderate intraaxial vasogenic edema is also seen around meningiomas (which are extraaxial masses) in up to 75% of cases. The finding of edema can be problematic, since its presence may be incorrectly suggestive of an intraaxial lesion (eg, glioma). This problem is compounded when the meningioma is small and the surrounding edema is extensive.

The cause of intraaxial peritumoral vasogenic edema associated with meningiomas is controversial. Some theories implicate active fluid production (secretion or excretion) by the tumor, with “flow” through the thinned contiguous cortex. Others have suggested that the tumor injures the brain mechanically (by means of direct compression) or ischemically (from parasitization of the cortical arteries, compression of the cortical veins, or frank involvement of the dural sinuses). Most likely, the edema is caused by a combination of different mechanisms. Reports about the importance of these factors have been conflicting. However, recent studies have found poor correlation between peritumoral edema and either the vascular supply of a meningioma or the presence of dural sinus invasion. Whatever the mechanisms, the degree of peritumoral edema in meningiomas has little correlation with tumor size.

• **Ring Enhancement**

As mentioned, meningiomas are usually fairly homogeneous masses, with homogeneous enhancement. However, they may have an atypical ringed appearance rather than occur as a solid mass. This unusual feature can be seen in both histologically typical meningiomas and in some malignant or aggressive histologic variants that may have cyst formation, hemorrhage, or necrosis. The peripheral enhancement represents the normal pattern for viable meningeal neoplasms, and the center is an avascular or necrotic region. The causes for the central nonenhancing zone vary and include bland tumor infarction, necrosis in aggressive histologic variants, and true cyst formation from benign fluid accumulation. A convexity meningioma with ring enhancement may easily be confused with a necrotic or cystic glioma, a metastasis, or even an abscess. If such a meningioma arises from the falx cerebri, bilateral growth can even mimic a “butterfly” glioma, which is usually a glioblastoma multiforme (grade 4 astrocytoma).
Figures 35. Ring enhancement with cystic changes. Unenhanced (A) and enhanced (B) CT scans of a 4-month-old infant with increasing head circumference show a large mass in the posterior fossa with internal calcification (arrow in a) and a low-attenuation center with a high-attenuation rim. The center of the mass does not enhance uniformly, compatible with cystic change. There is anterior displacement of the fourth ventricle (arrowhead in a) and associated hydrocephalus. In this age group, a necrotic medulloblastoma or cystic astrocytoma could be considered in the differential diagnosis. Ring enhancement with necrosis. (C) Contrast-enhanced CT scan of a 35-year-old white man who experienced loss of consciousness demonstrates ring enhancement in a meningioma. (D) Cut surface of the gross specimen illustrates the central necrosis in this histologically typical meningioma.
Figure 36. Hemangiopericytoma of the meninges in a 73-year-old man. (A) Contrast-enhanced CT scan shows homogeneously enhancing, markedly lobulated tumor indenting the parietal lobes. (B) Gross specimen from a different patient exhibits the characteristic lobulated tumor surface.

Figure 37. “Butterfly” meningioma. Contrast-enhanced CT scan (A) and enhanced MR image (B) demonstrate a falx meningioma with bilateral extension and central cavitation from necrosis in a 73-year-old white woman. This appearance is similar to that of a ‘butterfly’ glioblastoma multiforme. An unusual feature that can be seen in both histologically typical meningiomas and in some malignant and aggressive histologic variants that may have cyst formation, hemorrhage, or necrosis. The peripheral enhancement represents the normal pattern for viable meningeal neoplasms, and the center is an avascular or necrotic region. The causes for the central non-enhancing zone vary and include bland tumor infarction, necrosis in aggressive histologic variants, and true cyst formation from benign fluid accumulation. A convexity meningioma with ring enhancement may easily be confused with a necrotic or cystic glioma, a metastasis, or even an abscess. If such a meningioma arises from the falx cerebri, bilateral growth can even mimic a “butterfly” glioma, which is usually a glioblastoma multiforme (grade 4 astrocytoma).
MIMICS OF MENINGIOMA

Many atypical gross and imaging features of meningiomas have been presented here. It should also be recognized that other extraaxial soft-tissue lesions as well as some superficial intraaxial tumors may also exhibit a broad contact with the dural surface and homogeneous contrast enhancement thereby mimicking meningioma. For example, hematologic neoplasms such as leukemia or secondary involvement of the central nervous system by Hodgkin lymphoma, which is a late manifestation of the disease, will typically involve the extraaxial spaces rather than the brain parenchyma. Such cases may be difficult to differentiate from meningiomas. Other dural-based masses that may imitate meningioma include dural and calvarial metastases from breast cancer and metastatic neuroblastoma.

SPINAL MENINGIOMA

Spinal meningiomas are unique in that there is a 4:1 female-to-male predominance, and most patients are older than 40 years of age. Eighty percent of the lesions can be found in the thoracic spine, although some are located at the upper cervical or lumbar regions. They often are located anterolaterally or posterolaterally in the canal, and they are the most common tumor of the foramen magnum, where they are frequently located anteriorly or
laterally. Meningiomas are rarely both intradural and extradural (6%), or purely extradural (7%).

Meningiomas are the second most common tumor in the intradural extramedullary location, second only to tumors of the nerve sheath. Meningiomas account for approximately 25% of all spinal tumors. Approximately 80% of spinal meningiomas are located in the thoracic spine, followed by cervical spine (15%), lumbar spine (3%), and the foramen magnum (2%). Most intradural spinal tumors are benign and potentially resectable. The prognosis after surgical resection is excellent.

Spinal meningiomas are often located laterally or dorsolaterally in the thoracic spine. Meningiomas of the cervical and foramen magnum tend to be located ventral to the spinal cord. They are believed to arise from the arachnoid cluster cells located at the entry zone of the nerve roots or at the junction of dentate ligaments and dura mater, where the spinal arteries penetrate. For this reason, lateral tumors are more common than dorsal and ventral lesions. Most meningiomas are intradural and extramedullary. Occasionally, they can be purely extradural (7%) or intradural and extradural (6%).

Compression of the cord by the meningioma can cause deterioration of neurologic function. Improvement of neurologic findings can be expected after resection of the tumor. Spinal meningiomas differ from intracranial meningiomas by their slightly greater proclivity for psammomatous change. In general, histopathologic features of spinal meningiomas are similar to their intracranial counterparts. Meningotheliomatous and transitional features are most common in spinal lesions. Spinal meningiomas are typically globoid, and they vary in consistency depending on the extent of calcification. Multiple meningiomas are rare (2%) and most often associated with neurofibromatosis type II.

- **Frequency**

In the US: Intradural spinal tumors can be classified as intramedullary or extramedullary. The incidence of intradural spinal tumors is approximately 3-10 cases per 100,000 population. In children, 50% of intradural lesions are extramedullary, and 50% are intramedullary, whereas in adults, 70% are extramedullary, and 30% are intramedullary.

- **Mortality/Morbidity**

Meningiomas and schwannomas and/or neurofibromas are the most common intradural extramedullary spinal tumors. These benign lesions usually produce an insidious onset of clinical symptoms, which are characterized by myelopathy and radiculopathy, respectively. As tumors grow, the symptom complex may merge, and significant neurologic deficits, including paraplegia, may develop.

Resection of spinal meningiomas can result in excellent recovery, even in patients with notable preoperative deficits. The surgical morbidity rate is low because surgical resection of a meningioma can easily be accomplished by means of simple laminectomy. The recurrence rate is substantially lower than that seen in an intracranial lesion. This
observation may be secondary to the greater resectability of spinal meningiomas compared with intracranial lesions. Factors associated with poor outcome include calcified tumors, ventrally located lesions, age (ie, elderly patients), duration and severity of symptoms, subtotal resection, and an extradural component to the tumor.

- **Sex**

  Meningiomas most frequently affect women, with a 4:1 female-to-male ratio. Spinal meningiomas are typically seen in women older than 40 years. Most spinal meningiomas in women occur in the thoracic spine. Although meningiomas of the spine occur in males, they do so throughout the spinal canal without a predilection for the thoracic spine.

- **Age**

  Meningiomas are typically seen in women in the fifth and sixth decades. Approximately 3-6% of spinal meningiomas occur in children. Spinal meningiomas in children usually are associated with neurofibromatosis.

- **Anatomy**

  Spinal meningiomas often are located laterally or dorsolaterally in the spinal canal. They are believed to arise from the arachnoid cluster cells, and therefore, they are located at the entry zone of the nerve roots or the junction of the dentate ligaments and dura mater. Most meningiomas are intradural and extramedullary in location. The spinal cord is typically compressed and displaced away from the lesion. The subarachnoid space above and below the mass lesion is widened, with cerebrospinal fluid capping the lesion from above and below. On occasion, they can be purely extradural (7%) or intradural and extradural (6%).

- **Clinical Details**

  Symptoms produced by meningiomas are secondary to their broad dural attachment and the gradual growth of the tumor with compression of the cord. The clinical course may be insidious, and symptoms are often confused with symptoms of other lesions of the spine, peripheral nervous system, and thorax. The duration of symptoms may span 6-23 months. Because meningiomas do not arise from nerve root sheaths, as do schwannomas, they typically result in myelopathic rather than radiculopathic findings.

  On physical examination, sensory and motor deficits are seen almost equally. A high incidence of Brown-Sequard syndrome is seen, with ipsilateral paralysis, decreased tactile and deep sensation, and a contralateral deficit in pain and temperature sensation. This finding is most likely secondary to the high incidence of laterally positioned meningiomas. With substantial growth of the tumors, clinical findings may merge. Patients most frequently complain of regional back pain, especially at night, followed by sensorimotor changes and, eventually, bowel and bladder dysfunction.
Pathological details

Macroscopically, most meningiomas are globose and expand centripetally inside the dural sac. A few have an en plaque configuration, and a small fraction assume a dumbbell-shaped profile, growing centrifugally into the epidural space; multiple spinal meningiomas also have been reported. The histology is similar to their cranial counterparts in that they have a wide range of histopathologic appearances. Of the various subtypes, cyncytial, fibrous, and transitional meningiomas are the most common; however the psammomatous type seems to be the most frequent histologic variety of spinal meningiomas.

Figure 39. A, spinal meningioma, B, Intraoperative photograph obtained using the operative microscope demonstrating the intradural extamedullary meningioma attached to the lateral dura surface and severely compressing the spinal cord.
CT scans obtained without the intravenous injection of contrast material occasionally demonstrate a hyperattenuating lesion resulting from psammomatous calcification or dense tumor tissue. CT scans obtained with the intravenous injection of contrast material may show a homogeneous enhancing tumor.

Myelography or CT myelography is required to demonstrate the intradural extramedullary location of the mass.

The spinal cord is displaced away from the lesion and usually compressed. A sharp meniscus is seen where the contrast agent caps the lesion from above and below. The subarachnoid space on the side of the lesion is widened. On CT, the degree of confidence is moderate.

MR imaging

MRI demonstrates the intradural extramedullary location of meningiomas. Lesions are usually isointense to spinal cord on both T1-weighted and T2-weighted images. Lesions are sometimes hypointense on T1-weighted images and hyperintense on T2-weighted images. Homogeneous intense enhancement of the lesion is seen after an intravenous injection of gadolinium-based contrast agent.

Most spinal meningiomas demonstrate broad-based dural attachment. On occasion, a densely calcified meningioma may demonstrate hypointensity on both T1-weighted and T2-weighted images. The spinal cord is displaced away from the lesion and usually compressed. The subarachnoid space above and below the lesion is widened, and a meniscus capping the lesion may be seen. On MRI, the degree of confidence is high.

- False Positives/Negatives

A meningioma with intradural and extradural components occasionally mimic a nerve sheath tumor, or a nerve sheath tumor with a predominant intradural component may mimic a meningioma. However, nerve sheath tumors usually have hyperintensity on T2-weighted images, whereas meningiomas usually are isointense to the spinal cord on T2-weighted images. Most meningiomas are lateral or dorsal, whereas most nerve sheath tumors are ventral. Furthermore, a mass lesion with both intradural and extradural components is most likely to be a nerve sheath tumor.
Figure 40. Sagittal T1-weighted (A) and T2-weighted (B) MR images of the dorsal spine showing an isodense intradural extramedullary transitional meningioma compressing the spinal cord. A hemangioma in the adjacent vertebra also can be observed in B.

Figure 41. MRI T1 images precontrast (A) and postcontrast (B,C) showing a dorsal syncytial meningioma, notice the T1 hypointensity (A), the dense contrast enhancement and the dural tail (B,C)
Figure 42. MRI T1 images (A, precontrast and B, postcontrast) and T2 image (c) showing a high cervical syncytial meningioma, notice the precontrast T1 slight hypointensity, the dense contrast enhancement, the cavity caudal to the tumour (A) and the T2 hyperintensity (C). Also notice the CSF cleft that separate the tumour from the spinal cord (A)

Figure 43. A, Sagittal contrast-enhanced T1-weighted MR image of the cervical spine. Multiple extramedullary enhancing dural-based tumors (meningiomas) are seen at the C2 and C7-T1 levels (black solid arrows). The tumor at the C7-T1 level results in cord compression. In addition, an enhancing intramedullary tumor (white solid arrows) at the
T3-T4 level causes focal cord engorgement. An associated syrinx (open arrow) is seen in a small segment of the cord proximal to this tumor. The patient had neurofibromatosis type 2. B,C Lumbar meningioma

CONCLUSION

Meningioma is the most common nonglial primary neoplasm of the central nervous system. The diagnosis of meningioma is relatively uncomplicated when the tumor is in a typical location and has characteristic radiologic findings. However, it must be remembered that meningiomas may occur in unusual locations and with misleading or atypical imaging features.

References


44. Lusin JO, Nakagawa H. Multiple meningiomas evaluated by computed tomography. Neurosurgery 1981; 9:137-141.


The author: Professor Yasser Metwally

Professor of neurology, Ain Shams university, Cairo, Egypt

www.yassermetwally.com
INTRODUCTION & PATHOLOGY

Originally termed chromophobe adenomas, endocrine-inactive pituitary tumors were once considered the largest group of pituitary tumors. With advances in endocrinologic testing and modern immunohistochemical and immunoelectron microscope techniques, the incidence of adenomas with no evidence of hypersecretion or endocrine activity has decreased to about 25 per cent of pituitary adenomas. Histologically, these adenomas have secretory granules and immunocytochemically are growth hormone or prolactin-positive, despite no associated clinical changes or abnormal serum hormone levels about 5 per cent of the time. Inactive tumors have cells with no histologic, immunocytologic, or electron microscopic markers (Null cells). They are chromophobic and electron microscopy show
them to have poorly developed cytoplasm, indented nuclei, and sparse granules (100 to 250 microm) lined up along the cell membrane.

Figure 1. Nonfunctioning pituitary adenomas with suprasellar extension

It is the functionally active group of pituitary tumors that comprise the largest percentage of pituitary adenomas. They represent about 75 per cent of all pituitary tumors. Preoperative endocrinologic testing, as well as clinical symptomatology resulting from the adenoma's hypersecretion of hormones, helps to identify and classify these tumors. It is this functional classification confirmed with immunohistochemical and immunoelectromicroscopic techniques and not traditional light microscopic pathology that separates these tumors.
Figure 2. A, Pituitary Adenoma, the tumor is composed of cylindrical cells with a distinct perivascular arrangement. The similarity with a perivascular pseudorosette is quite apparent. This tumor can be easily confused with an ependymoma. B, Pituitary adenoma that has been immunostained with an antibody directed against corticotrophin.

**Prolactinomas** represent about 40 to 50 per cent of all patients with pituitary adenomas. Under light microscopy, prolactin cell tumors are chromophobic or acidophilic. Using immunoelectron microscopy, they may be classified as densely or sparsely granular, although the former type is quite rare. The densely granular resemble nontumor lactotrophic pituitary cells that are resting and nonsecreting. The sparsely granular type resemble the nontumor lactotrophic pituitary cells that are actively secreting. Their secretory granules are sparse, spherical, and measure 150 to 350 nm.

**Somototrophic adenomas**, resulting in **acromegaly**, account for 15 to 25 per cent of pituitary adenomas. Under light microscopy, these tumors may be termed acidophilic or chromophobic. Using immunoelectron microscopy, two distinct cell types can be identified: densely and sparsely granulated adenomas. The densely granulated cell type more closely resembles nontumor pituitary somotrophic cells and is characterized by well-developed endoplasmic reticulum, permanent Golgi complexes, and numerous spherical densely staining secretory granules. The sparsely granulated type differ from nontumorous pituitary somotrophic cells in that it has permanent Golgi complexes, irregular nuclei, few spherical secretory granules, and several centrioles.

Cushing's disease or Nelson's syndrome caused by corticotropin-secreting adenomas represent only about 5 per cent of all pituitary adenomas. Under light microscopy, corticotrophs are basophilic. Immunelectron microscopy shows these tumor cells to be similar to corticotrophic nontumorous pituitary cell types containing numerous spherical secreting granules that vary in density, measure 250 to 700 nm, and line up along the cell membranes.

The rarest of pituitary adenomas are those that secrete solely thyrotrophin or gonadotropin. Each type accounts for less than 1 per cent of pituitary adenomas. Under light microscopy, the thyrotropic adenomas are chromophobic and under electron microscopy, they have long cytoplasmic processes, sparse, spherical secreting granules (150 to 250 nm), and abundant endoplasmic reticulum.

<table>
<thead>
<tr>
<th>Adenoma type</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-functioning adenoma</td>
<td>25%</td>
</tr>
<tr>
<td><strong>Prolactinomas</strong></td>
<td>40%-50%</td>
</tr>
<tr>
<td>Acidophile adenomas (growth hormone)</td>
<td>15%-25%</td>
</tr>
<tr>
<td>ACTH secreting adenomas</td>
<td>5%</td>
</tr>
<tr>
<td>Others</td>
<td>&lt; 1%</td>
</tr>
</tbody>
</table>
Pituitary macroadenomas are, by definition, at least 10 mm in size or more, while microadenomas are less than 10 mm in size.

Patients with functional adenomas present with endocrine symptoms and, consequently, smaller lesions (microadenomas). It is therefore more typical for macroadenomas to cause symptoms related to compression of adjacent structures. Optic nerve and tract compression causes visual symptoms, including the classic presentation of bitemporal hemianopsia. If there is compression of the ventricular system or foramen of Monro, the patient presents with signs and symptoms of hydrocephalus.

Macroadenomas almost always cause sellar enlargement, which, however, is often also seen with other sellar masses. Sellar wall erosion, with infrasellar extension into the sphenoidal sinus, is more often a feature of macroadenomas than other tumors. The presence of necrosis, hemorrhage is common. Intratumoral hemorrhage occurs in 20% to 30% of patients with adenomas. Macroadenomas are more prone to hemorrhage as are tumors in patients who have been receiving bromocriptine therapy. Intratumoral hemorrhage can occur without clinical evidence of pituitary apoplexy.

Figure 3. Sagittal view of the brain in a patient with acromegaly. Notice the very large tumor that had grown above the sella turcica and had extended into the third ventricle. Notice the presence of hemorrhage within the tumor. This is what is known as "pituitary apoplexia" a devastating neurological catastrophe with the onset of sudden blindness and frequently resulting in death.

### GRADING OF PITUITARY ADENOMA

<table>
<thead>
<tr>
<th>GRADE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRADE I</td>
<td>Tumours have a diameter of less than 10 mm, and confined entirely within the sella. The sella might be focally expanded but remains intact [microadenoma].</td>
</tr>
<tr>
<td>GRADE II</td>
<td>The tumours have a diameter of 10 mm or more, the sella is enlarged, however the the sellar floor is not perforated by the tumours.</td>
</tr>
<tr>
<td>GRADE III</td>
<td>The tumours focally perforate the dural membrane and cortical bone of the anterior wall of the sellar floor and Extent into the sphenoid sinus.</td>
</tr>
<tr>
<td>GRADE VI</td>
<td>The tumours diffusely perforate the dural membrane and the cortical bone of anterior wall of the sellar floor and extent into the sphenoid sinus.</td>
</tr>
</tbody>
</table>
NORMAL ANATOMY OF THE PITUITARY GLAND

The pituitary gland lies within the sella turcica between the cavernous sinuses. Its density is similar to that of the sinuses and dura so that, with the possible exception of its upper surface, which is to a variable degree outlined by the chiasmatic cistern but partly covered by the pituitary diaphragm, the precise limits of the gland cannot be distinguished from the adjacent tissues on either plain or contrast-enhanced studies.

The shape and height of the pituitary gland is best assessed on the coronal views. The height should be less than 8 mm. The top of the gland should be flat or concave, and there should not be an upward convexity contour. The normal pituitary appears slightly hyperdense on the plain scan, and there is homogeneous contrast enhancement.

Figure 4. Normal appearance of the pituitary gland, notice the upper concave border, the diffuse enhancement of the pituitary gland and the well corticated sellar floor.

PITUITARY MICROADENOMA

These tumors may be 3 to 10 mm in size and may be located within a normal-sized sella turcica. They may cause symptoms of hormonal hypersecretion. These are most commonly caused by prolactin or growth hormone abnormalities, less commonly by adrenocorticotrophic hormone disturbances. The elevated pituitary hormone content may be caused by conditions other than pituitary neoplasms; therefore, sensitive neuroimaging studies are necessary to document the presence or absence of pituitary microadenomas.

Because of the small size of pituitary microadenomas, the measured sella volume may be within normal limits; however, even with normal size of the sella, the sellar shape and bone detail almost always show some detectable radiographic abnormalities. This may not always be detected by routine skull radiographs (or even utilizing coned-down views of the sella turcica), and these abnormalities may most sensitively be assessed by CT scan with a bone windows.
The most characteristic radiographic abnormal finding of pituitary microadenomas is an anterior-inferior bulge in the sella floor. This is most commonly seen in the lateral wall of the sella, correlating with the previously reported propensity of prolactin-secreting microadenomas located in the lateral portion of the pituitary gland. It has been reported that computerized tomography shows sella turcica bone abnormalities in 96 per cent of pituitary microadenomas. However, it is also important for the clinician to understand the pattern of normal variations in the development of sella turcica and the contiguous sphenoid bone. This understanding may avoid interpretative errors in assessing pituitary radiographic changes as being caused by tumor when these changes may actually be due to normal anatomic variants.

The CT findings that are suggestive of a pituitary microadenoma include (1) height that exceeds 8 mm with an upward bulging or a convexity to the superior surface of the gland, (2) focal hypodense lesion seen within the hyperdense gland (especially after contrast enhancement due to delayed enhancement of the microadenoma), (3) upward and lateral deviation, displacement and enlargement of the pituitary stalk or infundibulum.
If the infundibulum (as seen on the axial section) is larger than the basilar artery (located in the interpeduncular cistern) on the enhanced scan, this is considered to be abnormal, and this finding is suggestive of a pituitary mass. The upward extension and displacement of the infundibulum due to a pituitary tumor is best seen on the coronal views. The prolactin-secreting microadenomas are equally distributed between central and lateral location within the gland; whereas growth hormone and adrenocorticotrophin-secreting microadenomas are usually more central in location. After infusion of contrast material, the microadenoma enhances more slowly than the normal pituitary gland. This results in the focal hypodense appearance of the microadenoma. If the postcontrast scan is delayed, the focal hypodensity representing the microadenoma may not be seen.

Figure 7. Intrasellar microadenoma demonstrated as a well defined rounded hypodense mass due to delayed enhancement of the adenoma compared with the normal pituitary tissues (right postcontrast CT scan, left postcontrast T1 MRI image)

Utilizing high-resolution computed tomography, it is possible to detect pituitary microadenomas in most cases. A complete CT scan study must include direct coronal sections that are 1.5 to 2.0 mm in thickness. However, reformatted reconstructions (which are based upon the axial views and are then generated into the coronal and sagittal planes by computer analysis) may be utilized.

MRI is more sensitive than CT scan in detecting pituitary microadenomas. It is best demonstrated on the postcontrast T1 images as a rounded hypointensity that shows significant delay in enhancement compared with the normal pituitary gland tissues.
Characteristic plain x ray, CT & MRI findings of pituitary microadenomas

- The most characteristic radiographic abnormal finding of pituitary microadenomas is an anterior-inferior bulge in the sella floor.
- Height that exceeds 8 mm with an upward bulging or a convexity to the superior surface of the gland.
- Focal hypodense lesion seen within the hyperdense gland especially after contrast enhancement due to delayed enhancement of the microadenoma.
- Upward and lateral deviation displacement, and enlargement of the pituitary stalk or infundibulum.

PITUITARY MACROADENOMA

- Plain x ray & CT scan imaging of pituitary macroadenoma

The CT findings in pituitary macroadenomas are dependent upon several factors. These include size of tumor, major vector of expansion, and tumor pathologic characteristics. If the pituitary adenoma is a solid tumor, it usually appears iso- or hyperdense (noncalcified) on the noncontrast CT, and there may be dense homogeneous sharply margined contrast enhancement. Cystic adenomas appear as round hypodense lesions on the noncontrast CT scan, and there is usually a thin peripheral rim of enhancement. In rare instances, the cystic pituitary adenoma appears as a hypodense lesion without contrast enhancement. Hemorrhagic pituitary adenomas usually appear as hyperdense noncalcified lesions on the plain scan; there is dense homogeneous or peripheral rim enhancement.

Figure 8. Suprasellar pituitary macroadenoma
If the pituitary neoplasm, as demonstrated by CT scan contains necrotic liquefied tissue rather than solid hematoma, the plain scan may show a more mottled hypodense central region with a peripheral rim of enhancement. Invasive adenomas may appear as irregularly marginated hyperdense lesions; they may show heterogeneous enhancement. They are diffuse, widespread, and poorly marginated lesions; they also show marked bone erosion. The presence of intrasellar calcification should suggest an alternative diagnosis such as craniopharyngiomas, meningiomas, aneurysms; however, in rare instances, pituitary adenomas show evidence of calcification.

Figure 9. Suprasellar pituitary macroadenomaS

Figure 10. Invasive pituitary adenoma causing marked erosion of the sellar floor with double flooring and suprasellar extension
Because pituitary adenomas usually originate within the sella turcica, CT shows an enhancing round mass. There is usually no surrounding suprasellar cistern may be seen on axial sections.

Figure 11. Pituitary macroadenoma causing unilateral depression of the sellar floor, this commonly causes double flooring when viewed by plain x ray

However, these tumors are more clearly defined on coronal and sagittal sections. The superior (extending to the intraventricular foramina and anterior third ventricle) and inferior (into the sphenoid sinus) extension of the mass is best demonstrated with coronal CT. The sphenoid sinus is located directly underneath the floor of the sella. Tumor extension into the air-filled sinus and evidence of bone erosion of the sella floor is well visualized on coronal CT. Lateral extension of the pituitary adenoma may be demonstrated by displacement of the carotid arteries, which are paired structures located in the anterolateral portion of the suprasellar cistern.
The cavernous sinuses in the parasellar region appear as paired symmetrical vertically oriented densely enhancing parasellar bands. With lateral extensions of the adenoma, the cavernous sinus appears as a broad band that is thicker ipsilateral to the tumor. The asymmetry or lateral deviation of the broad band of cavernous sinus enhancement is consistent with lateral extension of the intrasellar mass. Anterior extension of adenomas is demonstrated by the presence of an enhancing mass located within the anterior portion of the suprasellar cistern. With more significant anterior extension, there are enhancing lesions in the frontal region seen with surrounding hypodensities. If there is posterior extension, there is distortion and posterior displacement of the interpeduncular cistern and basilar artery. Rarely, pituitary adenomas extend to the intraventricular foramina to cause obstructive hydrocephalus; however, this finding is more common with suprasellar masses such as craniopharyngiomas.
Figure 13. Enlargement of the sella turcica with double flooring and erosion of the dorsum sellae and posterior clinoids, the plain x ray characteristics of pituitary adenomas

- MRI imaging of pituitary macroadenoma

MR imaging of pituitary lesions is preferable to CT because one avoids beam hardening artifact and can evaluate better adjacent structures, such as the optic nerves and chiasm and cavernous sinuses. If clips are placed at surgery, significant artifact is encountered on postoperative CT examinations, whereas this presents less of a problem with MR imaging.

Pituitary macroadenomas are, by definition, at least 10 mm in size. They are well visualized on T1-weighted coronal images. In this plane, they can usually be differentiated from optic chiasm pathology. Coronal imaging also avoids partial volume artifact from the sphenoid sinus and carotid arteries. The relationship of the pituitary to the cavernous sinuses can also be assessed. CT can detect destruction of the floor of the sella, whereas MR imaging cannot. MR imaging clearly demonstrates tumor invasion of the sphenoid sinus and clivus, which may be more relevant clinically.

Macroadenomas almost always cause sellar enlargement, which, however, is often also seen with other sellar masses. Sellar wall erosion is more often a feature of macroadenomas than other tumors. The presence of necrosis, hemorrhage, or both in these lesions causes the variable appearance of macroadenomas on MR imaging. Generally, macroadenomas have signal intensity similar to gray matter on T1-weighted images and increased signal intensity on T2-weighted images. Cystic changes or necrosis is seen in 5% to 18% of macroadenomas. In the presence of necrosis, there is a relative decrease in signal on T1-weighted images and increase in signal on T2-weighted images. Enhancement of adenomas generally is mild and inhomogeneous, particularly when necrosis is present. A lesion with central necrosis can be difficult to distinguish from a pituitary abscess.

Pituitary abscesses can occur in patients with a sellar mass, such as an adenoma, Rathke's cleft cyst, or craniopharyngioma. Presenting symptoms vary and may be similar to those of a macroadenoma rather than of an infectious process. In the absence of hemorrhage, signal characteristics generally are those of a cystic lesion. In typical cases, MR imaging with intravenous contrast administration demonstrates a lesion with peripheral rim
enhancement and central low intensity.\textsuperscript{15,21} This may appear similar to an adenoma with necrosis, as described earlier. If present, meningeal enhancement can assist in making the diagnosis of pituitary abscess.\textsuperscript{21}

Intratumoral hemorrhage occurs in 20\% to 30\% of patients with adenomas. Macroadenomas are more prone to hemorrhage as are tumors in patients who have been receiving bromocriptine therapy.\textsuperscript{17,22} Intratumoral hemorrhage can occur without clinical evidence of pituitary apoplexy.\textsuperscript{17} Blood products may shorten T1 relaxation times leading to high signal foci within the adenoma as well as causing variable changes to T2 images. Because of the increased T1 signal, an adenoma with hemorrhage may be mistaken for a craniopharyngioma. The presence of a fluid level in the lesion is more suggestive of hemorrhage. The use of NMR spectroscopy to differentiate between adenomas and other parasellar masses, such as meningiomas, is experimental.\textsuperscript{12,13} The distinction between meningioma and pituitary adenoma is important because of the different surgical approach (craniotomy) used in the treatment of the former.

![Image](image_url)

**Figure 14.** Pituitary macroadenoma. A 63-year-old woman imaged because of chronic headaches. The patient had no visual symptoms or endocrine abnormalities. A, Sagittal T1-weighted image demonstrates an intrasellar and suprasellar mass. There is expansion of the bony margins of the sella. The signal within the lesion is less than that of the adjacent brain but more than that of CSF. Findings are consistent with central necrosis. B, T2-weighted axial image demonstrating fluid intensity signal within the mass. Again, the signal intensity is different from that of CSF. C, There is enhancement of the periphery of the lesion after administration of gadolinium.

The extent of tumor is generally well evaluated by MR imaging. Because the medial dural reflection is not seen on MR images, however, evaluation of cavernous sinus invasion by pituitary adenomas is difficult. Invasion of the cavernous sinus occurs in 6\% to 10\% of pituitary adenomas.\textsuperscript{16} The presence of abnormal tissue between the lateral wall of the cavernous sinus and the carotid artery is the most reliable imaging manifestation of invasion.\textsuperscript{16,18} A high serum prolactin level (1000 ng/mL) also correlates with cavernous sinus involvement.\textsuperscript{19}
Enlargement of pituitary adenomas during pregnancy is well documented and may be demonstrated by CT and MRI. Rarely hypopituitarism can develop in previously normal women during pregnancy or the postpartum period associated with extensive infiltration of the gland by lymphocytes and plasma cells, referred to as lymphocytic hypophysitis. CT reveals sellar enlargement by a homogeneously enhancing mass bulging into the suprasellar region.

CONTRAST ISSUES IN PITUITARY ADENOMAS

The general principles of MR imaging contrast dosage and image timing are not necessarily applicable to the imaging of pituitary adenomas. The normal pituitary gland enhances after contrast administration because it lacks a blood-brain barrier. Therefore, enhancing tissue may partially or totally surround lesions arising from the gland. In the case of macroadenomas, this situation does not present a significant problem because these tumors are not symptomatic until they have reached a relatively large size and impinge on structures external to the sella turcica, such as the optic chiasm. At this point, macroadenomas can be seen as a mass expanding or extending out of the sella turcica, and contrast material is not necessary for detection of the tumor. Pituitary microadenomas have different imaging considerations. Although often hormonally active, they are by definition small (<1 cm) and may not be detectable by mass effect alone. Microadenomas generally enhance to a lesser degree than normal pituitary tissue. Therefore, they must be perceptible as a low-intensity focus compared with the rest of the gland after Gd contrast administration. Davis et al. found that use of half-dose contrast material may be equal to or superior to full dose for imaging microadenomas. The decreased dose may prevent obscuration of the adenoma by intense enhancement in the rest of the gland. Half-dose imaging may also help delineate the cavernous sinus better than full dose.

Image timing may also be an important factor for improved adenoma detection. Hayashi et al. performed dynamic imaging of the pituitary during and just after slow hand injection (approximately 90-second injection time) over a total period of 350 seconds. They found that the maximal contrast of adenoma to the normal pituitary occurred between 145 and
300 seconds. Miki et al,\textsuperscript{26} used dynamic imaging at 1-minute intervals after intravenous bolus injection of a standard dose (0.1 mmol/kg) of gadopentetate, with heavily T1-weighted images (TR = 100, TE = 15), in patients with pituitary adenomas (microadenomas and macroadenomas). They reported maximal visual contrast between tumor and normal gland at either 1 or 2 minutes after injection in all cases, and there was improvement in contrast over a usual (nondynamic) imaging protocol in all cases. The preponderance of data on imaging pituitary adenomas suggests that half-dose contrast material may be used with equal or improved results to standard dose and that sensitivity may be increased with dynamic imaging.

**Figure 16.** Dynamic MR images of the pituitary in a 32-year-old woman with hyperprolactinemia. Four images from a dynamic pituitary study just before (upper left) and 60 seconds (upper right), 90 seconds (lower left), and 120 seconds (lower right) after injection of gadopentetate dimeglumine show a hypointense lesion in the left sella compatible with a microadenoma.

**PITUITARY APOPLEXY**

Pituitary apoplexy is due to infarction of or haemorrhage into a pituitary adenoma. Infarction may be indistinguishable from a low density pituitary swelling and may or may not show enhancement. Haemorrhagic pituitary apoplexy may reveal high density within the adenoma or brain substance or subarachnoid space in the acute phase and low density with or without marginal enhancement as the haematoma is absorbed. This condition will probably be considered by the clinician when an appropriate syndrome occurs in a patient known to have a pituitary adenoma, but pituitary tumours may first present as subarachnoid haemorrhage.

**Figure 17.** CT scan picture of pituitary apoplexy showing a hypodense rounded cystic suprasellar mass with enhancing walls.
The correct diagnosis should be recognized from CT or suspected from sellar erosion on plain films prior to neuroimaging studies. Pituitary apoplexy commonly results in spontaneous involution of the pituitary adenoma and if the patient survives, this might result in empty sella.

**EMPTY SELLA SYNDROME**

In patients with radiographic and polytomographic evidence of an abnormal sella turcica, it is important to differentiate a pituitary mass lesion, such as pituitary macroadenomas, intrasellar cysts, intrasellar aneurysms, from intrasellar cisternal herniation (an empty sella). In the empty sella syndrome, the sella turcica is enlarged, usually with none or only minimal bone erosion; however, bone erosion-identical to that seen in pituitary neoplasms may be seen in some cases. In the empty sella, the pituitary gland is flattened and atrophic; it is located in the posterior-inferior portion of the sella turcica. CT shows evidence of CSF-density extending into the sella turcica on both the coronal and sagittal views.

![Figure 18. Empty sella, notice the intrasellar extension of the suprasellar cistern with intrasellar CSF attenuation values](image)

There is no evidence of abnormal intrasellar enhancement. With thin section CT, the pituitary infundibulum may be seen extending downward into the sella. This is the most important point in differentiating an empty sella from a pituitary adenoma. In some cases, the diagnosis of an empty sella may only be established with metrizamide CT cisternography. The diagnosis is established by the finding of opacification of the intrasellar cistern. Metrizamide CT cisternogram is frequently necessary to differentiate an intrasellar subarachnoid cyst or a pituitary micro- or macroadenoma from an empty sella. It is important to be aware that surgically proved hormonally secreting pituitary microadenomas have occurred in patients with CT evidence of an empty sella.
Empty sella may complicate a pituitary tumour or occur in the presence of a microscopically normal pituitary gland. The first type may follow surgery or therapy for pituitary neoplasm.

In patients with a deficient pituitary diaphragm, intrasellar extension of the chiasmatic cistern may cause enlargement of the sella turcica and compress the normal pituitary gland to the periphery of the enlarged sella. Such patients are usually discovered when a skull radiograph is taken for investigation of an unrelated condition such as non-specific headache or trauma. The sella is usually symmetrically enlarged and commonly disproportionately deep or quadrangular in shape, although it may be asymmetrical or ballooned and thus simulate a pituitary tumour. High resolution thin CT sections of the pituitary fossa will show that the sellar contents are of CSF attenuation; the infundibulum can usually be traced lying closer to the dorsum than the anterior wall of the sella and extending down to the thinned pituitary gland, sometimes as little as 1 mm in depth, lying adjacent to the floor. The appearances are confirmed by coronal and sagittal reformatting. If head scanning shows no additional abnormality further investigation is contraindicated.

Figure 20. A case of an empty sella syndrome, notice ballooning of the sella turcica with intrasellar CSF attenuation values
However, in a patient with deficiency of the Pituitary diaphragm empty sella may be a complication of raised intracranial pressure. It is most commonly associated with pseudotumour cerebri and therefore in obese or hypertensive women, but sometimes with convexity block to CSF flow and with intracranial tumours. In such conditions visual field defects and visual loss may be caused by intrasellar herniation of the optic chiasm or nerves, and erosion of the walls of the sella may result in a fistula into the sphenoid air sinus, causing CSF rhinorrhoea and/or fluid in the sinus.

Pituitary apoplexy is due to infarction of or haemorrhage into a pituitary adenoma. Infarction may be indistinguishable from a low density pituitary swelling and may or may not show enhancement. Haemorrhagic pituitary apoplexy may reveal high density within the adenoma or brain substance or subarachnoid space in the acute phase and low density with or without marginal enhancement as the haematoma is absorbed.

This condition will probably be considered by the clinician when an appropriate syndrome occurs in a patient known to have a pituitary adenoma, but pituitary tumours may first present as subarachnoid haemorrhage. The correct diagnosis should be recognized from CT or suspected from sellar erosion on plain films prior to angiography. Pituitary apoplexy is one cause of spontaneous regression of pituitary adenoma and of empty sella.

References


INDEX

• INTRODUCTION
  o Radiological pathology of primary CNS lymphomas
  o Radiological pathology of diffuse astrocytomas

• THE BUTTERFLY TUMOURS

RADIOLOGICAL PATHOLOGY OF BUTTERFLY TUMOURS

Butterfly tumours are defined as tumours extending bilaterally (and forming bihemispheric mirror tumours) around the ventricular system like the wings of a butterfly. Butterfly tumours are formed by primary CNS lymphomas and diffuse astrocytomas. Central primary CNS Lymphomas start bilaterally in the centrifugal subependymal microvascular system then fungate centrifugally outward along the virchow robin spaces to form the characteristic butterfly periventricular tumours. On the other hand diffuse astrocytomas commonly start focally in one hemisphere then the astrocytoma tumor cells infiltrate locally between myelinated fibers in the nondestructive manner and gradually cross through the corpus callosum to the opposite hemisphere forming the characteristic butterfly gliomas. In this chapter we will talk about the radiological pathology of primary CNS lymphomas and diffuse astrocytomas and how these tumours progress to form the characteristic butterfly tumours.
Radiological pathology of primary CNS lymphomas

Primary CNS lymphoma is an uncommon disease that historically constituted approximately 1% of primary brain tumors. Sporadic disease is most common in older adults. With the advent of acquired immunodeficiency syndrome (AIDS)-associated lymphomas, there has been a marked increase in the number of cases, particularly in younger people, in whom the disease was previously rare. There has also been a significant increase in non-human immunodeficiency virus (HIV)-associated primary CNS lymphoma among older patients. A relationship between Epstein-Barr virus and HIV-associated lymphomas has been observed. The causes of sporadic cases and their increasing incidence in the nonimmunocompromised are unknown, but viral and environmental agents have been proposed as factors. Primary CNS lymphoma occurs throughout the brain, but it is characteristically periventricular. Sporadic cases tend to be limited to one or two sites, whereas AIDS-associated tumors are commonly multifocal.

The marked shrinkage of sporadic tumors on imaging studies after initiation of steroid therapy is almost diagnostic. The initial response to radiation is also gratifying. The tumors return within several months or with the cessation of steroids, however. Modern chemotherapy has resulted in a much improved prognosis for sporadic lymphomas, with a reported median survival of about 5 years. In contrast, AIDS-associated lymphomas
respond only transiently to therapy, and most patients die within a year of diagnosis.


Circumscribed lesions may have a gray, fleshy appearance similar to systemic lymphomas or may be soft, mottled, and otherwise indistinguishable from a high-grade astrocytoma. The borders are often vaguely defined. Some lesions produce architectural distortion without a definite mass.

The defining microscopic feature of primary CNS lymphoma is angiocentricity. Tumor cells surround and infiltrate the walls of small and medium-sized blood vessels. The lamellar arrangement of the perivascular tumor cells between layers of collagen creates an onion-skin or basket-weave appearance. The involvement of the blood vessels may be destructive, producing hemorrhage or infarcts. Lymphomas tend to spread in perivascular spaces along the Virchow-Robin space.

The defining microscopic feature of primary CNS lymphoma is angiocentricity. Tumor cells surround and infiltrate the walls of small and medium-sized blood vessels. The lamellar arrangement of the perivascular tumor cells between layers of collagen creates an onion-skin or basket-weave appearance. The involvement of the blood vessels may be destructive, producing hemorrhage or infarcts. Most tumors form a diffuse mass of noncohesive cells which may represent a confluence of a number of perivascular foci. The interface with brain often appears fairly sharp, with individual tumor cells appearing to infiltrate only a short distance. Perivascular tumor foci may be present at some distance from an apparently sharply defined tumor mass, however, presumably owing to spread in the Virchow-Robin space. Tumor necrosis, especially of single cells, and hemorrhage are common, but extensive confluent necrosis is the exclusive province of AIDS-associated disease. Most cerebral lymphomas, and particularly AIDS-associated tumors, are high-grade large cell lymphomas. The microscopic correlates include large cells with pleomorphic nuclei and a high mitotic rate. Primary CNS lymphoma may be subclassified by the systems used for systemic lymphomas, but this does not add prognostic information.
Primary CNS lymphomas have a characteristic topographic brain localization as follows:

- **Topographic localization of primary CNS lymphomas**

Lymphomas start either in the subependymal tissues and the periventricular gray matter and then fungate centrifugally outward into the periventricular white matter or spread subependymally to ensheathe the ventricular system (central periventricular). The second site is the cortico-meningeal site and the disease spreads either alongside the meninges or invades the brain parenchyma in a centripetal way. (peripheral corticomeningeal)

**TOPOGRAPHIC SUBTYPES OF PCNSL**

- **Central periventricular:** Starts either in the subependymal tissues or the periventricular gray matter and then fungates centrifugally outward into the periventricular white matter or spread subependymally to ensheathe the ventricular system, although it ultimately forms extensive periventricular butterfly fungative lesions or ensheathe the whole ventricular system, it shows little tendency to encroach upon the volume of the ventricular cavity.

- **Peripheral corticomeningeal:** The disease spreads either alongside the meninges or invades the brain parenchyma in a centripetal way. Corticomeningeal lymphomas are probably secondary CNS lymphoma that occur from spread of systemic disease to the CNS (non-Hodgkin's more common than Hodgkin's). Secondary lymphomas typically involve the leptomeninges, and CSF with parenchymal involvement is much less common. MR imaging findings include leptomeningeal/dural enhancement and hydrocephalus.

The topographic localization of primary CNS lymphomas are best explained by considering the cellular origin of lymphoma and the brain microvascular system.

PCNSL is derived from the microglial cells and was previously called microglioma. The microglial cells are more numerous in the cortical and the subcortical gray matter. (Thalamus and basal ganglia). The microglial cells are not of neural origin. They are derived from the blood monocytes and immigrate through the small perforating blood vessels to invade the neural tissue either from the pial or the subependymal arterial system. The microglial cells lies very close to the periadventitial spaces of the small penetrating blood vessels, They are phagocytic and function as macrophages. They represent a defense mechanism and are considered as a part of the reticuloendothelial system. To sum up the microglial cells and the penetrating blood vessels are very closely coupled together.

With regard to the brain microvascular system, 2 systems were described. The centrifugal subependymal system and the centripetal pial system. The centrifugal subependymal vascular system originates from the subependymal arteries which are terminal branches of the choroidal arteries, then extends centrifugally outward into the periventricular white matter. The centripetal pial vascular system originates from the pial arteries then extends
centripetally inward towards the ventricular system. As an artery penetrates the brain it carries a sheath of pia with it resulting in a potential perivascular space called Virchow-Robin space.  

To put things together, it is possible to state that the malignant lymphoma cells (being derived from the microglial cells) originate primarily in the periadventitial spaces of either the subependymal or the pial vascular systems, then the lymphoma cells creep alongside the penetrating arteries either centrifugally outward from the subependymal system, or centripetally inward from the pial system. This view point is consistent with the pathological findings of marked perivascular cuffing by lymphoma cells and tendency to spread along Virchow-Robin spaces. This also should support the theory that CNS lymphomas arise from the periadventitial microglial cells of the penetrating arterioles.  

It should also be pointed out that the subependymal spread of lymphoma that is observed in some cases most probably represent either spread alongside the subependymal arteriolar system or CSF seedling.  

Table 1. Ways of spread of primary CNS lymphomas

<table>
<thead>
<tr>
<th>Ways of Spread</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Lymphoma cells creep alongside the penetrating arteries in the Virchow Robin spaces either centrifugally outward from the subependymal system, or centripetally inward from the pial system. Infiltration along the meninges is common in corticomeningeal lymphomas.</td>
</tr>
<tr>
<td>• CSF seedling</td>
</tr>
</tbody>
</table>

Historical terms for cerebral lymphomas such as microglioma arose at a time when the nature of the tumor cells was uncertain. Immunohistochemical stains have clarified the origin of primary cerebral lymphomas and also are important diagnostically. Reactivity for common leukocyte antigen is used to confirm lymphoid origin and often reveals much greater parenchymal infiltration by individual cells than is apparent on routine hematoxylin and eosin staining. By far, most cerebral lymphomas are B-cell neoplasms, and monoclonal reactivity for K or k light chain may be helpful diagnostically. T-cell lymphoma occurs only rarely.  

Karyotype abnormalities found in CNS tumors are similar to those found in systemic lymphomas and involve structural alterations. Molecular studies have confirmed genetic lesions involving RAS genes, CDNK2A, CDNK2B, BCL2, BCL6, and MYCC.  

An interesting side effect of the dramatic initial response to steroids is that biopsy specimens obtained after initiation of therapy may be devoid of identifiable tumor cells. The appearance of modest perivascular and parenchymal infiltrates of small T cells and white matter changes that include myelin breakdown, edema, and gliosis has been dubbed the sentinel lesion of primary CNS lymphoma.
NEUROIMAGING OF PRIMARY CNS LYMPHOMAS

Neuroimaging of primary CNS lymphomas is very complex, as one must observe (1) the site, (2) the precontrast CT density, (3) the MRI T2 signal intensity, (4) the pattern of contrast enhancement, (5) the rapid changes that take place over a very short time as primary CNS lymphomas are very dynamic tumours in so far as the local spread of the disease is concerned.

Table 2. Radiological parameters while inspecting a study for possible primary CNS lymphoma

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Comment</th>
</tr>
</thead>
</table>
| Site                             | 1. Central periventricular  
                                2. Peripheral corticomeningeal |
| The precontrast CT density       | Hyperdense on unenhanced CT studies                                     |
| The MRI T2 signal intensity      | Hypointense or isointense to gray matter on T2-weighted images          |
| The pattern of contrast enhancement | 1. Prominent enhancement that tends to be solid and homogeneous in immunocompetent patient  
                             2. Enhancement patterns in immunocompromised individuals may be irregular and heterogeneous, often with a ring pattern |
| The rapid changes that take place over a very short time as primary CNS lymphomas are very dynamic in so far as the local spread of the disease is concerned. | The rapid centrifugal periventricular spread of the central subtype forming the butterfly lesions, or the centripetal growth of the corticomeningeal type. The central subtype might spread subependymally to ensheathe the whole ventricular system. |

Table 3. Common sites for central lymphomas

<table>
<thead>
<tr>
<th>Site</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalamus</td>
<td>100%</td>
</tr>
<tr>
<td>Parietal lobes, corpus callosum, cerebellum, brain stem, hypothalamus</td>
<td>25%</td>
</tr>
</tbody>
</table>

Primary CNS lymphoma is more common than secondary lymphomas. Most primary CNS lymphomas are high-grade non-Hodgkin's B-cell lymphomas. The site of origin is controversial because the CNS does not have endogenous lymphoid tissue or lymphatic circulation. The incidence is increasing in both immunocompromised and
Lesions can be multiple in up to 50% of cases, involving the basal ganglia, periventricular white matter, and corpus callosum. The lesions are very radiosensitive but frequently recur. The masses demonstrate high cellularity, with 90% isodense to hyperdense on CT, and isodense to hypointense to brain signal intensity on T2-weighted imaging. In immunocompetent individuals, there is prominent enhancement that tends to be solid and homogeneous. In these patients, lymphomas do not calcify, and hemorrhage is uncommon. Up to 75% of these masses are in contact with the ependyma or meninges. The imaging appearance is more heterogeneous in AIDS owing to hemorrhage and necrosis. Enhancement patterns in immunocompromised individuals may be irregular and heterogeneous, often with a ring pattern. In the AIDS population, CT and MR imaging cannot reliably distinguish between lymphoma and toxoplasmosis. SPECT imaging may be helpful in this setting.

**Figure 3.** Precontrast CT scan of a paraventricular lymphoma, each study is one week apart, notice that the lymphoma is hyperdense on precontrast scans, also notice the increase in size and the progressive periventricular fungation over a short period of time.

**Figure 4.** A postcontrast CT scan in a patient with central thalamic lymphoma showing dense contrast enhancement, notice the perilesional edema and the small nodules radiating from the mother lesion.
Previously an uncommon primary brain neoplasm, primary CNS lymphoma is increasing in frequency. Although the increase is most often attributed to acquired immunodeficiency syndrome (AIDS) and other immunocompromised disease states, primary CNS lymphoma is also increasing in frequency in immunocompetent patients. Peak incidence of primary CNS lymphoma in immunocompetent patients is in the 50s, and lesions are typically solitary; among immunocompromised individuals, it occurs at a younger age, and multiple lesions are common. It is one of two primary CNS tumors that extends across the corpus callosum with some frequency forming the bilateral butterfly lesions. (GBM is the other.) Lesions are commonly located deep within the brain substance, and T2 signal abnormality or enhancement often abuts an ependymal surface; however, primary CNS lymphoma can also occur peripherally or in the posterior fossa. On unenhanced CT studies, primary CNS lymphoma is classically hyperdense, and enhancement can be solid or ringlike.
On MR images, the signal intensity on T1-weighted images can vary; however, similar to other lesions that are hyperdense on unenhanced CT studies, primary CNS lymphoma tends to be hypointense or isointense to gray matter on T2-weighted images. Surrounding edema and mass effect ranges from minimal to marked. Enhancement is the norm on MR imaging; it may be homogeneous, heterogeneous or ringlike. In a patient with AIDS and an enhancing mass lesion, the primary differential diagnostic consideration is toxoplasmosis. Although lymphoma is statistically more common, primary CNS lymphoma cannot be reliably distinguished from toxoplasmosis with conventional CT or MR imaging. A variety of techniques, including thallium-201 SPECT, fluorodeoxyglucose PET, and MR spectroscopy, have been advocated to distinguish between the two diseases.

Low signal intensity in a nonhemorrhagic tumor on T2-weighted images can be due to high cellularity, a high nuclear-to-cytoplasmic ratio, or minimal extracellular fluid. Primary tumors that are commonly lower in signal intensity on T2-weighted images include primitive neuroectodermal tumors (e.g., medulloblastoma, neuroblastoma) and lymphoma. Metastases from a systemic mucinous adenocarcinoma primary can also exhibit low signal intensity on T2-weighted images.
Figure 6. MRI T1 precontrast (A,B), postcontrast (C), MRI T2 (D) and MRI proton density (E,F) Notice that the periventricular lymphoma is hypointense on precontrast scans, also notice the dense contrast enhancement. Notice the densely enhanced butterfly lesions in (C), the butterfly lesions are iso-to hypointense on the MRI T2 and proton density scans (D,E,F)

Figure 7. MRI T1 postcontrast coronal scan of a patient with central lymphoma showing progressive increase in the size of the lymphoma with periventricular fungation over a short period of time. Each image was done about 5 days before the next starting from A to F, this was coupled clinically with progressive clinical deterioration. Notice the dense contrast enhancement and the well formed butterfly lesion in E,F. The lesions are surrounded with hypointense edema with positive mass effect.
Figure 8. MRI T1 postcontrast coronal scan of a patient with central lymphoma showing periventricular fungation. Notice the dense contrast enhancement and the well formed butterfly lesions. The lesions are surrounded with hypointense edema with positive mass effect.

Figure 9. MRI T1 postcontrast showing the characteristic periventricular fungation, left MRI image is one week earlier than the right image, notice the observable periventricular spread of lymphoma in such a short time.

Figure 10. Postcontrast CT scan showing a thalamic lymphoma (left image) that started to fungate centrifugally outward on follow up CT scan (middle image) forming later on the characteristic butterfly lesion (right image), these changes occurred over 2 weeks of the patient hospitalization.
Figure 11. MRI T2 images A, B and postcontrast image C. A was done 5 days before B. Notice the progressive increase in size of the central lymphoma over a short period of time, also notice that the central lymphoma is markedly hypointense on the MRI T2 image (B), the central lymphoma showed marked and dense contrast enhancement. The surrounding edema is marked in this patient (the edema is hyperintense on the T2 images and hypointense on the T1 image)
Figure 12. MRI T1 precontrast image (A) and postcontrast T1 images (B,C) and MRI T2 images (D,E) in a patient with a butterfly infratentorial lymphoma around the 4th ventricle lymphoma. The lymphoma is hypointense on precontrast T1 image (A) and iso to hypointense on MRI T2 images (D,E), the peripheral part of the butterfly lymphoma is more hypointense probably it is more cellular than other parts of the tumour with dense contrast enhancement (B,C), also notice the perilesional edema.

From the radiological point of view, the existence of butterfly lesions and the subependymal disease are the most characteristic radiological criteria of PCNSL. In central lymphomas the thalamus is the most frequently involved site.
Table 4. The radiological characteristics of primary CNS lymphomas

1. The existence of butterfly lesions
2. The existence of subependymal lymphomatous sheath around the ventricular system, best seen in postcontrast scans
3. The lesions are hypointense on the MRI T2 images
4. The lesions are slightly hyperdense on precontrast CT scans
5. The existence of dense contrast enhancement
6. Perilesional edema is present to a variable degree
7. Lymphomas are characterized by being a very dynamic pathology with rapid increase in size and periventricular fungation over a short period of time during the hospitalization of the patient

- Radiological pathology of diffuse astrocytomas

Astrocytomas are tumors predominantly composed of astrocytes. Unless otherwise indicated, the term usually applies to diffusely infiltrating neoplasms (WHO grades II through IV). The pilocytic astrocytoma (WHO grade I), pleomorphic xanthoastrocytoma, and giant cell astrocytomas have distinctly different biological, genetic, and phenotypic features. This distinction should be kept in mind during the discussion of astrocytomas.

Of the estimated 17,000 primary brain tumors diagnosed in the United States each year, approximately 60% are gliomas. Gliomas comprise a heterogeneous group of neoplasms that differ in location within the central nervous system (CNS), age and sex distribution, growth potential, extent of invasiveness, morphological features, tendency for progression, and response to treatments.

Although there are only three major tumor types recognized, corresponding to the three types of glial cells (astrocytes, oligodendrocytes, and ependymal cells), gliomas encompass a broad spectrum of histopathologic and imaging findings. The variation in the phenotype and biological behavior of gliomas likely reflects the nature of the transformation-associated genes involved in the development of neoplasia. There have been numerous classification schemes and staging criteria proposed for glial neoplasms. The WHO classification is generally used as a reference.

www.yassermetwally.com
Low grade brain astrocytomas consist of relatively normal-appearing astrocytes, but there are just too many of them.

Primary cerebral gliomas account for up to 45% of intracranial tumors, with peak incidence in the seventh decade of life. In children, most (70% to 80%) of gliomas are infratentorial. In the adult, GBM accounts for more than half (55%) of all gliomas. The remaining subtypes in decreasing order of frequency include astrocytoma (20.5%), ependymoma (6%), medulloblastoma (6%), oligodendroglioma (5%), and choroid plexus papilloma (2% to 3%). Histopathology may range from benign or "low-grade" tumors to the highly malignant anaplastic astrocytoma and GBM. Glial neoplasms can be heterogeneous, with anaplasia developing focally. This can limit the diagnostic accuracy of small surgical biopsies. Furthermore, there can be significant change in the degree of malignancy over time. Morbidity and mortality of these lesions can also be significantly influenced by the location of the lesion, which may limit surgical accessibility.

All gliomas, particularly the diffusely infiltrating variety, have a tendency toward progression to more malignant forms. Genetic alterations that appear to be common across low-grade to higher-grade astrocytomas include p53 mutations. Mutations in pl6 and...
CDK4 gene amplification are present in both anaplastic astrocytomas and glioblastomas, whereas loss of heterozygosity of chromosome 10 and EGF-R gene amplification are almost exclusively found in glioblastomas.

Clinical presentation includes focal neurological signs or symptoms related to increased intracranial pressure (ICP). Signs and symptoms of increased ICP include headache (typically more severe in the morning), nausea, vomiting, and visual disturbances. In GBMs and anaplastic astrocytomas, these signs can develop rapidly and are progressive. Because many of these neoplasms tend to develop and grow in the deep white matter, they can be clinically silent until achieving relatively large sizes. Patients who present with focal neurological signs or seizures tend to have a more optimistic prognosis due to an earlier presentation.

In the absence of contraindications such as pacemakers, ferromagnetic aneurysm clips, metallic foreign bodies in the eye, or cochlear implants, contrast-enhanced MR imaging is the modality of choice for the diagnosis and follow-up of brain neoplasms. MR imaging is more sensitive than CT in the detection of gliomas, in the assessment of tumor extent, and for identification of potential complications (ie, herniation syndromes, venous thrombosis, leptomeningeal and ependymal spread). Functional MR imaging can be added to the preoperative assessment of patients for identification of critical motor and language areas. This assessment is facilitated by the use of high field strength units (1.5 T) with echoplanar imaging capabilities. In addition, intraoperative interactive navigational workstations can be used to review combined functional and anatomic information during biopsy and surgical resection of tumors.

Despite the exquisite sensitivity of MR imaging for identifying alterations in water content, it lacks specificity in the determination of histological grade. In general, the presence of contrast enhancement and hemorrhage correlate with increasing grade of tumor. However, the presence or pattern of contrast enhancement or degree of T2-prolongation cannot be used to grade these lesions. In addition, it has been well recognized that regions of "normal-appearing brain" in patients with infiltrative or anaplastic astrocytomas and GBMs can harbor malignancy.
Figure 16. A, Glioblastoma multiforme with necrosis and haemorrhage, glioblastomas are often multicolored on cross section due to hemorrhage and necrosis.

MR spectroscopy has long held the promise of in vivo histopathologic specificity. Preliminary work indicates that N-acetylaspartate (NAA) and gamma-aminobutyric acid are decreased in brain tumors, whereas choline is elevated. Lactate levels may correlate with histologic grade, and alanine may be associated with benign tumors. NAA is found primarily in neuronal cells. Any process that either replaces normal neurons, or causes neuronal loss, can be expected to decrease the NAA level. For example, meningiomas are reported to have low NAA, low creatine, a prominent choline peak, and a mild elevation in lactate. The H spectrum of gliomas appears to be dependent on the grade of the tumor, with higher grade lesions having lower levels of creatine and more significant elevations of lactate and choline. Currently, MR spectroscopy may be useful in distinguishing tumor from other lesions that may mimic a neoplasm, such as encephalitis. However, the histopathologic specificity has been predominantly anecdotal, and its clinical usefulness has been limited by long imaging times and limited voxel resolutions. This may change with improvements in imaging hardware and novel imaging pulse sequences.
Common pathological characteristics of diffuse astrocytomas

- Diffuse astrocytomas are tumors predominantly composed of astrocytes. Unless otherwise indicated, the term usually applies to diffusely infiltrating neoplasms (WHO grades II through IV).
- Diffuse astrocytoma is unusual in the first decade of life and most commonly presents in older children or young adults up to the age of 40 to 45.
- All diffuse astrocytomas, particularly the diffusely infiltrating variety, have a tendency toward progression to more malignant forms. Diffuse astrocytomas have a peculiar tendency to change its grade over time into the next higher grade of malignancy and the condition is age dependant. A change in the grade of diffuse astrocytoma is more likely to occur in the older age group.
- Diffuse astrocytomas commonly start as grade II at a younger age group then gradually change its grade over time into the next higher grade until they ultimately dedifferentiate into glioblastomas (secondary glioblastoma multiforme), on the other hand, glioblastoma multiforme in older patients are usually primary—that is, they occur as glioblastoma multiforme from their inception, without progression from a lower-grade tumor.44,45,46,47,48
- Diffuse astrocytomas appear to form a continuum of both biological and histological aggression. They vary from lesions with almost normal cytology (grade I and grade II astrocytomas) through intermediate stages (grade III, anaplastic astrocytomas) and up to the most aggressive of all human brain tumours (grade IV astrocytomas or glioblastoma multiforme).42,43
- Diffuse astrocytoma often spreads widely through the brain but without destruction and also without interruption of normal function. Microscopically, tumor cells infiltrate between myelinated fibers in a nondestructive manner. The local spread of diffuse astrocytomas (forming gliomatosis cerebri and butterfly gliomas) does not mean that the tumour grade is grade IV (glioblastoma multiforme), local spread can occur in grade II and grade III and in the author experience gliomatosis cerebri and butterfly gliomas are much more commonly seen in grade II astrocytomas and has not been encountered in grade III (anaplastic astrocytomas) and grade IV (glioblastoma multiforme). It takes a long time for a diffuse astrocytoma to cross the corpus callosum to the opposite hemisphere to form a butterfly glioma. Patients harbouring glioblastomas have a much shorter life span for their tumours to form butterfly gliomas, however cases were reported for glioblastomas forming butterfly tumours.
- In practice considerable histological heterogeneity in astrocytic tumours is found (i.e., low grade areas with Rosenthal fibers and calcification can be intermixed with frankly malignant ones).42,50
- The differences in histologic features, potential for invasiveness, and extent of progression likely reflect genetic differences acquired during astrocytoma growth.
- Grade IV astrocytomas (glioblastoma multiforme) differ from diffuse astrocytoma grade II and grade III (anaplastic astrocytomas) in the presence of gross necrosis, and microscopically in the presence of vascular endothelial hyperplasia and tumour hemorrhage.

www.yassermetwally.com
Figure 17. Astrocytoma grade II showing diffuse infiltration of the left temporal lobe with gray and white matter involvement (arrowhead). Note the relative lack of mass effect for the degree of infiltration. The white matter infiltration extends across the corpus callosum (white arrow) and involves bilateral deep white matter tracts (double arrow) forming the characteristic butterfly glioma.

Radiologically the tumor is usually identified by a combination of brain asymmetry, enlargement of a portion of the brain, or abnormal signal intensity on MR or abnormal attenuation on CT. The lesions typically have precontrast CT attenuation and MRI signal changes suggesting increased water content and lower than normal specific gravity (diffuse low CT scan densities with MRI T1 hypointensities and diffuse MRI T2 hyperintensities).

Figure 18. Butterfly glioblastoma multiforme

It is tempting to consider that these changes represent edema. The question then arises: Is this vasogenic edema or cytotoxic edema? Because the blood-brain barrier is intact in these tumors, vasogenic edema is unlikely. The cells are not dead or dying, so that cytotoxic edema is also unlikely. Perhaps the edema results from the increased number of astrocytic cells that spread apart the normal myelinated axons of the white matter. The presence of significant amount of normal appearing astrocytes (hyperplasia), with marked cytoplasmic hypertrophy and low nuclear to cytoplasm ratio result in total increase in the water content.
of the brain. These cells may merely have different physical and chemical properties than the normal tightly packed bundles of axons that traverse through the brain. 

Astrogliosis is commonly associated with widened fluid filled extracellular spaces (microcavititations) which definitely increase tissues water content resulting in the characteristic CT scan/MRI picture. Absence of significant edema coupled with the very slow growth rate of these tumours result in minimal mass effect.

**Figure 19.** Astrocytes have extensive vascular foots, Astroglisis (astrocytic hyperplasia) commonly results in the formation of a mesh with enlargement of extracellular spaces and extensive fluid-filled microcavitatinations. This, coupled with marked cytoplasmic hypertrophy of astrocytes-that results in low nuclear to cytoplasm ratio- are responsible for the neuroimaging picture of low grade astrocytomas

**THE BUTTERFLY TUMOURS**

In the author experience, the progressive centrifugal butterfly fungation of primary CNS lymphomas is something that can be observed clinically. When successive flow up neuroimaging studies are done (on several days) to a patient with CNS lymphoma during hospitalization, it was possible, in the author experience, to observe the progressive centrifugal butterfly fungation of the lymphoma. This is probably due to the rapid growth of the neoplasm (see figures 7,8,9,10,11), this is in sharp contrast with the butterfly bihemispheric spread of astrocytomas which has never been observed "taking place" in action in a single patient by the author, this is probably because the growth and the local spread of astrocytoma cells is slower compared with that of lymphoma cells. 

[www.yassermetwally.com](http://www.yassermetwally.com)
The spread of lymphoma cells is different from that of astrocytoma cells. Lymphoma cells spread locally along the periarteriolar spaces in the Virchow-Robin spaces, while Astrocytoma tumor cells infiltrate locally between myelinated fibers in the nondestructive manner. Spread of lymphoma cells along the Virchow Robin spaces is probably faster than the spread of astrocytoma cells by infiltration between myelinated fibers (probably Virchow Robin spaces facilitate spread of lymphoma cells) and this is probably another reason that explains the more rapid local spread lymphoma cells compared with that of astrocytoma cells.

Although both astrocytomas and lymphomas are hypercellular neoplasms, however their MRI T2 signal intensity is different (astrocytomas are hyperintense on the MRI T2 images while lymphomas are hypointense on the MRI T2 images). The cells of lymphomas have a high nuclear to cytoplasmic ratio with minimal extracellular water, resulting in T2 shortening (hypointense on the T2 MRI images), while astrocytoma cells have a low nuclear to cytoplasmic ratio with increased extracellular fluid resulting in T2 prolongation (hyperintense on the T2 MRI images). For the same reasons lymphomas are hyperdense
on precontrast CT scan (because of hypercellularity with high nuclear to cytoplasmic ratio), while astrocytomas are hypodense on precontrast CT scan because of hypercellularity with a low nuclear to cytoplasmic ratio associated with increased extracellular fluid.

Figure 22. (A), A patient presented with a clinical picture resembling Alzheimer dementia, post contrast CT scan revealed a butterfly tumour. The tumour is hypodense, with absence of mass effect, edema, or contrast enhancement, histopathology revealed an astrocytoma grade II. (B,C), belongs to a patient with butterfly CNS lymphoma, notice that the tumour is hyperdense on noncontrast CT scan (B), with patchy, ring like enhancement. The lesion has a positive mass effect, and surrounded by massive edema.

Mass effect, perilesional edema and contrast enhancement are very prominent in lymphomas and in the author experience all butterfly gliomas were astrocytomas grade II. Edema, mass effect and contrast enhancement is not a feature of astrocytoma grade II and many of these tumours were initially mistaken with old infarctions, see table 5. Butterfly tumour was seen by the author infratentorially around the 4th ventricle in one case if primary CNS lymphoma, see fig 12, while it has however been observed infratentorially by the author in case of astrocytomas.
Figure 23. A, Glioblastoma involving the corpus callosum. Axial postcontrast CT image in young male patient presenting with psychosis. Note the huge mass in the genu and anterior body of the corpus callosum with enhancement at the margins. Note dilatation of the lateral ventricles caused by obstructing mass. B, Lymphoma of the corpus callosum. Axial postcontrast CT image in young male patient presenting with psychosis. The tumor crossed the corpus callosum and involved both frontal lobes.

Table 5. Comparison between the astrocytoma butterfly tumors and lymphoma butterfly tumors

<table>
<thead>
<tr>
<th></th>
<th>Astrocytoma grade II</th>
<th>Lymphomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of origin</td>
<td>Diffuse astrocytomas commonly start focally in one hemisphere</td>
<td>start bilaterally around centrifugal subependymal microvascular system.</td>
</tr>
<tr>
<td>Pattern of spread</td>
<td>The astrocytoma tumor cells infiltrate locally between myelinated fibers in the nondestructive manner and gradually cross through the corpus callosum to the opposite hemisphere forming the characteristic butterfly gliomas.</td>
<td>The lymphoma cells fungate centrifugally outward along the virchow robin spaces to form the characteristic butterfly periventricular tumours.</td>
</tr>
<tr>
<td>Rate of spread</td>
<td>Very slow</td>
<td>Very rapid</td>
</tr>
<tr>
<td>Precontrast CT scan</td>
<td>Hypodense</td>
<td>Hyperdense</td>
</tr>
<tr>
<td>MRI T2 signal intensity</td>
<td>Hyperintense</td>
<td>Hypointense</td>
</tr>
<tr>
<td>Edema</td>
<td>Not a feature</td>
<td>Very prominent</td>
</tr>
<tr>
<td>Mass effect</td>
<td>Not present</td>
<td>Very prominent</td>
</tr>
<tr>
<td>Contrast enhancement</td>
<td>Not present</td>
<td>Very prominent</td>
</tr>
</tbody>
</table>
In the author experience, all butterfly gliomas were astrocytoma grade II except in one case where the histopathology was glioblastoma multiforme. When the histopathology is glioblastoma multiforme one should expect mass effect, patchy enhancement, the presence of edema and the presence of tumour necrosis. Local spread in case glioblastoma multiforme will be much more rapid with extensive tissue destruction and marked clinically disability within a very short time.

REFERENCES


www.yassermetwally.com


Brain edema accompanies a wide variety of pathologic processes and contributes to the morbidity and mortality of many neurologic diseases. It plays a major role in head injury, stroke, and brain tumor, as well as in cerebral infections, including brain abscess, encephalitis and meningitis, lead encephalopathy, hypoxia, hypo-osmolality, the disequilibrium syndromes associated with dialysis and diabetic ketoacidosis, and the various forms of obstructive hydrocephalus. Brain edema occurs in several different forms; clearly it is not a single pathologic or clinical entity.

Brain edema is defined best as an increase in brain volume due to an increase in water and sodium content. Brain edema, when well localized or mild in degree, is associated with little or no clinical evidence of brain dysfunction; however, when it is severe it causes focal or generalized signs of brain dysfunction, including various forms of brain herniation and medullary failure of respiration and circulation. The major forms of herniation are uncal, cerebellar tonsillar, upward cerebellar, cingulate, and transcalvarial herniation.
Brain edema has been classified into three major categories: vasogenic, cellular (cytotoxic), and interstitial (hydrocephalic).

**VASOGENIC EDEMA**

Vasogenic edema is characterized by increased permeability of brain capillary endothelial cells (as consequence of vascular injury with disruption of the BBB, or due to defective endothelial lining of the newly formed blood vessels in brain neoplasms) to macromolecules, such as the plasma proteins and various other molecules, whose entry is limited by the capillary endothelial cells (blood brain barrier). Grossly, the gyri are flattened and the sulci narrowed; the white matter is moist and swollen. Microscopically, there is micro-vacuolization of the white matter, poor staining, and "halo's" around nuclei.

Vasogenic edema is the most common type of edema associated with brain tumors, venous congestion and other causes and results from local disruption of the blood brain barrier. This leads to extravasation of protein-rich filtrate of plasma into the interstitial space, with subsequent accumulation of vascular fluid. This disruption results from loosening of the tight junctions between endothelial cells, and the neoformation of pinocytic vesicles. Once the barrier is breached, hydrostatic and osmotic forces work together to extravasate intravascular fluid. Once extravasated, fluid is retained outside the vasculature, mostly in the white matter of the brain, and within the bundles of myelinated axons of long tracts and commissural fibers. This is because axons run in parallel bundles of fibres with loose extracellular space (that offer low resistance and facilitates the extension of vasogenic edema along myelinated axons which are spreaded apart by the edema) as opposed to gray matter, which has high cell density and is enmeshed in an interwoven network of connecting fibres that offer high resistance to the formation and spread of edema. By definition, this type of edema is confined to the extracellular space. (70)

- More detailed information about the pathophysiology of vasogenic brain edema

Cerebral edema may be defined broadly as a pathologic increase in the amount of total brain water content leading to an increase in brain volume. It occurs when plasma-like fluid enters the brain extracellular space through impaired capillary endothelial tight junctions in tumors (vasogenic edema) and is a significant cause of morbidity and mortality. The molecular constituents of brain endothelial tight junctions consist of transmembrane proteins occludin, claudin 1 and 5, and junctional adhesion molecules that bind their counterparts on neighboring cells, “gluing” the cells together and creating the blood-brain barrier (BBB). Intracellularly, the occludins and claudins bind to zonula occluden (ZO) 1, ZO2, and ZO3, which in turn are attached to the actin cytoskeleton. Normal astrocytes help to maintain a normal BBB, which is illustrated in Plate. 1. In high-grade tumors, the deficiency of normal astrocytes leads to defective endothelial tight junctions, resulting in BBB disruption, allowing passage of fluid into the extracellular space. In addition, tumor cells produce factors, such as vascular endothelial growth factor (VEGF) and scatter factor/hepatocyte growth factor, which increase the...
permeability of tumor vessels by downregulation of occludin and ZO1\textsuperscript{40,44,46,47}. In addition, the membrane water channel protein, aquaporin-4 (AQP4), is upregulated around malignant brain tumors\textsuperscript{40}. AQP4-mediated transcellular water movement is important for fluid clearance in vasogenic brain edema, suggesting AQP4 activation or upregulation as a novel therapeutic target in vasogenic brain edema\textsuperscript{40,46}. High VEGF expression is reported in human anaplastic astrocytoma and glioblastoma (GBM)\textsuperscript{49,50}, meningiomas\textsuperscript{44}, and brain metastases\textsuperscript{51}. VEGF is important especially when tumors outgrow their blood supply. Hypoxia is the driving force for VEGF production in glioblastomas and the most important trigger for angiogenesis and cerebral edema formation in glioblastoma\textsuperscript{52}.

Plate 1. The BBB. Normal BBB demonstrating tight junctions between endothelial cells forming a barrier between the circulation and the brain parenchyma. Peritumoral edema formation occurs through defective endothelial junctions of an abnormal BBB.
Neuroimaging of vasogenic brain edema

The increase in permeability is visualized when contrast enhancement is observed with CT or MRI. Increased CSF protein levels are also indicative of increased endothelial permeability. MRI is more sensitive than CT in demonstrating the increased brain water and increased extracellular volume that characterize vasogenic edema. Vasogenic edema is characteristic of clinical disorders in which there is frequently a positive contrast-enhanced CT or increased signal intensity with MRI, including brain tumor, abscess, hemorrhage, infarction, and contusion. It also occurs with lead encephalopathy or purulent meningitis.

Figure 1. A, Loss of the gray-white interface with obscuration of the lentiform nucleus, loss of the insular ribbon, sulcal effacement and mass effect are seen in the left hemisphere due to vasogenic edema, B, Grossly, the gyri are flattened and the sulci narrowed; the white matter is moist and swollen. Notice uncal herniation (arrow).

The functional manifestations of vasogenic edema include focal neurologic deficits, focal EEG slowing, disturbances of consciousness, and severe intracranial hypertension. In patients with brain tumor, whether primary or metastatic, the clinical signs are often caused more by the surrounding edema than by the tumor mass itself. Ultimately, these changes can lead to herniation.

Figure 2. Occipital glioblastoma surrounded by vasogenic edema involving only the white matter

Highly aggressive tumors (glioblastomas, metastatic tumours, etc.) occur at all ages; however, there is a strong trend toward increasing malignancy with age. Highly malignant tumours and rapidly growing tumours are more commonly surrounded by vasogenic tumours than more benign tumours and tumours with a lower grade of malignancy. Highly
aggressive tumors are diffusely invasive tumors that typically have a destructive cellular core. Radiological signs characteristic of vasogenic brain edema is described in the following table.

<table>
<thead>
<tr>
<th>RADILOGICAL SIGN</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrast enhancement.</td>
<td>Contrast enhancement is due to break down of blood brain barrier which is the cornerstone in the aetiopathogenesis of vasogenic edema. The microscopic correlate of enhancement is hypercellularity, mitotic activity, neovascularity (in brain tumours) and breakdown of blood brain barrier resulting in increased permeability of brain capillary endothelial cells to macromolecules, such as the plasma proteins and various other molecules, whose entry is limited by the capillary endothelial cells (blood brain barrier).</td>
</tr>
<tr>
<td>Diffuse low density on CT scan, diffuse MRI T1 hypointensity and diffuse MRI T2 hyperintensity with loss of the gray-white interface, obscuration of the lentiform nucleus, loss of the insular ribbon.</td>
<td>Obscuration of the lentiform nucleus, loss of the insular ribbon is simply due to loss of the gray-white interface.</td>
</tr>
<tr>
<td>Sulcal effacement.</td>
<td>Grossly, the gyri are flattened and the sulci narrowed; the white matter is moist and swollen. Microscopically, there is microvacuolization of the white matter, poor staining, and &quot;halo's&quot; around nuclei.</td>
</tr>
<tr>
<td>Mass effect, with ventricular effacement.</td>
<td>Is a common cause of brain herniation.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ZONE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>CENTRAL ZONE</td>
<td>FORMED OF NECROTIC TUMOUR TISSUE</td>
</tr>
<tr>
<td>INTERMEDIATE CONTRAST ENHANCING RIM</td>
<td>FORMED OF VIOLENT TUMOUR TISSUE</td>
</tr>
<tr>
<td>PERIPHERAL DIFFUSE ZONE</td>
<td>FORMED OF ODEMA, REACTIVE GLIOSIS AND MALIGNANT INFILTRATIONS</td>
</tr>
</tbody>
</table>

The relationship between neuroimaging actual tumor extent is critical to the use of these studies in diagnosis and treatment design. In general three zones are identified in malignant brain tumours (1) A central zone (hypointense on the MRI T1 images, hyperintense on the MRI T2 images and hypodense on CT scan) (2) A peripheral enhanced rim with multiple enhanced mural nodules and (3) An ill-defined diffuse large zone surrounding the first two zones. The first zone corresponds to the necrotic tumour tissues, the microscopic correlate of
enhancement is hypercellularity, mitotic activity, and neovascularity with breakdown of
blood brain barrier resulting in increased permeability of brain capillary endothelial cells
to macromolecules, such as the plasma proteins and various other molecules, whose entry is
limited by the capillary endothelial cells (blood brain barrier), while the third zone
corresponds to edema, malignant glial cell infiltrations and reactive gliosis. The
surrounding zone of edema demonstrates a decreasing gradient of infiltrating tumor cells.
**The infiltrating tumor cells primarily follow white matter tracts, accompanied by vasogenic edema that may facilitate migration.** Although tumor cells may spread a great
distance, typically, most are within 2 cm of the enhancing margin.

Glioblastomas characteristically send malignant cells streaming into the surrounding brain. This
mode of spread is apparently facilitated by the widened extracellular spaces created through
vasogenic edema.

- **Vasogenic edema and peritumoral cyst formation**

Two types of cysts—peritumoral and intratumoral— are associated with CNS tumors. Peritumoral cysts develop within the brain or spinal cord and form at the margin of the
tumor. Alternatively, intratumoral cysts develop within the tumor itself and are usually the
result of intratumoral necrosis. Overall, cysts are associated with approximately 10% of
benign, malignant, and metastatic tumors of the CNS. They are most frequently associated
with hemangioblastomas (83%), cerebellar astrocytomas (77%), and cerebral astrocytomas
(29%). The presence of peritumoral cysts can lead to significant neurological impairment
due to mass effect and increased intracranial pressure. Based on advances in imaging,
histological, and molecular techniques, insight into the mechanism behind peritumoral cyst
formation has been provided, and evidence indicates that peritumoral edema precedes and
underlies the propagation of these cysts.

Peritumoral cysts (those arising immediately adjacent to the tumor mass) are frequently
associated with benign and malignant tumors of the brain and spinal cord (syringomyelia).
The cystic component of central nervous system (CNS) tumors and associated peritumoral
cysts are often the cause of clinical symptoms. Because of the common occurrence of
peritumoral cysts with CNS neoplasms and the morbidity associated with them, advanced
imaging, histological, and molecular techniques have been used to determine the
mechanism underlying cyst formation and propagation. Based on evidence from such
studies, edema appears to be a common precursor to peritumoral cyst formation in the
CNS. Mediators of vascular permeability acting locally in the tumor and/or hydrodynamic
forces within abnormal tumor vasculature appear to drive fluid extravasation. When these
forces overcome the ability of surrounding tissue to resorb fluid, edema and subsequent
cyst formation occur. These findings support the concept that the tumor itself is the source
of the edema that precedes cyst formation and that resection of tumors or medical
therapies directed at decreasing their vascular permeability will result in the resolution of
edema and cysts.
Management of vasogenic edema

Cerebral edema tends to extend along white matter tracts. CT and MRI are helpful in the diagnosis of edema. Therapy includes tumor-directed measures, such as debulking surgery, radiotherapy (RT), chemotherapy, and the use of corticosteroids. Ingraham and coworkers pioneered the use of cortisone to treat postoperative cerebral edema in neurosurgical patients in 1952. He first used steroids in an attempt to ameliorate postoperative adrenal insufficiency in patients undergoing craniotomy for craniopharyngioma resection and noted the favorable effect on postoperative cerebral edema. Galicich and colleagues and French and Galicich introduced dexamethasone therapy as the standard treatment for tumor-associated edema. Despite their well-known side effects, better alternatives do not exist and corticosteroids have remained the mainstay of treatment ever since.

The mechanism of action of corticosteroids is not well understood. It has been argued that their antiedema effect is the result of reduction of the permeability of tumor capillaries by causing dephosphorylation of the tight junction component proteins occludin and ZO1. Corticosteroids usually are indicated in any patients who have brain tumor who have symptomatic peritumoral edema. Dexamethasone is used most commonly as it has little mineralocorticoid activity and, possibly, a lower risk for infection and cognitive impairment compared with other corticosteroids. The choice of starting dose of a corticosteroid largely is arbitrary and depends on the clinical context. The usual starting dose is a 10-mg load, followed by 16 mg per day in patients who have significant symptomatic edema. Lower doses may be as effective, especially for less severe edema. The dose may be increased up to 100 mg per day if necessary. Dexamethasone can be given twice daily, although many clinicians prescribe it 4 times daily. As a general rule, patients should be treated with the smallest effective dose for the shortest time possible to avoid the harmful effects of steroids. For asymptomatic patients who have peritumoral edema on imaging studies, corticosteroids are unnecessary. Dexamethasone usually produces symptomatic improvement within 24 to 72 hours. Generalized symptoms, such as headache and lethargy, tend to respond better than focal ones. Improvement on CT and MRI studies often lags behind clinical improvement. Contrast enhancement of tumors typically decreases, suggesting partial restoration of the BBB, whereas tumor perfusion can increase because of reduced peritumoral water content and local tissue pressure. Using diffusion tensor MRI, administration of corticosteroids decreases peritumoral extracellular water content in edematous brain without affecting the water content of contralateral normal brain.

Occasionally, when there is significant mass effect and impending herniation, other measures may be required until corticosteroids have had a chance to take effect or until patients undergo debulking surgery. These include elevation of the head of the bed, fluid restriction, mannitol, hypertonic saline, diuretics, and hyperventilation.

After more surgical debulking, steroids should be tapered. The taper can start within a week after surgery but should be delayed in symptomatic patients undergoing RT. In general, patients who have brain tumors exerting significant mass effect should receive
steroids for 24 hours before starting RT to reduce intracranial pressure and minimize neurologic symptoms.

**CELLULAR (CYTOTOXIC) EDEMA**

Cellular edema is characterized by swelling of all the cellular elements of the brain (neurons, glia, and endothelial cells), with a concomitant reduction in the volume of the extracellular fluid space of the brain. Capillary permeability is not usually affected in the various cellular edemas. Patients so affected have a normal CSF protein and isotopic brain scan. CT does not reveal enhancement with contrast, and MRI is normal.

Cellular swelling, usually of astrocytes in the grey matter, and classically is seen following cerebral ischemia caused by cardiac arrest or minor head injury. The blood brain barrier (BBB) is intact. Intracellular edema is usually not clinically significant, and is reversible in its early phases.

There are several causes of cellular edema: hypoxia, acute hypo-osmolality of the plasma, and osmotic" disequilibrium syndromes. Hypoxia after cardiac arrest results in cerebral energy depletion. The cellular swelling is osmotically determined by the appearance of increased intracellular osmoles (especially sodium, lactate, and hydrogen ions) that induce the rapid entry of water into cells. Acute hypo-osmolality of the plasma and extracellular fluid is caused by acute dilutional hyponatremia, inappropriate secretion of antidiuretic hormone, or acute sodium depletion. The brain adapts to hyponatremia by losing intracellular osmoles, chiefly potassium, thereby preserving cellular volume. Osmotic disequilibrium syndromes occur with hemodialysis or diabetic ketoacidosisis, in which excessive brain intracellular solutes result in excessive cellular hydration when the plasma osmolality is rapidly reduced with therapy. The precise composition of the osmotically active intracellular solutes responsible for cellular swelling in the disequilibrium syndromes that are associated with hemodialysis and diabetic ketoacidosis is not known.
Table 2. Causes of cytotoxic brain edema

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxia</td>
<td>Cerebral energy depletion. The cellular swelling is osmotically determined by the appearance of increased intracellular osmoles (especially sodium, lactate, and hydrogen ions) that induce the rapid entry of water into cells.</td>
</tr>
<tr>
<td>Acute hypo-osmolality of the plasma and extracellular fluid</td>
<td>Caused by acute dilutional hyponatremia, inappropriate secretion of antidiuretic hormone, or acute sodium depletion. The brain adapts to hyponatremia by losing intracellular osmoles, chiefly potassium, thereby preserving cellular volume.</td>
</tr>
<tr>
<td>Osmotic disequilibrium syndromes occur with hemodialysis or diabetic ketoacidosis.</td>
<td>Excessive brain intracellular solutes result in excessive cellular hydration when the plasma osmolality is rapidly reduced with therapy. (In uremia, the intracellular solutes presumably include a number of organic acids, which have been recovered in the dialysis bath. In diabetic ketoacidosis, the intracellular solutes include glucose and ketone bodies; however, there are also unidentified, osmotically active, intracellular solutes, termed idiogenic osmoles that favor cellular swelling.</td>
</tr>
</tbody>
</table>

In uremia, the intracellular solutes presumably include a number of organic acids, which have been recovered in the dialysis bath. In diabetic ketoacidosis, the intracellular solutes include glucose and ketone bodies; however, there are also unidentified, osmotically active, intracellular solutes, termed idiogenic osmoles that favor cellular swelling. Increased intracellular osmolality in excess of the plasma level not only causes cellular swelling but also is responsible for complex changes in brain metabolism affecting the concentrations of the neurotransmitter amino acids, ammonia, and other metabolites, which in turn have profound effects on brain function.

Major changes in cerebral function occur with the cellular edemas, including stupor, coma, EEG changes and asterixis, myoclonus, and focal or generalized seizures. The encephalopathy is often severe with acute hypo-osmolality but, in more chronic state's of hypo-osmolality of the same severity, neurologic function may be spared. Acute hypoxia causes cellular edema, which is followed by vasogenic edema as infarction developes. Vasogenic edema increases progressively for several days after an acute arterial occlusion. The delay in obtaining contrast enhancement with CT following an ischemic stroke illustrates the passage of time that is needed for defects in endothelial cell function to develop and mature.

**ISCHEMIC BRAIN EDEMA**

Most patients with arterial occlusion have a combination of first cellular and then vasogenic edema, together termed ischemic brain edema. The cellular phase takes place
after acute ischemia over minutes to hours and may be reversible. The vasogenic phase
takes place over hours to days and results in infarction, a largely irreversible process,
although the increased endothelial cell permeability usually reverts to normal within
weeks. the factors that determine the reversibility of ischemic edema at the cellular level
are poorly understood.

Figure 3. Vasogenic brain edema following acute embolic brain infarctions, notice loss of
white-gray matter interface, loss of sulcation and mass effect

- Parenchyma changes of acute infarction
  - Pathophysiology

The CT detection of acute infarcts depends on the development of edema within the brain
parenchyma, which produces subtle density changes and mass effect. To understand better
the CT findings of acute ischemia, a brief review of the histologic changes that occur during
a stroke are presented.

Normal cerebral blood flow ranges from 50 to 60 mL/100 g tissue/min. During an ischemic
infarct, blood supply to a portion of the brain is significantly reduced. As cerebral blood
flow decreases, injury occurs in the brain progressing from electrical dysfunction to
reversible cellular damage and eventually to cell death. At approximately 20 mL/100 g,
electrical activity in the brain ceases, and water homeostasis begins to be disrupted. At
critical flow rates of 10 to 15 mL/100 g, there is disruption of ion homeostasis within the
cells producing rapid increases of extracellular potassium and intracellular sodium. This disruption causes water to shift into the intracellular compartment producing astrocytic swelling (cytotoxic edema).

Severe ischemia can cause a 7 to 8 HU change at 1 hour that should be visible on CT. With marginal cerebral blood flows between 15 and 20 mL/100 g, ischemic edema takes longer to develop and may not be detected on early CT scans.

The development of cytotoxic edema aggravates ischemia by causing progressive compression of the microcirculation, which further decreases blood flow. As the ischemic changes worsen, capillary walls become permeable allowing leakage of intracellular proteins and subsequent accumulation of extracellular water (vasogenic edema). Worsening edema produces additional mass effect causing a decrease in cerebral perfusion pressure and collateral flow. Cytotoxic edema may be detectable within 1 hour of the onset of stroke; however, vasogenic edema usually does not develop until 6 hours or more after ictus.

Figure 4. Acute infarctions with mass effect due to edema
Figure 5. Acute infarction with mass effect and obscuration of the lentiform nucleus, loss of the insular ribbon, loss of the gray-white interface, and sulcal effacement.

Table 3. Comparison between the cytotoxic and vasogenic edema of recent infarction

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cytotoxic (intracellular)</th>
<th>Vasogenic (extracellular)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>Within 1 hour of the onset of stroke</td>
<td>Does not develop until 6 hours or more after ictus.</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>At critical flow rates of 10 to 15 mL/100 g, there is disruption of ion homeostasis within the cells producing rapid increases of extracellular potassium and intracellular sodium. This disruption causes water to shift into the intracellular compartment producing astrocytic swelling (cytotoxic edema).</td>
<td>The development of cytotoxic edema aggravates ischemia by causing progressive compression of the microcirculation, which further decreases blood flow. As the ischemic changes worsen, capillary walls become permeable allowing leakage of intracellular proteins and subsequent accumulation of extracellular water (vasogenic edema).</td>
</tr>
<tr>
<td>Composition</td>
<td>Increased intracellular water and sodium</td>
<td>Plasma filtrate including plasma proteins</td>
</tr>
<tr>
<td>Location of edema</td>
<td>Gray and white matter</td>
<td>Chiefly white matter</td>
</tr>
<tr>
<td>Pathology</td>
<td>Cellular swelling, usually of astrocytes in the grey matter.</td>
<td>Grossly, the gyri are flattened and the sulci narrowed; the white matter is moist and swollen. Microscopically, there is microvacuolization of the white matter, poor staining, and &quot;halo's&quot; around nuclei.</td>
</tr>
<tr>
<td>Capillary</td>
<td>Normal</td>
<td>Increased</td>
</tr>
</tbody>
</table>
Figure 6. A, In vasogenic edema the gyri are flattened and the sulci narrowed; the white matter is moist and swollen. B, left sided acute embolic brain infarction, showing evidence of brain edema with mass effect, flattened gyri and sulcal effacement.

Ischemic changes that occur above 15 mL/100 g can be reversible. At flow rates below 10 to 15 mL/100 g, tissue damage is usually irrevocable after 1 hour of hypoperfusion. Other factors also play a role in the reversibility of ischemic changes. During low levels of perfusion, small amounts of glucose may be available to brain tissue for glycolysis, but oxidation cannot occur. The subsequent development of lactic acidosis adversely affects the viability of brain tissue.

- Sensitivity of CT in Evaluating Acute Ischemia: How Early Can Stroke Be Detected?

How quickly an acute infarct can be visualized is governed primarily by the severity of hypoperfusion; however, the duration, size, and location of ischemia also play important roles. When cerebral blood flow drops below the critical value of 10 to 15 mL/100 g, ischemic changes are usually irreversible, and edema develops fast, permitting early detections.
As edema progresses, water content within the parenchyma increases. This increase causes a subsequent decrease in the brain's specific gravity, which is linearly proportional to CT attenuations. In other words, as edema increases, brain density proportionately decreases. A 1% change in water content changes the CT attenuation by 2.6 HU. Typically a change of 4 HU or greater is needed to detect the change visually. In cases of severe ischemia caused by proximal MCA occlusion, cytotoxic edema can produce a 3% increase in water within 1 hour of the onset of symptoms. This can increase to 6% at 2 to 4 hours. Therefore, severe ischemia can cause a 7 to 8 HU change at 1 hour that should be visible on CT. With marginal cerebral blood flows between 15 and 20 mL/100 g, ischemic edema takes longer to develop and may not be detected on early CT scans.

In the future, more advanced imaging techniques, such as MR perfusion and xenon CT, may play an important role in determining the cerebral blood flow of ischemic areas to help determine tissue viability. Until then, noncontrast CT can provide important information. If hypoperfusion is less severe and collaterals to an ischemic area are adequate, edema may not develop, and early CT scans are negative. Conversely the presence of more extensive edema on an early CT scan indicates severe hypoperfusion and may predict a less favorable outcome after thrombolytic therapy.

The sensitivity of early CT scans in detecting acute strokes also depends on the duration, location, and size of the infarct. As the time of ischemia increases, CT abnormalities become more obvious; however, the absolute presence or absence of edema primarily relies on the severity of hypoperfusion and adequacy of collateral circulation. Larger infarcts are visible earlier than smaller infarcts because of the increased volume of tissue involved (i.e., MCA infarcts are detected sooner than small cortical or lacunar infarcts).

Several researchers have studied the sensitivity and accuracy of detecting infarcts on CT. Bryan et al performed MR imaging and CT scans on 31 stroke patients within 24 hours of the onset of their symptoms. The locations of the infarcts included the posterior fossa as well as supratentorial cortical, subcortical, and combined lesions. Eighty-two percent of early MR imaging scans showed an abnormality compared with 58% of CT scans. On follow-up examinations performed 7 to 10 days later, approximately 90% of both MR imaging and CT scans were abnormal. Mohr et al demonstrated that although CT showed deep and brain stem infarcts less often than MR imaging, it was equally sensitive in detecting convexity lesions.

When analysis is restricted to the assessment of MCA infarcts, the overall sensitivity of CT significantly increases. Moulin et al reviewed 100 patients with MCA stroke. Ninety-four percent of all CT scans performed within 14 hours after the onset of symptoms were abnormal; 88% of CT scans obtained within 6 hours of ictus were abnormal. These results compare favorably with data of von Kummer et al. A review of 44 patients demonstrated that CT performed within 6 hours of the onset of symptoms has an accuracy of 95% and a mean sensitivity of 82% of detecting MCA infarcts. CT scans performed within the first 2 hours of symptoms, however, were much less sensitive in detecting early ischemia. Truwit
and Tomura et al described subtle findings of MCA stroke that can increase the sensitivity of CT to greater than 90% in detecting major MCA occlusions.

The presence of parenchymal changes on early CT scans also correlates with the degree of intracranial occlusive disease. Horowitz et al studied 50 patients with ischemic strokes that produced at least hemiparesis. CT scans were performed within 4 hours of ictus and were correlated with angiography or carotid ultrasound. Acute CT abnormalities, including hypodensities and mass effect, were seen in 56% of patients. When there was major vascular occlusion, however, either occlusion of the MCA trunk or two or more MCA branches, the CT scan was positive in 86% of cases.

**CT Findings**

Several articles describing early CT findings of acute infarcts have been published in recent years. These findings have primarily focused on MCA ischemia and have significantly improved the overall sensitivity of CT in detecting early MCA infarcts. The major CT findings of acute MCA stroke include (1) obscuration of the lentiform nucleus, (2) loss of the insular ribbon, (3) diffuse low density with loss of the gray-white interface, and (4) sulcal effacement.

- **Obscuration of the Lentiform Nucleus.**

In 1988, Tomura et al described obscuration of the lenticular nucleus as an early sign of MCA infarct. This finding is caused by cellular edema arising within the basal ganglia and closely correlates with a proximal MCA occlusion. Twenty-five patients who had clinical evidence of MCA infarcts underwent CT scanning within 6 hours of the onset of symptoms. The scans were then retrospectively reviewed for obscuration of the lenticular nuclei as well as decreased density within the brain parenchyma and sulcal effacement. Twenty-three of the patients (92%) demonstrated an obscured outline or partial disappearance of the lentiform nucleus. This sign was visualized earlier than other CT findings and in a few cases was present within 1 hour after the onset of the stroke. Parenchymal hypodensities and sulcal effacement occurred later and were present on significantly fewer initial scans.

The lenticular nuclei receive their blood supply from the lenticulostriate arteries which arise from the MI trunk of the MCA. Collateral circulation to this area is poor compared with the cortex. Occlusion of the proximal MCA disrupts the primary blood supply to these structures. As a result of the insufficient collaterals as well as the relatively high metabolic rate of the lenticular nuclei, proximal MCA occlusion can quickly cause critically low cerebral blood flow, which produces early ischemic changes on CT.

Firlick et al performed CT, xenon CT, and angiography on 20 patients with acute MCA infarcts. Early CT changes in the basal ganglia were associated with significantly lower cerebral blood flows in the MCA territory compared with patients with normal CT scans. An early basal ganglia hypodensity correlated with a mean cerebral blood flow in the affected MCA territory of less than 10 mL/100 g. Patients with more distally located
occlusions, beyond the origins of the lenticulostriate arteries, preserve blood supply to the basal ganglia and do not develop this early sign.

Bozzao et al evaluated 36 patients with acute MCA infarcts with CT and angiography and correlated changes on early CT scans with the angiographic findings. CT scans were performed within 4 hours, and angiograms were obtained within 6 hours from the onset of symptoms. Bozzao et al noted that all patients with early CT findings of MCA infarcts demonstrated an arterial occlusion on angiography. Involvement of the lenticular nuclei corresponded closely with a proximal MCA occlusion.

- **Loss of the Insular Ribbon. (LIR)**

Another early sign of acute MCA infarction is loss of the insular ribbon (LIR) which is described as loss of definition of the gray-white interface in the lateral margins of the insula. This area is supplied by the insular segment of the MCA and its claustral branches and is the region most distal from anterior and posterior cerebral collateral circulation. As a result, collateral flow to the insular region is decreased compared with other portions of the cerebral cortex.

Truwit et al performed both retrospective and prospective evaluations of CT scans in patients with clinical evidence of acute MCA distribution infarcts to evaluate the sensitivity and accuracy of the LIR sign. In a retrospective analysis of 11 cases, LIR was seen in all patients (100%). In a prospective study, the LIR sign was identified in 12 of 16 patients (75%). Obscuration of the lenticular nucleus occurred less frequently and was identified in 73% and 63% of patients. They concluded that LIR is more frequently observed in acute MCA infarcts than other early CT findings.

In two patients, the LIR was localized to the posterior segment of the insula and was associated with a more limited infarct. This situation may be due to more distal occlusion of posterior MCA branches within the operculum.

The presence of obscuration of the lenticular nucleus or LIR without other signs of extensive infarct does not preclude the use of thrombolytic agents. These patients may receive significant benefit from intravenous or intraarterial thrombolysis; because of the presence of early CT changes, however, they may be more likely to have areas of irreversible damage compared with patients with negative CT scans.

- **Diffuse Parenchymal Hypodensity and Sulcal effacement.**

As ischemic changes progress, both cytotoxic and vasogenic edema increase producing areas of hypoattenuation throughout the affected circulation. In larger infarcts, mass effect also increases producing effacement of sulci and compression of ventricles.
Figure 7. A 52-year-old woman who presented with sudden onset of left arm weakness. A and B, CT scan performed three hours after the onset of symptoms demonstrates focal loss of the insular ribbon posteriorly (arrows). A more superior image performed through the lateral ventricles demonstrates an area of low attenuation in the right posterior frontal cortex with loss of the gray-white interface (arrows) consistent with ischemic change in the right MCA distribution.

Detection of anterior and posterior cerebral artery infarcts as well as posterior fossa lesions relies predominantly on the presence of parenchymal hypodensity and sulcal effacement. As a result of the lack of other subtle CT findings, such as obscuration of the lenticular nucleus and LIR, these infarcts may not be detected as early as large MCA strokes.

In cases of MCA infarcts, extensive parenchymal hypodensity on early CT scans is associated with a high mortality rate as well as a poor clinical outcome in survivors. When greater than 50% of the vascular territory was involved, the mortality rate increased up to 85% because of malignant brain edema. Early craniectomy decreases the mortality rate for patients with severe edema; however, clinical outcome remains poor.

Figure 8. A 67-year-old man who presented with a 5-hour history of left leg weakness. A and B, CT scan shows subtle low attenuation and loss of sulcation in the right parasagittal frontal lobe extending to the convexity (arrowheads) consistent with an anterior cerebral
artery distribution infarct. C, MR diffusion scan demonstrates abnormal high signal in the right frontal parasagittal region confirming the diagnosis of an ACA infarct.

The presence of extensive ischemic change typically excludes the use of thrombolytic therapy. The likelihood of clinical improvement is low, whereas the rate of complication, including hemorrhage, is significantly increased. In the future, faster mechanical methods of removing clot within the MCA may offer benefit to these patients; however, in most cases, irreversible damage has been done.

Table 4. Early CT scan features of acute ischemic stroke

<table>
<thead>
<tr>
<th>Radiological feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse Parenchymal Hypodensity and Sulcal effacement.</td>
<td>A 1% change in water content changes the CT attenuation by 2.6 HU. Typically a change of 4 HU or greater is needed to detect the change visually. In cases of severe ischemia caused by proximal MCA occlusion, cytotoxic edema can produce a 3% increase in water within 1 hour of the onset of symptoms. This can increase to 6% at 2 to 4 hours. Therefore, severe ischemia can cause a 7 to 8 HU change at 1 hour that should be visible on CT. If hypoperfusion is less severe and collaterals to an ischemic area are adequate, edema may not develop, and early CT scans are negative. Conversely, the presence of more extensive edema on an early CT scan indicates severe hypoperfusion and may predict a less favorable outcome after thrombolytic therapy.</td>
</tr>
<tr>
<td>Loss of the Insular Ribbon. (LIR)</td>
<td>Loss of definition of the gray-white interface in the lateral margins of the insula.</td>
</tr>
<tr>
<td>Obscuration of the Lentiform Nucleus.</td>
<td>Obscuration of the lenticular nucleus is an early sign of MCA infarct. This finding is caused by cellular edema arising within the basal ganglia and closely correlates with a proximal MCA occlusion.</td>
</tr>
</tbody>
</table>

CEREBRAL EDEMA ASSOCIATED WITH NONTRAUMATIC CEREBRAL HEMORRHAGE

Traditionally, ICH was believed to cause permanent brain injury directly by mass effect. However, the importance of hematoma-induced inflammatory response and edema as contributors to secondary neuronal damage has since been recognized.

At least three stages of edema development occur after ICH (Table 5). In the first stage, the hemorrhage dissects along the white matter tissue planes, infiltrating areas of intact brain. Within several hours, edema forms after clot retraction by consequent extrusion of osmotically active plasma proteins into the underlying white matter. The second stage
occurs during the first 2 days and is characterized by a robust inflammatory response. In this stage, ongoing thrombin production activates by the coagulation cascade, complement system, and microglia. This attracts polymorphonuclear leukocytes and monocyte/macrophage cells, leading to up-regulation of numerous immunomediators that disrupt the blood-brain barrier and worsen the edema. A delayed third stage occurs subsequently, when red blood cell lysis leads to hemoglobin-induced neuronal toxicity. Perihematomal edema volume increases by approximately 75% during the first 24 hours after spontaneous ICH and has been implicated in the delayed mass effect that occurs in the second and third weeks after ICH.

Thrombin is an essential component of the coagulation cascade, which is activated in ICH. In low concentrations thrombin is necessary to achieve hemostasis. However, in high concentrations, thrombin induces apoptosis and early cytotoxic edema by a direct effect. Furthermore, it can activate the complement cascade and matrix metalloproteinases (MMP) which increase the permeability of the blood brain barrier.

Delayed brain edema has been attributed, at least in part, to iron and hemoglobin degradation. Hemoglobin is metabolized into iron, carbon monoxide, and biliverdin by heme oxygenase. Studies in animal models show that heme oxygenase inhibition attenuates perihematomal edema and reduces neuronal loss. Furthermore, intracerebral infusion of iron causes brain edema and aggravates thrombin-induced brain edema. In addition, iron induces lipid peroxidation generating reactive oxygen species (ROS), and deferoxamine, an iron chelator, has been shown to reduce edema after experimental ICH.

Table 5. Stages of edema after ICH

<table>
<thead>
<tr>
<th>First stage (hours)</th>
<th>Second stage (within first 2 days)</th>
<th>Third stage (after first 2 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Clot retraction and extrusion of</td>
<td>• Activation of the coagulation cascade and thrombin synthesis</td>
<td>• Hemoglobin induced neuronal toxicity</td>
</tr>
<tr>
<td>osmotically active proteins</td>
<td>• Complement activation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Perihematomal inflammation and leukocyte infiltration</td>
<td></td>
</tr>
</tbody>
</table>
EDEMA DUE TO MENINGITIS

Early in the course of meningitis, changes take place in the meningeal and cerebral capillaries, including an increase in permeability of the blood-brain barrier. The major physiologic consequence of this altered vascular permeability is vasogenic edema. The observed brain edema may also have a cytotoxic component emanating from inflammatory mediators in the meningeal exudate and from parenchymal hypoxia and a complex interstitial (edematous) component resulting from impaired cerebrospinal fluid absorption resulting from arachnoid villi dysfunction from blockage by fibrin and leukocytes. Increased intracranial pressure resulting from cerebral edema and reduced cerebrospinal fluid resorption produce vomiting and obtundation. In extreme instances, cerebral edema may produce transtentorial herniation with brain stem compression and eventual respiratory arrest and death.

INTERSTITIAL (HYDROCEPHALIC) EDEMA

Interstitial edema is the third type of edema, best characterized in obstructive hydrocephalus, in which the water and sodium content of the periventricular white matter is increased because of the movement of CSF across the ventricular walls. Obstruction of the circulation of the CSF results in the transepndymal movement of CSF and thereby an absolute increase in the volume of the extracellular fluid of the brain. This is observed in obstructive hydrocephalus with CT and MRI. Low-density changes are observed at the angles of the lateral ventricles. The chemical changes are those of edema, with one exception: the volume of periventricular white matter is rapidly reduced rather than increased. After successful shunting of CSF, interstitial edema is reduced and the thickness of the mantle is restored.
Periventricular hyperintensities is seen in this patient with obstructive hydrocephalus. Obstruction of the circulation of the CSF results in the transependymal movement of CSF and thereby an absolute increase in the volume of the extracellular fluid of the brain.

Functional manifestations of interstitial edema are usually relatively minor in chronic hydrocephalus unless the changes are advanced, when dementia and gait disorder become prominent. This finding indicates that the accumulation of CSF in the periventricular extracellular fluid space is much better tolerated than is the presence of plasma in the extracellular fluid space, as seen with vasogenic edema, which is characterized by focal neurologic signs.

**SUMMARY**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Vasogenic</th>
<th>Cytotoxic</th>
<th>Interstitial (Hydrocephalic)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pathogenesis</strong></td>
<td>Increased capillary permeability</td>
<td>Cellular swelling (neuronal, endothelial, glial)</td>
<td>Increased brain fluid due to block of CSF absorption</td>
</tr>
<tr>
<td><strong>Location of edema</strong></td>
<td>Chiefly white matter</td>
<td>Gray and white matter</td>
<td>Chiefly periventricular white matter in hydrocephalus</td>
</tr>
<tr>
<td><strong>Edema fluid composition</strong></td>
<td>Plasma including proteins</td>
<td>filtrate plasma</td>
<td>Increased intracellular water</td>
</tr>
<tr>
<td><strong>Capillary permeability to large molecules (RISA, inuhn)</strong></td>
<td>Increased</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Disease conditions</strong></td>
<td>Brain tumor, abscess, infarction, trauma, Hypoxia, hypo-osmolality</td>
<td>Obstructive hydrocephalus</td>
<td></td>
</tr>
</tbody>
</table>

Figure 10.
**RADIOLOGICAL PATHOLOGY OF ASTROGLIOSIS**

Astrogliosis (reactive astrogliosis as seen in old infarction, old MS plaques, head trauma, etc. and neoplastic astrogliosis as seen in low grade gliomas) is seen hypodense of CT scan, hypointense on T1 MRI images and hyperintense on the T2 MRI images. This radiological picture would suggest edema. The question then arises: Is this vasogenic edema or cytotoxic edema? Because the blood-brain barrier is intact, vasogenic edema is unlikely. The cells are not dead or dying, so that cytotoxic edema is also unlikely.

![Image](image1.png)

**Figure 11.** A, subacute infarction, B, old infarction with extensive gliosis and cavitations

![Image](image2.png)

**Figure 12.** (A) Old infarction with extensive gliosis, microcavitations, the infarction is hypodense with negative mass effect (B)
Perhaps the edema results from the increased number of astrocytic cells that spread apart the normal myelinated axons of the white matter. The presence of significant amount of normal appearing astrocytes (hyperplasia), with marked cytoplasmic hypertrophy and low nuclear to cytoplasm ratio result in total increase in the water content of the brain. These cells may merely have different physical and chemical properties than the normal tightly packed bundles of axons that traverse through the brain. Astrogliosis is commonly associated with widened fluid filled extracellular spaces (microcavitations and macrocavitations) which definitely increase tissues water content resulting in the characteristic CT scan/MRI picture.

Figure 13. With progression of time (from A to C) the infarction gets more hypodense and the mass effect gradually decreases with time due to gradual reduction of brain edema because the blood brain barrier is once again sealed. The initial hypodensity in acute infarction is due to edema (A) while the the ultimate hypodensity in old infarction (C) is due to astrogliosis with widened fluid filled extracellular spaces (microcavitations and macrocavitations). During the evolution of the infarction the edema and the swelling decreases and the infarction boundary becomes better defined , and the infarcted area becomes more hypodense.
Astrocytes have extensive vascular foots. 

Astrogliosis (astrocytic hyperplasia) commonly results in the formation of a mesh with enlargement of extracellular spaces and extensive fluid-filled microcavitations. This, coupled with marked cytoplasmic hypertrophy of astrocytes that results in low nuclear to cytoplasm ratio, are responsible for the CT scan picture of old infarction.

### Table 6. Comparison between CT hypodensity of recent and old infarctions

<table>
<thead>
<tr>
<th>Aetiology of CT hypodensity</th>
<th>Recent infarction</th>
<th>Old infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aetiology of CT hypodensity</td>
<td>Vasogenic edema (cytotoxic edema does not contribute to CT hypodensity)</td>
<td>Astroglisis with widened fluid filled extracellular spaces (microcavitations and macrocavitations)</td>
</tr>
</tbody>
</table>
Figure 15. MRI T2, FLAIR, and T1 postcontrast images showing a well circumscribed lesion in the left frontal lobe, the lesion is hyperintense in T2 and FLAIR images, hypointense on T1 image with no postcontrast enhancement. This radiological picture would suggest edema probably due to neoplastic astrogliosis.

COMPLICATIONS OF BRAIN EDEMA

- **Brain herniation**

The cranial cavity is partitioned by the tentorium cerebelli and falx cerebri. When a part of the brain is compressed by an extrinsic lesion such as a subdural hematoma or is expanded because of a contusion or other intrinsic pathology, it is displaced (herniates) from one cranial compartment to another. Three major herniations can occur, either alone or in combination.

Is a major consequence of cerebral edema. Because of the rigid skull and partitioning of the cranial vault by the falx cerebri and tentorium cerebelli, when the brain swells it is displaced relative to these partitions or is pushed toward the foramen magnum. There are several types of brain herniations - classified by the part that is herniated or the structure under which it has been pushed.

Subfalcial herniation is displacement of the cingulate gyrus from one hemisphere to the other, under the falx cerebri. Subfalcial herniation can compress the pericallosal arteries, causing an infarct in their distribution.
Figure 16. **Subfalcine herniation (arrows).** Subfalcial herniation is displacement of the cingulate gyrus from one hemisphere to the other, under the falx cerebri. Subfalcial herniation can compress the pericallosal arteries, causing an infarct in their distribution.

Uncal (transtentorial) herniation is herniation of the medial temporal lobe from the middle into the posterior fossa, across the tentorial notch. The uncus of the temporal lobe is forced into the gap between the midbrain and the tentorium.

**Figure 17.** A, This figure represents a view of the ventral part of both cerebral hemispheres. The brain stem has been removed at the mid brain level. The occipital lobes shows the dura representing the tentorium of the cerebellum. There is bilateral herniation of the hippocampal gyri (arrows). B, The right hippocampus (seen on the left side of the photograph) shows the larger herniation. Uncal (transtentorial) herniation is herniation of
the medial temporal lobe from the middle into the posterior fossa, across the tentorial notch. The uncus of the temporal lobe is forced into the gap between the midbrain and the tentorium.

Figure 18. As the herniating uncus displaces the midbrain laterally, the contralateral cerebral peduncle is compressed against the edge of the tentorium, causing paralysis on the same side as the primary lesion, another false localizing sign. Caudal displacement of the brainstem and stretching of its vessels causes a variety of hemorrhagic lesions in the midbrain and pons (secondary brainstem hemorrhages) - so-called Duret hemorrhages - that can devastate the reticular activating substance and other brainstem centers, resulting in focal neurological deficits and coma.

Figure 20. Postmortem specimens showing hemorrhage within the dorsal brainstem consistent with a Duret's hemorrhage. The so-called Duret hemorrhages seen here in the pons are secondary to downward compression that leads to stretching, ischemia and rupture of perforating arterioles and brain stem hemorrhage.
This compresses the ipsilateral oculomotor nerve, causing a fixed and dilated pupil, and collapses the ipsilateral posterior cerebral artery, causing an infarct in its distribution. Cortical blindness resulting from this infarct is a false localizing sign because it gives the erroneous impression that the primary lesion is in the occipital lobe. As the herniating uncus displaces the midbrain laterally, the contralateral cerebral peduncle is compressed against the edge of the tentorium, causing paralysis on the same side as the primary lesion, another false localizing sign. Caudal displacement of the brainstem and stretching of its vessels causes a variety of hemorrhagic lesions in the midbrain and pons (secondary brainstem hemorrhages) that can devastate the reticular activating substance and other brainstem centers, resulting in focal neurological deficits and coma. Bilateral temporal lobe herniation occurs in global cerebral edema.

Pressure on the posterior fossa contents from above or from within flattens the pons against the clivus and displaces the cerebellar tonsils into the foramen magnum (cerebellar tonsillar herniation). Compression of the pons and medulla damages vital centers for respiration and cardiac function, and causes cardiorespiratory arrest.

Cerebral edema in TBI, HIE, brain tumors, meningitis, brain abscess, and other pathologies is caused by accumulation of water in interstitial spaces due to increased vascular permeability (vasogenic edema) and in some cases also by accumulation in injured cells (cytotoxic edema). Vasogenic edema involves more severely the white matter and extends along the optic nerves. The edematous optic papillae protrude forward into the vitreous chamber and displace the retina causing blurring of vision. Fundoscopic examination reveals blurred disk margins.

Understanding the anatomy and warning signs of herniations and promptly taking measures to reduce intracranial pressure will save lives. Herniations are important not only in trauma but in any condition associated with cerebral edema and increased intracranial pressure, including HIE, stroke, meningitis, brain abscess, brain tumors, and hydrocephalus.

![Cerebellar tonsillar herniation](image)

- **Complication of brain herniation**
  - **Coma**
As the midbrain is compressed and shifted the reticular activating system may be damaged, causing coma.

- **Cardio-respiratory arrest**

If the medulla is compressed by severe transtentorial herniation or by tonsillar herniation, the cardio-respiratory centers may be damaged, causing death.

- **Kernohan's notch**

Unilateral cerebral expansion with uncal herniation may push the contralateral cerebral peduncle against the tentorium, secondarily damaging it. A pressure groove (Kernohan's notch) may be seen on the peduncle. Thus, while the primary lesion may directly cause contralateral hemiparesis, the secondary damage to the contralateral peduncle may cause hemiparesis ipsilateral to the primary lesion.

---

**Figure 22. Kernohan's notch**

---

**THERAPEUTIC CONSIDERATION**

The therapy of brain edema depends on the cause. Appropriate and early treatment of intracranial infection is essential. Surgical therapy is directed toward alleviating the cause by excision or decompression of intracranial mass lesions, as well as by a variety of shunting procedures. A patent airway, maintenance of an adequate blood pressure, and the avoidance of hypoxia are fundamental requirements in the care of these patients.

The administration of appropriate parenteral fluids to meet the needs of the patient is also essential. Caution is necessary in the choice of isotonic parenteral fluids. Administration of salt-free fluids should be avoided. Intravenous infusion of a 5% glucose solution results in a
significant increase in intracranial pressure, which may be avoided with use of normal saline or 5% glucose in saline. If the excessive administration of salt is to be avoided, the use of 2.5% or 5% glucose in half-normal saline is satisfactory. In patients with cerebral edema, serum hypo-osmolality has deleterious effects and should be avoided.

The pharmacologic treatment of brain edema is based on the use of glucocorticoids, osmotherapy, and drugs that reduce CSF formation. Hyperventilation, hypothermia, and barbiturate therapy have also been tested experimentally and in clinical practice.

- **Glucocorticoids**

The rationale for the use of steroids is largely empirical. There is widespread conviction that glucocorticoids dramatically and rapidly (in hours) begin to reduce the focal and general signs of brain edema around tumors. The major mechanism suggested to explain their usefulness in vasogenic brain edema is a direct effect on endothelial cell function that restores normal permeability.

The biochemical basis, of the changes in membrane integrity that underlie vasogenic and cellular edema is now under study. Attention has focused on the role of free radicals (i.e., superoxide ions and singlet oxygen) and on the effect of polyunsaturated fatty acids, most notably arachidonic acid, in the peroxidation of membrane phospholipids. The ability of adrenal glucocorticoids to inhibit the release of arachidonic acid from cell membranes may explain their beneficial effects in vasogenic edema; however, steroids have not been shown to be therapeutically useful in the brain edema of hypoxia or ischemia. Cellular damage is more important than brain edema in these conditions.

There are no convincing data, clinical or Experimental, that glucocorticoids have beneficial effects in the cellular edema associated with hypo-osmolality, asphyxia, or hypoxia in the Absence of infarction with mass effects. There is little basis for recommending steroids in the treatment of the cerebral edema associated with cardiac arrest or asphyxia.

When intracranial hypertension and obstructive hydrocephalus occur because of inflammatory changes in the subarachnoid space or at the arachnoid villi, whether attributable to leukocytes or to blood, there is a reasonable rationale for the use of steroids. However, despite the frequent use of steroids in purulent or tuberculous meningitis, few data are available to document the effectiveness of steroids against the brain edema of the acute disease. There are conflicting reports about the efficacy of steroids in acute bacterial meningitis or tuberculous meningitis. The use of steroids has not been shown to affect the subsequent incidence of chronic sequelae such as obstructive hydrocephalus or seizures. Steroids appear useful in the management of other conditions characterized by an inflammatory CSF, such as chemical meningitis following meningeal sarcoidosis, or cysticercosis.
• **Osmotherapy**

Hypertonic solutions (including urea, mannitol, and glycerol) have been used to treat the intracranial hypertension associated with brain edema. The several solutes have been difficult to compare because a large variety of laboratory models, dosages, time intervals, and pathologic processes have been used.

A few principles seem certain. First, brain volume falls as long as there is an osmotic gradient between blood and brain. Second, osmotic gradients obtained with hypertonic parenteral fluids are short-lived because each of the solutes reaches an equilibrium concentration in the brain after a delay of only a few hours. Third, the parts of the brain most likely to "shrink" are normal areas; thus, with focal vasogenic edema, the normal regions of the hemisphere shrink but edematous regions with increased capillary permeability do not. Fourth, a rebound in the severity of the edema may follow use of any hypertonic solution because the solute is not excluded from the edematous tissue; if tissue osmolality rises, the tissue water is increased. Finally, there is scant rationale for chronic use of hypertonic fluids, either orally or parenterally, because the brain adapts to sustained hyperosmolality with an increase in intracellular osmolality due to the solute and to idiogenic osmoles.

There is some uncertainty about the size of an increase in plasma osmolality that causes a therapeutically significant decrease in brain volume and intracranial pressure in humans. Acute increases as small as 10 mOsm/L may be therapeutically effective. It should be emphasized that accurate dose-response relationships in different clinical situations have not been well defined with any of the hypertonic agents.

Other therapeutic Measures. Hyperventilation, hypothermia, and barbiturates have been used in the management of intracranial hypertension, but none is established and the extensive literature is not reviewed here. Acetazolamide and furosemide reduce CSF formation in animals but have limited usefulness in the management of interstitial edema.

• **Prevention and treatment of increased intracranial pressure (ICH)**

In addition to the effects of the edema itself, there are a number of possible contributors to increased ICP. They need to be treated aggressively since any increases in ICP result in the lowering of cerebral perfusion pressure (CPP), which results in further compromise of neurological function. They include: hypertension, hypoxia, hyperthermia, seizures, and elevations of intrathoracic pressure. Hypertension in patients with a mass lesion results in increased CPP in areas of brain with impaired autoregulation, contributing to the formation of brain oedema. There are no specific guidelines for the management of hypertension in this setting, except for the maintenance of normal CPP, in the 60-70 mmHg range. The medications of choice are those without cerebral vasodilator properties, and a useful combination is labetalol and furosemide.

However, in instances of severe hypertension the use of rapid-acting vasodilators such as nitroprusside is justified, as they produce rapid and easily titrable management of blood
pressure in emergency situations. Hypoxia produces an increase in cerebral blood flow (CBF) and cerebral blood volume, with an increase in ICP in patients with poor cerebral compliance. Adequate oxygenation is thus essential in patients with ICH and increased ICP, with the aim of maintaining pO₂ in the 100-150 mmHg range. Hyperthermia increases CBF and ICP, and also elevates arterial pCO₂, the latter partially counteracting the effects of therapeutic hyperventilation. This calls for vigorous treatment of fever and infections. The occurrence of seizures in the setting of acute ICH, especially likely in the lobar variety, can result in increased CBF, cerebral blood volume, and ICP. Their control is generally achieved by using intravenous diazepam, followed by loading doses of phenytoin or phenobarbitone. Elevations in intrathoracic pressure produced by endotracheal suction, coughing, chest therapy, and the use of positive end-expiratory pressure can result in transient elevations in ICP. These measures, otherwise critically important in maintaining airway potency and adequate oxygenation, need to be used judiciously and monitored closely in the setting of ICH with increased ICP.

The specific measures that are useful in the treatment of increased ICP are listed in Table 7. Hyperventilation reduces ICP by producing vasoconstriction, which is maximal in normal areas of the brain, where autoregulation is preserved. The ideal partial pressure of carbon dioxide (pCO₂) for this purpose is between 28 and 35 mmHg. The effects of hyperventilation are transient, as compensatory mechanisms within the central nervous system overcome the vasoconstriction that results from hypocarbia. A potential side-effect of the use of therapeutic hyperventilation is hypotension, that results from lowered cardiac filling pressure. It can be avoided by maintaining a normal intravascular volume, with isotonic or slightly hypertonic solutions. The use of osmotic diuretics is highly effective in rapidly lowering elevated ICP. Their effect is exerted by shifting water from the brain substance into the intravascular space, along with a small additional effect of reducing cerebrospinal fluid production and volume. High-dose intravenous barbiturates effectively reduce CBF and brain metabolism, resulting in a decrease in ICP. The most commonly used agent is thiopentone, 1-5 mg/kg. Its main side-effects are hypotension and markedly reduced neurological function, at times making the neurological examination useless as a way of monitoring therapy. The use of corticosteroids in the treatment of increased ICP in ICH is controversial, since their value in reducing brain oedema in other conditions, such as brain metastases, has not been established in patients with ICH. In a controlled, randomized, double-blind clinical trial conducted by Poungvarin et al (1987), dexamethasone was not superior to placebo in terms of mortality at 21 days from onset of ICH, and the rate of complications was significantly higher in the dexamethasone-treated group.
Table 7. Major therapies for acutely raised ICP Treatment

<table>
<thead>
<tr>
<th>Major therapies for acutely raised ICP Treatment</th>
<th>Dose</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypocarbia [hyperventilation]</td>
<td>pCO₂ 25-33 mmHg , RR 10-16/minute</td>
<td>Immediate onset, well tolerated</td>
<td>Hypotension, short duration</td>
</tr>
<tr>
<td>Osmotic</td>
<td>Mannitol, 0.5-1 g/kg</td>
<td>Rapid onset, titrable, predictable</td>
<td>Hypotension, hypokalaemia, short duration</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Pentobarbital, 1.5 mg/kg</td>
<td>Mutes BP and respiratory fluctuation</td>
<td>Hypotension, small fixed fluctuations pupils, long duration</td>
</tr>
</tbody>
</table>

The goal of pharmacotherapy is to reduce morbidity and prevent complications.

**Drug Category: Corticosteroids** - Reduces edema around tumor, frequently leading to symptomatic and objective improvement.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dexamethasone (Decadron, Dexasone) - Postulated mechanisms of action of corticosteroids in brain tumors include reduction in vascular permeability, cytotoxic effects on tumors, inhibition of tumor formation, and decreased cerebrospinal fluid (CSF) production.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Dose</td>
<td>16 mg/d PO/IV in significant peritumoral divided q6h; May continue dose until patient shows improvement; tapered to discontinue or to minimum effective dose</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>0.15 mg/kg/d PO/IV divided q6h in pediatric tumors</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity; active bacterial or fungal infection, peptic ulcer disease, psychosis, or hypertension; in peritumoral edema, carefully watched for adverse sequelae</td>
</tr>
<tr>
<td>Interactions</td>
<td>Effects decrease with coadministration of barbiturates, phenytoin and rifampin; decreases effects of salicylates and vaccines used for immunization</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>C - Safety for use during pregnancy has not been established.</td>
</tr>
</tbody>
</table>
Precautions

Increases risk of multiple complications, including severe infections; monitor adrenal insufficiency when tapering drug; abrupt discontinuation of glucocorticoids may cause adrenal crisis; hyperglycemia, edema, osteonecrosis, Cushing's syndrome, myopathy, peptic ulcer disease, hypokalemia, osteoporosis, euphoria, psychosis, myasthenia gravis, growth suppression, and infections are possible complications of glucocorticoid use

References


INTRODUCTION

It is well known that primary brain tumors also has a peculiar tendency to spread within the CNS (brain to brain metastasis) through multiple way which include perineural satellitosis, CSF dissemination and Leptomeningeal metastasis, spread in the Virchow - Robin spaces along the penetrating arterioles or spread intravascularly to CNS sites remote from the bulk of the origin tumors, this pathological process is frequently called perilesional satellitosis. While it is unusual for any primary central nervous system tumor to spread to remote sites outside the CNS, medulloblastoma, glioblastoma multiforme and meningioma have the highest rates of extraneural metastasis (22). Extraneural spread occurs via the blood stream. The aim of this chapter is to review the pathology, pathogenesis and neuroimaging findings of different patterns of dissemination of primary CNS tumors.

PERINEURAL / PERINEURONAL / INTRAFASCICULAR SATELLITOSIS

- Perineuronal / intrafascicular satellitosis
Perineuronal satellitosis is characteristic of diffuse astrocytoma (grade II,III,IV) oligodendroglioma, Dysembryoplastic neuroepithelial tumour (DNT), primary CNS lymphoma and probably other primary brain tumors.

Diffuse astrocytoma often spreads widely through the brain but without normal brain tissue destruction and also without interruption of normal brain function. Microscopically, tumor cells infiltrate between myelinated fibers, white matter tracts (intrafascicular spread) and neurons (perineuronal satellitosis) in a nondestructive manner (perineuronal satellitosis). The local spread of diffuse astrocytomas (forming gliomatosis cerebri and butterfly gliomas) does not mean that the tumour grade is grade IV (glioblastoma multiforme), local spread can occur in grade II and grade III and in the author experience gliomatosis cerebri and butterfly gliomas are much more commonly seen in grade II/III astrocytomas and has much less been encountered in grade IV diffuse astrocytoma. It takes a long time for a diffuse astrocytoma to cross the corpus callosum to the opposite hemisphere to form a butterfly glioma. Patients harbouring glioblastomas have a much shorter life span for their tumours to form butterfly gliomas, however cases were reported for glioblastomas forming butterfly tumours.

These glioma cells migrate through the normal parenchyma, collect just below the pial margin (subpial spread), surround neurons and vessels (perineuronal and perivascular satellitosis), and migrate through the white matter tracks (intrafascicular spread). This invasive behavior of the individual cells may correspond to the neoplastic cell's reacquisition of primitive migratory behavior during central nervous system development. The ultimate result of this behavior is the spread of individual tumor cells diffusely over long distances and into regions of brain essential for survival of the patient. The extreme example of this behavior is a condition referred to as gliomatosis cerebri, in which the entire brain is diffusely infiltrated by neoplastic cells with minimal or no central focal area of tumor per se. Furthermore, 25% of patients with glioblastoma multiforme have multiple or multicentric glioblastoma multiforme at autopsy. Although GBMs can be visualized on MRI scans as mass lesions that enhance with contrast, the neoplastic cells extend far beyond the area of enhancement. Fig. 2 illustrates a typical result of "gross total resection" of a temporal lobe glioblastoma multiforme followed 6 months later by recurrence at the surgical margin and elsewhere. Even with repeat surgeries for tumor recurrences, the patients die from tumor spread into vital regions of the brain.
Figure 1. Demonstrating migration of glioma cells through normal brain structures. (A) Glioma cells surrounding blood vessels (perivascular satellitosis) (arrow). (B) Perineuronal satellitosis (arrow). (C) Collection of cells below pial surface (subpial spread) (arrow). (D) Intrafascicular spread of tumor cells through the corona radiata

Perineuronal / intrafascicular satellitosis (which takes the form of neoplastic cells radiating from the main bulk of the tumour) are facilitated by vasogenic edema because the widened extracellular spaces created by the vasogenic edema (common in highly malignant gliomas) will facilitate malignant gliomas sending cells streaming into the surrounding brain tissues. Perineuronal satellitosis is usually prominent in gray matter in oligodendrogiomas.
Figure 2. MRI scans of a patient with a right temporal GBM illustrating the spread of the disease. (A) Presurgical scan, GBM (arrow) is surrounded with edema. (B) Scan after surgery and radiation therapy showing "gross total resection" and clear resection cavity, and (C) six months later, showing recurrence not only at the resection margin (arrow) but a second focus of GBM across the Sylvian fissure in the frontal lobe (arrow). (D) Postresection scans of both recurrent tumors. (E) Scan 3 months later, showing the tumor recurring at the resection margin and crossing the corpus callosum to the other hemisphere (arrow).

<table>
<thead>
<tr>
<th>Type</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrafascicular satellitosis</td>
<td>Tumor cells infiltrate between myelinated fibers, white matter tracts.</td>
</tr>
<tr>
<td>Perineuronal satellitosis</td>
<td>Tumor cells infiltrate around neurons.</td>
</tr>
<tr>
<td>Perivascular satellitosis</td>
<td>Tumor cells infiltrate around blood vessels.</td>
</tr>
</tbody>
</table>

- **Perineuronal satellitosis**

Perineuronal satellitosis, which is defined as spread of tumor cells along a nerve, is one of the more insidious forms of tumor growth. Facial, skin, sinus, nasopharyngeal, and salivary gland tumors have a propensity to spread along this pathway. Most of these are malignant tumors, such as squamous cell carcinoma (SCCa), adenocystic carcinoma (ACC), lymphoma, and metastatic tumor. Other rarer malignant tumors, such as rhabdomyosarcoma, can also spread along these pathways in the suprathyroid head and neck region. Benign tumors, such as schwannoma, neurofibroma, meningioma, hemangioma, and juvenile angiofibroma, may spread along this pathway as well.
Leptomeningeal metastasis refers to diffuse seeding of the leptomeninges by primary brain tumors or secondary tumor metastases and was first reported in 1870 although the term was not used until the early 20th century. Subarachnoid seeding is commonly reported in Medulloblastomas, ependymomas, pineal region germinomas, CNS teratomas, glioblastoma multiforme, Melanoma, lymphoma, choroid plexus papilloma, and Primitive Neuroectodermal Tumor. Leptomeningeal metastatic involvement can also occur in non-neurological systemic cancer and this type of spread occurs in an estimated 20% of patients diagnosed with cancer and is most commonly found in breast carcinoma, lung carcinoma, and melanoma in adults and hematogenous malignancies. The antemortem diagnosis is becoming more common, as newer therapies increase the life span of cancer patients and improvements in technology increase the sensitivity of imaging studies.

Patients typically present with symptoms caused by the effects of tumor emboli on subarachnoid nerve roots, direct invasion into the spinal cord or brain, or cerebrospinal fluid (CSF) obstruction. MR and CT demonstrate multiple masses within the subarachnoid space, hydrocephalus without a discernible cause, or diffuse leptomeningeal enhancement. The latter enhancement pattern has been referred to as cake icing or zuckerguss (German for sugar icing) and can be found in the brain, spine, or both.

Early diagnosis is important to begin therapy prior to neurologic deterioration. While there are clinical signs and radiologic findings that strongly suggest leptomeningeal metastasis, most cases typically are diagnosed by CSF cytology or leptomeningeal biopsy. As the diagnostic accuracy of a single lumbar puncture (LP) is only 50-60% and 90% after
3 LPs, MR is considered complementary and can be invaluable, detecting up to 50% of cases with false-negative LPs.

Without appropriate therapy, the outlook is grim, and untreated patients are unlikely to survive more than 4-6 weeks. Intrathecal chemotherapy and/or radiation can increase survival to some extent, but most patients succumb to their disease within 6-8 months. Survival depends to some extent on the cell type of tumor involved, but the eventual outcome is invariably the same.

- **Pathophysiology**

Primary tumors can spread to the leptomeninges in a variety of ways.

1. Direct extension may occur from an intraparenchymal or periventricular primary brain tumor that forms in tissue near the CSF, and this is commonly found in medulloblastomas and other PNETs, ependymoma, and occasionally in glioblastoma multiforme. Arterial metastases can invade the CSF by pial rupture, ependymal invasion, or by extension along Virchow-Robin spaces.
2. Tumors also can extend in a perineural fashion along cranial nerves to eventually enter the subarachnoid space, and this pathway is particularly associated with squamous cell tumors of the head and neck. A similar method of spread along perineural spaces of the spinal nerves can occur with vertebral body or lymph node metastases.
3. Venous hematogenous access to the subarachnoid space can occur by a number of pathways, such as Batson plexus (internal vertebral venous plexus), the choroid plexus, or through the vessels of the arachnoid. Leukemia classically spreads hematogenously and has been shown to gain access to the CSF by invading the walls of arachnoid veins as well as through microinfarcts that break down the blood-brain barrier.
4. A less common route for CSF metastases is iatrogenic spread of tumor, during surgical manipulation of primary or secondary brain tumors, which is becoming more frequent now that resection of solitary brain metastases has been shown to be beneficial to patients.

Metastatic seeding of the leptomeninges may be explained by the following 5 postulated mechanisms:

- Hematogenous spread to choroid plexus and then to leptomeninges
- Primary hematogenous metastases through the leptomeningeal vessels
- Metastasis via the Batson venous plexus
- Retrograde dissemination along perineural lymphatics and sheaths
- Centripetal extension along perivascular and perineural lymphatics from axial lymphatic nodes and vessels through the intervertebral and, possibly, cranial foramina to the leptomeninges
The choroid plexus forms approximately 500 cc of CSF per day, which circulates throughout the subarachnoid space surrounding the brain and spinal cord before being resorbed at the arachnoid granulations and superior sagittal sinus. CSF motion is caused by pulsations of the brain and spinal cord caused by the large amount of blood flowing through these tissues with each heartbeat, the constant formation and resorption of CSF, gravity, and the patient’s body movements.

Tumor cells that enter the CSF flow freely throughout the subarachnoid space, often lodging a significant distance away from their entry point. Once the tumor cells have gained access to the subarachnoid space, they spread to other portions of the meningeal surface by direct extension or by shedding cells that are then carried to different parts of the neuraxis by CSF flow.

The pattern of growth of leptomeningeal tumor consists of either (1) a sheetlike extension along the pial surface from direct extension occasionally with a secondary inflammatory reaction, or (2) as multiple nodules of various sizes studding the surface of the brain, spinal cord, and nerve roots. The latter appearance typically is seen within the cerebellar folia and the cerebral sulci and easily can be mistaken as intraparenchymal metastases on MR and CT if the association of the tumors with the deep sulci of the brain is not recognized.

Tumor foci may occur throughout the spine or brain surface, as well as within the ventricular system, but demonstrate a predisposition to forming larger tumor masses and thicker leptomeningeal coating in regions of relative CSF stasis, such as the basal cisterns and cerebellopontine angles of the brain and the cauda equina in the spine.

When the tumor mass in the basal cisterns grows large enough, obstructive hydrocephalus occurs. Nonobstructive hydrocephalus also is common in leptomeningeal metastasis secondary to obstruction of CSF resorption at the arachnoid granulations by tumor cells, hemorrhage, and debris.

As the leptomeninges also cover the cranial nerves, tumor seeding of the cranial nerves is not uncommon and can be seen extending into the orbit and Meckel cave. These cranial nerve metastases frequently cause symptoms either from encasement of the nerve or by direct invasion with subsequent axonal destruction and demyelination.

- **Neuroimaging of leptomeningeal metastasis**

Spread via the leptomeninges is the usual path of extension or many primary brain tumors and leptomeningeal involvement of the spinal cord is the most common site of spread, ostensibly as a result of CSF flow from the posterior fossa into the spinal axis (7,9). Supratentorial involvement frequently involves the frontal and subfrontal regions and can be found anywhere CSF is present (eg, cranial cisterns and ventricles) (10).

CT findings suggestive of leptomeningeal spread include sulcal and cisternal effacement, ependymal-subependymal enhancement, widened tentorial enhancement, and communicating hydrocephalus (11). Both conventional myelography and CT myelography
markedly improved the detection and depiction of the true extent of metastatic disease and can still be used today in cases in which MR imaging is not feasible (12,13). Nerve root thickening, nodularity, thecal sac irregularity, and spinal cord enlargement are readily detected in these examinations. However, all of these studies have been supplanted by contrast-enhanced MR imaging as the current imaging study of choice to evaluate patients for this condition. Besides obviating the intrathecal injection of contrast material, contrast-enhanced MR imaging is more sensitive than CT myelography in the detection of these lesions (Figs 16, 17) (15–17). Nodular enhancement of the spinal cord surface or nerve roots, clumped nerve roots, and diffuse enhancement of the thecal sac are common findings. Because the normal flow of CSF from the cisterna magna travels first along the posterior margin of the spinal cord before returning to the cistern along the ventral surface of the spinal cord, most metastases are found along the posterior margin of the spinal cord as the greatest concentration of malignant cells would be expected to be found there (12,13).

**SUBEPENDYMAL / SUBPIAL SPREAD**

Subependymal/subpial spread is characteristic of some primary brain tumors such as primary CNS lymphoma and diffuse astrocytoma. Subependymal spread probably occur along subependymal vascular network (perivascular satellitosis) and is manifested radiologically as subependymal enhancement and nodularity. Spread through CSF pathways might give a similar radiological picture due tumor cells lodging at the ependymal lining of the ventricular system. Subpial spread probably occur secondary to perineuronal / intrafacicular/perivascular satellitosis.

**PERIVASCULAR AND INTRAVASCULAR CNS DISSEMINATION**

- **Perivascular dissemination (perivascular lymphomatosis, perivascular satellitosis)**

Perivascular disseminating in the Virchow Robin spaces along the penetrating arterioles is a characteristic findings in primary CNS lymphomas and is responsible for the formation of paraventricular butterfly lesions frequently observed in primary CNS lymphomas. Perivascular satellitosis has also been reported in diffuse astrocytoma and glioblastoma multiforme.

The defining microscopic feature of primary CNS lymphoma is angiocentricity. Tumor cells surround and infiltrate the walls of small and medium-sized blood vessels. The lamellar arrangement of the perivascular tumor cells between layers of collagen creates an onion-skin or basket-weave appearance. The involvement of the blood vessels may be destructive, producing hemorrhage or infarcts. Lymphomas tend to spread in perivascular spaces along the Virchow-Robin spaces.

- **Intravascular lymphomatosis**

The intravascular malignant lymphomatosis (IML), also known as angiotropic large cell lymphoma, represents only 3% of the non-Hodgkin lymphomas and affects middle-aged...
and elderly patients (median 61 years) with a cerebral manifestation in 74% of the individuals. Signs of dementia or disorientation are reported in the literature in 53% and seizures in 25% of patients.

Intravascular lymphomatosis usually affects the nervous system and skin, although involvement of most organs has been reported. Neurologic sequelae result from vascular occlusion by the lymphoma cells and are typically manifested by one of four syndromes: progressive, multifocal infarcts; paraparesis, pain, and incontinence; subacute encephalopathy; or cranial or peripheral neuropathy. The clinical diagnosis of intravascular lymphomatosis may be difficult, and in most reported cases the diagnosis has been made at autopsy. The prognosis is poor despite aggressive chemotherapy and radiotherapy. (50)

<table>
<thead>
<tr>
<th>Perivascular dissemination (perivascular lymphomatosis)</th>
<th>Intravascular lymphomatosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic findings in primary CNS lymphomas</td>
<td>Represents only 3% of the non-Hodgkin systemic lymphomas</td>
</tr>
<tr>
<td>The tumor cells might invade the vessel wall, inducing vessel occlusion leading to circulation disturbances resulting in multiple, ischemic microinfarctions and stroke like episodes.</td>
<td>Migration out of the vascular spaces is rarely seen in intravascular lymphomatosis.</td>
</tr>
<tr>
<td>Neuroimaging commonly shows intraparenchymal intraaxial mass lesions.</td>
<td>Mass lesions is not commonly seen in intravascular lymphomatosis, and the classical neuroimaging findings in intravascular lymphomatosis is multiple infarct-like lesions with a clinical picture simulating multi-infarct dementia.</td>
</tr>
</tbody>
</table>

Figure 4. A, Intravascular lymphomatosis, B, perivascular lymphomatosis
EXTRANEURAL HEMATOGENOUS METASTASIS

While it is unusual for any central nervous system tumor to spread to remote sites outside the CNS, medulloblastoma, glioblastoma multiforme and meningioma have the highest rates of extraneural metastasis (22). Extraneural spread occurs via the blood stream. Primary CNS lymphoma rarely induces system metastasis.

PATTERNS OF CNS DISSEMINATION OF COMMON PRIMARY BRAIN TUMORS

- Diffuse astrocytoma & glioblastoma multiforme (grade II,III,IV)

Diffuse astrocytoma most commonly metastasize from their original location by direct extension along white matter tracts (perineuronal satellitosis); however, cerebrospinal fluid, subependymal, and hematogenous spread also can occur. Given the rapidly growing body of knowledge about diffuse astrocytoma, the radiologist's role is more important than ever in accurate and timely diagnosis.

Dissemination of Diffuse astrocytoma occurs most commonly by local extension (perineuronal satellitosis), and spread through cerebrospinal fluid is seen in less than 2% of patients (1). Hematogenous metastases are even less common and usually occur in patients who have undergone surgery. The greatest morbidity and mortality from diffuse astrocytoma is caused by local growth and direct extension from the site of origin within the brain.

Less commonly, diffuse astrocytoma/glioblastoma multiforme, like other central nervous system neoplasms, may spread via cerebrospinal fluid pathways (Figure 5). Less than 2% of Diffuse astrocytomas exhibit cerebrospinal fluid seeding, either within the central nervous system or through ventriculoperitoneal or ventriculopleural shunts. Subependymal spread of diffuse astrocytoma/glioblastoma multiforme is another uncommon but characteristic pattern of dissemination (Figure 5) that correlates with a poor prognosis.
Figure 5. Dissemination of a primary glioblastoma multiforme via cerebrospinal fluid pathways and subependymal spread. (A and B) Axial A and coronal B gadolinium-enhanced MR images of the same patient demonstrate leptomeningeal seeding by cerebrospinal fluid pathways (arrowheads) and subependymal spread (arrows) of a glioblastoma multiforme. C. Photograph of an autopsy specimen from a similar case shows diffuse subependymal spread of glioblastoma multiforme (arrows).

Perhaps the least common mode of dissemination is hematogenous spread to extraneural sites. This pattern is so rare that Bailey and Cushing asserted that it did not occur (2). This pathway is a rare cause of dense, osteoblastic bone lesions (Figure 6) and is seen primarily in patients who have undergone surgical treatment of glioblastoma multiforme.
Figure 6. Hematogenous dissemination of glioblastoma multiforme. Chest radiographs demonstrate osteoblastic bone lesions in the spine A and the scapula (arrow) B.

- Multifocal diffuse astrocytoma/glioblastoma multiforme

There are three pathways that can result in multifocal GBM. First, a primary GBM may spread, usually through cerebrospinal fluid pathways or through white matter, to other locations as discussed (Figure 5; see also Figure 24). Usually, when this occurs, the primary lesion is clearly seen or may have been previously known. Occasionally, it is necessary to image the entire neuraxis to locate the primary tumor.

Second, in a patient with a diffuse, low-grade astrocytoma, multiple areas of malignant degeneration may occur. All astrocytomas, other than grade I circumscribed astrocytomas, to some degree infiltrate through nearby white matter tracts, regardless of their apparent demarcation on radiologic images. Occasionally, within a large area of brain infiltrated by a diffuse but low-grade astrocytoma, multiple areas of malignant transformation occur, giving rise to multifocal GBM. In these cases, the presence of the underlying diffuse astrocytoma may be occult on images, but several distinct foci of ring-enhancing lesions will be seen, suggestive of high-grade tumor or metastases. One clue to the true nature of the abnormality is that the lesions of multifocal GBM tend to be largely within the deep white matter, whereas multiple metastases are usually centered at or near the gray matter-white matter junction (Figure 7).
If a diffuse astrocytoma is hemispheric, or even bihemispheric, the term gliomatosis cerebri is used. In the WHO II grading scale of biologic potential, gliomatosis cerebri is considered a grade III-IV lesion. Even without evidence of focal malignant change, such a diffuse abnormality is presumed to have a high degree of biologic aggressivity, although this point has not been accepted universally. Occasionally, the underlying diffuse neoplasm is clinically occult and the patient comes to clinical attention because of focal or multifocal areas of degeneration to a more typical GBM (Figure 8).
Figure 8. Axial gadolinium-enhanced T2-weighted A and T1-weighted B MR images demonstrate gliomatosis cerebri with multifocal GBM.

Third, in a patient with a genetic abnormality, multiple areas of GBM may arise de novo, without the presence of an underlying low-grade lesion. These tumors may arise from cells that, although not neoplastic in themselves, are nevertheless "primed" by an inherited or acquired genetic defect.

- Diffuse astrocytoma of the Corpus Callosum

One common and usefully characteristic appearance for a diffuse astrocytoma is the so-called butterfly glioma. Because glioblastoma multiforme is thought to arise from preexisting low-grade diffuse astrocytomas, they too may extend through the commissural white matter tracts, crossing the midline in more than half the cases. Extension through the corpus callosum may occur in a relatively symmetric pattern, giving rise to a butterfly-like appearance (Figure 9, Figure 10). Because the corpus callosum is relatively resistant to infiltration by edema or infection, any lesion seen extending across the midline in this way, whether symmetric or asymmetric, should always be suspected of being a diffuse astrocytoma. Other considerations in the differential diagnosis include primary central nervous system lymphoma, particularly if the patient has acquired immunodeficiency syndrome (AIDS). Cavitation and necrosis are relatively uncommon in central nervous system lymphoma; however, in the setting of AIDS, these atypical features are somewhat more common.
Figure 9. Butterfly glioblastoma multiforme. A Axial T2-weighted MR image shows a butterfly GBM arising from the splenium of the corpus callosum. B Photograph of an autopsy specimen from a different case shows a glioblastoma multiforme of the same region.
Figure 10. Butterfly glioblastoma multiforme. (A and B) Axial contrast-enhanced CT scan A and gadolinium-enhanced T1-weighted image B demonstrate a butterfly glioblastoma multiforme arising from the genu of the corpus callosum in two different patients. C Photograph of a gross pathologic specimen from a different case shows the glioblastoma multiforme diffusely involving the genu of the corpus callosum.

Diffuse astrocytoma/glioblastoma multiforme may arise in any part of the corpus callosum and may grow exophytically into the lumen of the ventricle (Figure 11). This type of manifestation may lead, erroneously, into the differential diagnosis of masses of primary intraventricular origin, including choroid plexus papilloma, meningioma (both of which
attach to the choroid plexus), central neurocytoma (which attaches to the pellucid septum), and subependymal giant cell astrocytoma (which attaches to the lateral ventricular surface in the region of the head of the caudate nucleus). Usually, careful analysis of imaging findings will prevent this mistake. The appearance of a broad-based abnormality extending into a ventricle with evidence of extraventricular enhancement or mass effect should heighten the suspicion for an exophytic diffuse astrocytoma/glioblastoma multiforme (Figure 12).

Figure 11. Photograph of a gross pathologic specimen shows a glioblastoma multiforme arising in the body of the corpus callosum and projecting into the lateral ventricle.
Figure 12. Glioblastoma multiforme arising from the splenium of the corpus callosum mimicking the appearance of an intraventricular tumor. A On the axial T2-weighted MR image, the tumor is seen in the atrium of the right lateral ventricle and seems primarily intraventricular. B On the coronal T2-weighted view, however, one sees more clearly the broad base of attachment and the abnormal signal intensity in the splenium, which is where the tumor originated before growing exophytically into the ventricle.

Extraaxial glioblastoma multiforme

Both benign and malignant glial neoplasms occasionally manifest as a diffuse leptomeningeal process, usually as a result of dissemination through the cerebrospinal fluid from a primary intraaxial tumor. Primary leptomeningeal glioblastomatosis is a rare neoplastic condition that may originate from ectopic neuroglial cell rests within the pia mater and arachnoid (3).

Radiologic features in cases of primary leptomeningeal gliomatosis/glioblastomatosis consist of either a diffuse or focal thickening of the leptomeninges, usually with contrast material enhancement (Figure 13). The differential diagnosis for pathologic conditions with this appearance is broad: Inflammatory disease, both infectious (tuberculosis) and noninfectious (Langerhans cell histiocytosis or sarcoidosis); metastatic deposits (especially from breast carcinoma and lymphoma); and cerebrospinal fluid spread of a primary central nervous system neoplasm such as medulloblastoma, germinoma, or pineoblastoma all may have this radiologic appearance. In addition, surgical scarring, as well as old subarachnoid hemorrhage or even a diagnostic lumbar puncture, can produce enhancing leptomeningeal tissue. Almost any of these other possibilities is more common than leptomeningeal gliomatosis (whether in the form of glioblastoma multiforme or another tumor, such as oligodendroglioma), and a careful search for other causes is mandatory.
before the diagnosis is established. In fact, the diagnosis of leptomeningeal glioblastomatosis is generally made by the pathologist to the amazement of all others.

Figure 13. Primary leptomeningeal glioblastomatosis. A Axial gadolinium-enhanced T1-weighted image reveals diffuse leptomeningeal enhancement. B Sagittal gadolinium-enhanced T1-weighted image of the cervical spine shows a similar appearance. C Photograph of the corresponding pathologic specimen from the region of the pons shows diffuse leptomeningeal thickening. These findings are nonspecific and may be seen with metastatic disease, with granulomatous disease such as tuberculosis or sarcoidosis, or in cases of bacterial meningitis.

Even more uncommon is the occurrence of leptomeningeal gliosarcomatosis (Figure 14), whose imaging features are virtually indistinguishable from those of leptomeningeal glioblastomatosis. Theoretically, if leptomeningeal gliosarcomatosis contained enough of a nodular component, one might be able to see a slightly higher degree of attenuation on unenhanced CT scans, but in practical terms, it is very difficult to make this claim prospectively. Again, this diagnosis generally requires tissue examination by the neuropathologist.
Figure 14. Primary leptomeningeal gliosarcomatosis. A Axial gadolinium-enhanced T1-weighted image shows an enhancing mass in the quadrigeminal plate cistern. B Photograph of the corresponding pathologic specimen shows the mass.

- **Spinal diffuse astrocytoma**

The most common glioma of the spinal cord is the ependymoma; however, diffuse astrocytomas are also found to arise within the white matter tracts of the spinal cord. The most common location reported is the cervical region, which is also the most frequent location for lower-grade astrocytic neoplasms, including juvenile pilocytic astrocytoma. At radiologic examination, a spinal diffuse astrocytomas is seen as an intramedullary mass enlarging the spinal cord; the mass demonstrates variable contrast enhancement and evidence of hemorrhage and necrosis (Figure 15).
Figure 15. Spinal glioblastoma multiforme. A Sagittal T2-weighted MR image demonstrates a hyperintense mass that has greatly expanded the spinal cord. B Photograph of the corresponding pathologic specimen shows the expanded spinal cord with necrosis. C Axial gadolinium-enhanced T1-weighted image of the same patient shows an area of intramedullary enhancement. D Coronal gadolinium-enhanced T1-weighted image of the brain in the same patient shows diffuse leptomeningeal spread via cerebrospinal fluid pathways.
Medulloblastoma

Spread of medulloblastoma into the intracranial and spinal subarachnoid spaces and the ventricular system occurs more commonly than other pediatric posterior fossa neoplasms. If ventricles are shunted, seeding of tumor may occur at the other end of the shunt tube. For evaluation of recurrent or residual tumor, T2-weighted MR images should be obtained in conjunction with gadolinium-enhanced MR images because not all residual or recurrent tumors show contrast enhancement. Conversely, the presence of gadolinium-enhancement does not necessarily indicate the presence of residual neoplasm because radiation necrosis may present as areas of gadolinium enhancement.

- Leptomeningeal Seeding

Subarachnoid seeding is common in medulloblastomas, occurring in up to 33% of all patients at the time of initial diagnosis (9). Some investigators believe that the prevalence of CSF seeding may be actually much higher and perhaps present in all patients with the disease (5,6). Ventriculoperitoneal shunt involvement is common (20% of cases) and may lead to metastatic spread in the abdominal cavity (7). Numerous studies have shown that patients with evidence of CSF spread have a poorer prognosis compared with those in whom it is absent (8). Therefore, its detection is crucial to optimal patient management, and those who review these imaging studies must be aware of its imaging manifestations.

Spread via the leptomeninges is the usual path of extension and leptomeningeal involvement of the spinal cord is the most common site of spread, ostensibly as a result of CSF flow from the posterior fossa into the spinal axis (7,9). Supratentorial involvement frequently involves the frontal and subfrontal regions and can be found anywhere CSF is present (eg, cranial cisterns and ventricles) (10).

CT findings suggestive of leptomeningeal spread include sulcal and cisternal effacement, ependymal-subependymal enhancement, widened tentorial enhancement, and communicating hydrocephalus (11). Both conventional myelography and CT myelography markedly improved the detection and depiction of the true extent of metastatic disease and can still be used today in cases in which MR imaging is not feasible (12,13). Nerve root thickening, nodularity, thecal sac irregularity, and spinal cord enlargement are readily detected in these examinations. However, all of these studies have been supplanted by contrast-enhanced MR imaging as the current imaging study of choice to evaluate patients for this condition. Besides obviating the intrathecal injection of contrast material, contrast-enhanced MR imaging is more sensitive than CT myelography in the detection of these lesions (Figs 16, 17) (15–17). Nodular enhancement of the spinal cord surface or nerve roots, clumped nerve roots, and diffuse enhancement of the thecal sac are common findings. Because the normal flow of CSF from the cisterna magna travels first along the posterior margin of the spinal cord before returning to the cistern along the ventral surface of the spinal cord, most metastases are found along the posterior margin of the spinal cord as the greatest concentration of malignant cells would be expected to be found there (12,13).
Figure 16. Leptomeningeal metastatic spread from medulloblastoma in a 4-year-old boy with decreased level of consciousness and new onset of seizures. (a) Axial T2-weighted MR image shows ill-defined mild hyperintensity of the sulcal spaces bilaterally and hyperintensity within the corona radiata and external capsule region. (b) Contrast-enhanced axial T1-weighted MR image reveals diffuse bilateral leptomeningeal enhancement. (c) Contrast-enhanced coronal T1-weighted MR image shows similar features with more involvement on the right side than the left side. (d) Photograph of the brain sliced in the coronal plane correlates with the findings in c. Extensive leptomeningeal spread is evident (arrowheads)
Figure 17. Leptomeningeal metastatic spread from medulloblastoma in a 3-year-old boy with lethargy, malaise, weight loss, headache, nausea, and vomiting of several weeks’ duration. (a) Contrast-enhanced sagittal T1-weighted MR image shows intense enhancement of a mass arising in the cerebellar vermis. Diffuse leptomeningeal enhancement (arrowheads) is also noted along the ventral margin of the brain stem and upper cervical spinal cord. (b) Contrast-enhanced sagittal T1-weighted MR image reveals thin linear enhancement (arrowheads) along the margin of the thoracolumbar spinal cord to the tip of the conus medullaris. Note also the focal collection of enhancement (arrow) in the distal margin of the thecal sac.

Detection of CSF seeding by means of cytopathologic analysis has been difficult, since only 15%–60% of patients with leptomeningeal metastasis have positive results (15). At least one report indicated that contrast-enhanced MR imaging is more sensitive (83%) than CSF cytologic analysis (60%–78%) in establishing the presence of CSF dissemination, even when multiple CSF samples were obtained (8). Other authors demonstrated that neither MR imaging nor CSF cytologic analysis alone is sufficient but that the two methods should be used in combination to establish the diagnosis (18). False-positive results, either from the presence of methemoglobin or from leptomeningeal irritation caused by subarachnoid blood, may be seen if MR imaging is performed within the first 2 weeks following surgery (19). For this reason, such studies should be avoided in this time frame or, alternatively and perhaps best of all, assessment of the spinal axis should be performed preoperatively during the initial MR imaging examination (20).
Figure 18. A, Cauda equina of a patient with a medulloblastoma. The nerve roots are markedly enlarged due to neoplastic infiltration and some of them at their ends show tumor nodules (arrows). B, Right cerebral hemisphere of a patient with a medulloblastoma. Notice the presence of leptomeningeal seeding on the medial surface of the occipital lobe and on the inferior surface of the temporal lobe. The sulci have been obliterated and they are lined with neoplastic cells.
Figure 19. Recurrent medulloblastoma with seeding in a 1 year old boy. A, Postgadolinium axial T1-weighted image (SE 500/15). Abnormal enhancement is seen in areas such as the interpeduncular fossa, ambient cistern, cisterna lamina terminalis, and along the interhemispheric fissure, consistent with subarachnoid seeding. B, Postgadolinium axial T1-weighted image (SE 500/15). Abnormal enhancement is seen in the left lateral ventricle, consistent with intraventricular seeding. Note the shunt tube in the right lateral ventricle. C, Sagittal T1-weighted image (SE 555/15). Enlargement of the cervical cord (arrows) with mixed signal intensity is seen. Increased marrow fat in vertebral bodies represents prior radiotherapy treatment. D, Postgadolinium T1-weighted image (SE 555/15). A focal area of contrast enhancement projects within the enlarged cord inferiorly (arrow). Again, note increased fat in marrow.
Figure 20. Drop metastasis in a case of medulloblastoma. MRI T1 postcontrast images showing a large, densely enhanced mass extending for several vertebral segments and compressing the spinal cord in a case of recurrent medulloblastoma.

Figure 21. Since the cells of origin are destined for the cerebellum, medulloblastomas are posterior fossa tumors usually located in the midline of the cerebellum as indicated above. The tumor fills the fourth ventricle (A, arrows) and characteristically invades the subarachnoid space and seeds up and down the cerebrospinal fluid pathway. This accounts for a generally poor prognosis, though survival is vastly improved following heavy, total neuraxis irradiation. In (B) a huge mass of tumor cells is seen in the subarachnoid space (arrows) and compressing spinal cord.

Although nodular leptomeningeal enhancement is more commonly seen in neoplastic disease rather than infectious meningitis, there is no specific imaging appearance for the
former and it may not be possible to exclude the latter (21). At best, only 70% of MR imaging studies will show abnormal enhancement, even when positive CSF cytologic results are obtained (18). Corroboration with clinical and cytopathologic CSF findings is therefore crucial to substantiate the diagnosis of CSF dissemination from the medulloblastoma or other malignant tumors (18).

- **Extraneural Spread**

While it is unusual for any central nervous system tumor to spread to remote sites, medulloblastoma has the third highest rate of extraneural metastasis, following glioblastoma multiforme and meningioma (22). The prevalence of remote spread in children is increased in patients of a younger age, of male gender, and with diffuse subarachnoid disease (23). The addition of chemotherapy to the routine treatment protocol of patients with medulloblastoma is associated with a significantly decreased prevalence of extraneural metastasis (25). Still, extraneural metastasis may manifest up to several years after initial treatment, with a median time of 12–32 months (24,25).

By compiling data on 119 cases reported in the literature, Rochkind et al (26) determined the overall prevalence of extraneural metastasis at 7.1% of patients with a medulloblastoma. Bone is the most common (77% of cases) extraneural site in both children and adults, followed by the lymph nodes (33%). In children, liver (15% of cases), lung (11%), and muscle (2%) are the next most common sites, whereas lung (17%), muscle (13%), and liver (10%) are the next most common sites in adults (26). Less frequently, the pancreas (4%), kidneys (2%), testes (2%), ureters (1%), ovaries (1%), and breast (1%) may be involved (14,24,26). Peritoneal metastases may result from ventriculoperitoneal shunt transmission, although it is less likely since the incorporation of the millipore filter in the early 1970s (9,10). Interestingly, no adrenal metastasis has ever been identified in a patient with a medulloblastoma (26).

Osseous lesions are usually sclerotic (65% of cases) on radiographs and CT scans (71). Lytic (35% of cases) and mixed (5%) lesions occur less often (25). On T1-weighted MR images, the lesions produce hypointensity relative to normal marrow signal intensity, with a reversion to normal signal intensity occurring as a successful response to chemotherapy (22,25). On T2-weighted MR images, iso- to hypointense signal is typical but not always present (Fig 22) (22,25).
Figure 22. Medulloblastoma in a 13-year-old girl with nausea, vomiting, nystagmus, and ataxia. Physical examination revealed bilateral papilledema. (a) Axial T1-weighted MR image shows a heterogeneous mass within the left cerebellar hemisphere. The mass appears to extend to the surface of the cerebellum. (b) Axial T2-weighted MR image reveals marked heterogeneity within the mass. (c) Contrast-enhanced axial T1-weighted MR image demonstrates intense enhancement of the soft-tissue portions of the mass. (d) Contrast-enhanced coronal T1-weighted MR image shows exophytic extension (arrow) of the mass into the cerebellopontine angle. Ten months after surgical resection, the patient developed a single sacral metastasis (not shown). Despite radiation therapy, she developed neck and back pain 19 months later. (e) Postlaminectomy sagittal T2-weighted MR image shows multiple areas of abnormal hyperintensity (arrowheads) involving several cervical and thoracic vertebrae, indicative of metastatic disease. (f) Bone scan obtained 1 month later reveals diffuse increased uptake in the entire cervical spine and skull base as well as the humeral head.

The survival rates of patients with systemic metastasis are similar to those of patients with recurrence (24). At histologic examination, systemic metastases appear to contain areas of anaplasia more frequently than do medulloblastomas overall, and transformation to a more aggressive form of medulloblastoma has been commonly noted in the metastasis compared with the original tumor (24).
CNS lymphoma

Intracranial lymphomas include primary brain lymphomas and epidural secondary (pachymeningeal) lymphomatous deposits. Primary CNS lymphomas are primary intraparenchymal disease involving the brain (more common) or spinal cord (less common). Spinal and brain disease might coexist but this is quite rare.

- Primary brain lymphomas

Primary CNS lymphoma is an uncommon disease that historically constituted approximately 1% of primary brain tumors. Sporadic disease is most common in older adults. (28,29) With the advent of acquired immunodeficiency syndrome (AIDS)-associated lymphomas, there has been a marked increase in the number of cases, particularly in younger people, in whom the disease was previously rare. (30,31,32) There has also been a significant increase in non-human immunodeficiency virus (HIV)-associated primary CNS lymphoma among older patients. (28) A relationship between Epstein-Barr virus and HIV-associated lymphomas has been observed. The causes of sporadic cases and their increasing incidence in the nonimmunocompromised are unknown, but viral and environmental agents have been proposed as factors. (28,29,33,34) Primary CNS lymphoma occurs throughout the brain, but it is characteristically periventricular. Sporadic cases tend to be limited to one or two sites, whereas AIDS-associated tumors are commonly multifocal.

The marked shrinkage of sporadic tumors on imaging studies after initiation of steroid therapy is almost diagnostic. (29,35) The initial response to radiation is also gratifying. (29) The tumors return within several months or with the cessation of steroids, however. Modern chemotherapy has resulted in a much improved prognosis for sporadic lymphomas, with a reported median survival of about 5 years. (36) In contrast, AIDS-associated lymphomas respond only transiently to therapy, and most patients die within a year of diagnosis. (3,31,33,36,37)

Figure 23. Gross specimen showing the butterfly lesions characteristic of lymphomas and astrocytomas. The demonstrated lesion is a highly vascular non-Hodgkin lymphoma.
Circumscribed lesions may have a gray, fleshy appearance similar to systemic lymphomas or may be soft, mottled, and otherwise indistinguishable from a high-grade astrocytoma. The borders are often vaguely defined. Some lesions produce architectural distortion without a definite mass.

The defining microscopic feature of primary CNS lymphoma is angiocentricity. (37,38,39) Tumor cells surround and infiltrate the walls of small and medium-sized blood vessels. The lamellar arrangement of the perivascular tumor cells between layers of collagen creates an onion-skin or basket-weave appearance. The involvement of the blood vessels may be destructive, producing hemorrhage or infarcts. Most tumors form a diffuse mass of noncohesive cells which may represent a confluence of a number of perivascular foci. The interface with brain often appears fairly sharp, with individual tumor cells appearing to infiltrate only a short distance. Perivascular tumor foci may be present at some distance from an apparently sharply defined tumor mass, however, presumably owing to spread in the Virchow-Robin space. Tumor necrosis, especially of single cells, and hemorrhage are common, but extensive confluent necrosis is the exclusive province of AIDS-associated disease. (37) Most cerebral lymphomas, and particularly AIDS-associated tumors, are high-grade large cell lymphomas. (56) The microscopic correlates include large cells with pleomorphic nuclei and a high mitotic rate. Primary CNS lymphoma may be subclassified by the systems used for systemic lymphomas, but this does not add prognostic information.

Figure 24. A, Perivascular cuffing of monomorphic lymphocytes. (All lymphocytes look similar and there are no other types of cells such as macrophages or plasma cells.) Also note the lack of reactive cells within the CNS parenchyma (a distinguishing feature from
The defining microscopic feature of primary CNS lymphoma is angiocentricity. Tumor cells surround and infiltrate the walls of small and medium-sized blood vessels. These blood vessels are thus leaky resulting in profound Perilesional edema, and intense contrast enhancement.

The involvement of the blood vessels may be destructive, producing hemorrhage or infarcts, and this is responsible for the clinical picture of some patients with primary CNS lymphoma that simulates cerebrovascular disorders. (TIAs, Rinds, Stroke, multi-infarct dementia). (27)

Primary CNS lymphomas have a characteristic topographic brain localization and a peculiar clinical presentation.

Topographic localization of primary CNS lymphomas

Lymphomas start either in the subependymal tissues and the periventricular gray matter and then fungate centrifugally outward into the periventricular white matter or spread subependymally to ensheathe the ventricular system (central periventricular). The second site is the cortico-meningeal site and the disease spreads either alongside the meninges or invades the brain parenchyma in a centripetal way. (peripheral corticomeningeal) (27)

TOPOGRAPHIC SUBTYPES OF PCNSL*

- **Central periventricular**: Starts either in the subependymal tissues or the periventricular gray matter and then fungates centrifugally outward into the periventricular white matter or spread subependymally to ensheathe the ventricular system, although it ultimately forms extensive periventricular butterfly fungative lesions or ensheathe the whole ventricular system, it shows little tendency to encroach upon the volume of the ventricular cavity.

- **Peripheral corticomeningeal**: The disease spreads either alongside the leptomeninges or invades the brain parenchyma in a centripetal way. MR imaging findings in corticomeningeal lymphomas include leptomeningeal/dural enhancement and hydrocephalus. (46)

*Central and peripheral lymphomas rarely coexist in single patient, a patient with both disease was reported before. (27) See fig. 37
Figure 25. A,B Coronal autopsy specimen A, and CT post contrast B, show prominent subependymal lymphoma (open white arrow) lining and traversing lateral ventricular system (white arrow). Multiple small hemorrhages (black arrowheads) are also seen in the immediate periventricular region. Dilated ventricles are secondary to periventricular atrophy. C, Malignant lymphoma (four frontal sections). Large, poorly delimited, pale tumour symmetrically invading the basal ganglia (butterfly lymphoma). D, Coronal autopsy specimen at level of caudate nucleus shows well-defined mass (*) with color between that of white and gray matter. There is a second mass with a surrounding brownish rim (black arrowhead), representing hemorrhage, immediately superior to the larger lesion.

- Clinical presentation of primary CNS lymphomas

Many patient with PCNSL are presented initially, with a history that simulates cerebrovascular disorders. (TIAs, Rinds, Stroke, multi-infarct dementia). (27)
The clinical presentation and topographic localization of primary CNS lymphomas are best explained by considering the cellular origin of lymphoma and the brain microvascular system.

PCNSL is derived from the microglial cells and was previously called microglioma. The microglial cells are more numerous in the cortical and the subcortical gray matter. (Thalamus and basal ganglia). The microglial cells are not of neural origin. They are derived from the blood monocytes and immigrate through the small perforating blood vessels to invade the neural tissue either from the pial or the subependymal arterial system. The microglial cells lies very close to the periadventitial spaces of the small penetrating blood vessels. They are phagocytic and function as macrophages. They represent a defense mechanism and are considered as a part of the reticuloendothelial system. To sum up the microglial cells and the penetrating blood vessels are very closely coupled together. (27)

With regard to the brain microvascular system, 2 systems were described. The centrifugal subependymal system and the centripetal pial system. The centrifugal subependymal vascular system originates from the subependymal arteries which are terminal branches of the choroidal arteries, then extends centrifugally outward into the periventricular white matter. The centripetal pial vascular system originates from the pial arteries then extends centripetally inward towards the ventricular system. As an artery penetrates the brain it carries a sheath of pia with it resulting in a potential perivascular space called Virchow-Robin space. (27)

To put things together, it is possible to state that the malignant lymphoma cells (being derived from the microglial cells) originate primarily in the periadventitial spaces of either the subependymal or the pial vascular systems, then the lymphoma cells creep alongside the penetrating arteries either centrifugally outward from the subependymal system, or centripetally inward from the pial system. This view point is consistent with the pathological findings of marked perivascular cuffing by lymphoma cells and tendency to spread along Virchow-Robin spaces. This also should support the theory that CNS lymphomas arise from the periadventitial microglial cells of the penetrating arterioles. (27)

It should also be pointed out that the subependymal spread of lymphoma that is observed in some cases most probably represent either spread alongside the subependymal arteriolar system or CSF seedling. (27)

The clinical presentation of primary CNS lymphomas is best explained by putting forward the intimate relationship between the lymphoma cells and the penetrating arterioles. The involvement of the blood vessels in primary CNS lymphomas may be destructive, producing hemorrhage or infarcts. The lymphoma cells by infiltrating the wall of the penetrating arterioles can produce thrombo-occlusive changes that can give rise, clinically, to TIAs, Rinds or stroke. (27)
Table 1. Ways of spread of primary CNS lymphomas

- Lymphoma cells creep alongside the penetrating arteries in the Virchow Robin spaces either centrifugally outward from the subependymal system, or centripetally inward from the pial system. Infiltration along the leptomeninges is common in corticomeningeal lymphomas.
- CSF seedling

Table 2. Differences between central periventricular, and peripheral corticomeningeal primary CNS lymphomas.

<table>
<thead>
<tr>
<th>Central periventricular lymphomas</th>
<th>Corticomeningeal lymphomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>More common</td>
<td>Less common</td>
</tr>
<tr>
<td>Common in males</td>
<td>Common in females</td>
</tr>
<tr>
<td>Patients are older</td>
<td>Patients are younger</td>
</tr>
<tr>
<td>Starts bilaterally</td>
<td>Starts unilaterally</td>
</tr>
<tr>
<td>Tendency towards ventricular system ensheathing</td>
<td>Spread along the leptomeningeal covering of the brain with tendency to invade the brain.</td>
</tr>
<tr>
<td>Centrifugal Parenchymal spread</td>
<td>Centripetal Parenchymal spread</td>
</tr>
<tr>
<td>Parenchymal involvement is common</td>
<td>Parenchymal involvement is less common</td>
</tr>
<tr>
<td>Invariably a primary CNS diseases</td>
<td>Invariably a primary CNS diseases</td>
</tr>
</tbody>
</table>

Historical terms for cerebral lymphomas such as microglioma arose at a time when the nature of the tumor cells was uncertain. Immunohistochemical stains have clarified the origin of primary cerebral lymphomas and also are important diagnostically. (29,34,37,40) Reactivity for common leukocyte antigen is used to confirm lymphoid origin and often reveals much greater parenchymal infiltration by individual cells than is apparent on routine hematoxylin and eosin staining. By far, most cerebral lymphomas are B-cell neoplasms, and monoclonal reactivity for K or k light chain may be helpful diagnostically. (29,34,37,40) T-cell lymphoma occurs only rarely. (29,42)

Karyotype abnormalities found in CNS tumors are similar to those found in systemic lymphomas and involve structural alterations. Molecular studies have confirmed genetic lesions involving RAS genes, CDNK2A, CDNK2B, BCL2, BCL6, and MYCC. (41)

An interesting side effect of the dramatic initial response to steroids is that biopsy specimens obtained after initiation of therapy may be devoid of identifiable tumor cells. The appearance of modest perivascular and parenchymal infiltrates of small T cells and white matter changes that include myelin breakdown, edema, and gliosis has been dubbed the sentinel lesion of primary CNS lymphoma. (43)
NEUROIMAGING OF PRIMARY CNS LYMPHOMAS

Neuroimaging of primary CNS lymphomas is very complex, as one must observe (1) the site, (2) the precontrast CT density, (3) the MRI T2 signal intensity, (4) the pattern of contrast enhancement, (5) the rapid changes that take place over a very short time as primary CNS lymphomas are very dynamic tumours in so far as the local spread of the disease is concerned.

Table 3. Radiological parameters that must be taken care of while inspecting a study for possible primary CNS lymphoma

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td>1. Central periventricular</td>
</tr>
<tr>
<td></td>
<td>2. Peripheral corticomeningeal</td>
</tr>
<tr>
<td>The precontrast CT density</td>
<td>Hyperdense on unenhanced CT studies</td>
</tr>
<tr>
<td>The MRI T2 signal intensity</td>
<td>Hypointense or isointense to gray matter on T2-weighted images</td>
</tr>
<tr>
<td>The pattern of contrast enhancement</td>
<td>1. Prominent enhancement that tends to be solid and homogeneous in immunocompetent patient</td>
</tr>
<tr>
<td></td>
<td>2. Enhancement patterns in immunocompromised individuals may be irregular and heterogeneous, often with a ring pattern</td>
</tr>
<tr>
<td>The rapid changes that takes place over a very short time as primary CNS lymphomas are very dynamic in so far as the local spread of the disease is concerned.</td>
<td>The rapid centrifugal periventricular spread of the central subtype forming the butterfly lesions, or the centripetal growth of the corticomeningeal type. The central subtype might spread subependymally to ensheathe the whole ventricular system.</td>
</tr>
</tbody>
</table>

Table 4. Common sites for central lymphomas (27)

<table>
<thead>
<tr>
<th>Site</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalamus</td>
<td>100%</td>
</tr>
<tr>
<td>Parietal lobes, corpus callosum, cerebellum, brain stem, hypothalamus</td>
<td>25%</td>
</tr>
</tbody>
</table>

Primary CNS lymphoma is more common than secondary lymphomas. (44) Most primary CNS lymphomas are high-grade non-Hodgkin's B-cell lymphomas. (45) The site of origin is controversial because the CNS does not have endogenous lymphoid tissue or lymphatic circulation. (46) The incidence is increasing in both immunocompromised and
immunocompetent individuals. Lesions can be multiple in up to 50% of cases, involving the basal ganglia, periventricular white matter, and corpus callosum. The lesions are very radiosensitive but frequently recur. The masses demonstrate high cellularity, with 90% isodense to hyperdense on CT, and isodense to hypointense to brain signal intensity on T2-weighted imaging. In immunocompetent individuals, there is prominent enhancement that tends to be solid and homogeneous. In these patients, lymphomas do not calcify, and hemorrhage is uncommon. (47) Up to 75% of these masses are in contact with the ependyma or meninges. (47) The imaging appearance is more heterogeneous in AIDS owing to hemorrhage and necrosis. (48) Enhancement patterns in immunocompromised individuals may be irregular and heterogeneous, often with a ring pattern. (44) In the AIDS population, CT and MR imaging cannot reliably distinguish between lymphoma and toxoplasmosis. SPECT imaging may be helpful in this setting.

Figure 26. Precontrast CT scan of a paraventricular lymphoma, each study is one week apart, notice that the lymphoma is hyperdense on precontrast scans, also notice the increase in size and the progressive periventricular fungation over a short period of time.

Figure 27. A postcontrast CT scan in a patient with central thalamic lymphoma showing dense contrast enhancement, notice the perilesional edema and the small nodules radiating from the mother lesion (perivascular satellitosis).
Figure 28. Lymphoma. A, Axial T2-weighted image shows relatively low signal intensity of the mass indicating high cellularity (black arrow) with surrounding edema high signal intensity B, Postcontrast T1-weighted image demonstrates marked enhancement of the mass in the right centrum semiovale with surrounding edema.

Previously an uncommon primary brain neoplasm, primary CNS lymphoma is increasing in frequency. Although the increase is most often attributed to acquired immunodeficiency syndrome (AIDS) and other immunocompromised disease states, primary CNS lymphoma is also increasing in frequency in immunocompetent patients. (27) Peak incidence of primary CNS lymphoma in immunocompetent patients is in the 50s, and lesions are typically solitary; among immunocompromised individuals, it occurs at a younger age, and multiple lesions are common. (49) It is one of two primary CNS tumors that extends across the corpus callosum with some frequency forming the bilateral butterfly lesions. (GBM is the other.) Lesions are commonly located deep within the brain substance, and T2 signal abnormality or enhancement often abuts an ependymal surface; however, primary CNS lymphoma can also occur peripherally or in the posterior fossa. On unenhanced CT studies, primary CNS lymphoma is classically hyperdense, and enhancement can be solid or ringlike. (50)
Figure 29. MRI T1 precontrast (A,B), postcontrast (C), MRI T2 (D) and MRI proton density (E,F) Notice that the periventricular lymphoma is hypointense on precontrast scans, also notice the dense contrast enhancement. Notice the densely enhanced butterfly lesions in (C), the butterfly lesions are iso-to hypointense on the MRI T2 and proton density scans (D,E,F)

In the author experience, the progressive centrifugal butterfly fungation of primary CNS lymphomas is something that can be observed clinically. When successive flow up neuroimaging studies are done (on several days) to a patient with CNS lymphoma during hospitalization, it was possible, in the author experience, to observe the progressive centrifugal butterfly fungation of the lymphoma (i.e. lymphomas are tumours that one can see getting enlarged and spreading during a very short time in a single patient). This is probably due to the rapid growth of the neoplasm (see figures 30,31,32,33,34). This is in sharp contrast with the butterfly bihemispheric spread of astrocytomas which has never been observed "taking place" in action in any single patient by the author, this is probably
because the growth and the local spread of astrocytoma cells is slower than that of lymphoma cells. (27)

The spread of lymphoma cells is different from that of astrocytoma cells. Lymphoma cells spread locally alongside the periarterioles in the Virchow-Robin spaces (Perivascular satellitosis), while Astrocytoma tumor cells infiltrate locally between myelinated fibers in the nondestructive manner (perineuronal/intrafascicular satellitosis). Spread of lymphoma cells along the Virchow Robin spaces is probably faster than the spread of astrocytoma cells by infiltration between myelinated fibers (probably Virchow Robin spaces facilitate spread of lymphoma cells) and this is probably another reason that explains the more rapid local spread lymphoma cells compared with that of astrocytoma cells. Perivascular satellitosis can also occur in diffuse astrocytoma but it is probably less frequent that perineuronal/intrafascicular satellitosis.

Although both astrocytomas and lymphomas are hypercellular neoplasms, however their MRI T2 signal intensity is different (astrocytomas are hyperintense on the MRI T2 images while lymphomas are hypointense on the MRI T2 images). The cells of lymphomas have a high nuclear to cytoplasmic ratio with minimal extracellular water, resulting in T2 prolongation (hypointense on the T2 MRI images), while astrocytoma cells have a low nuclear to cytoplasmic ratio with increased extracellular fluid resulting in T2 prolongation (hyperintense on the T2 MRI images).
Figure 30. MRI T1 postcontrast coronal scan of a patient with central lymphoma showing progressive increase in the size of the lymphoma with periventricular fungation.
(perivascular satellitosis) over a short period of time (satellitosis). Each image was done about 5 days before the next starting from A to F, this was coupled clinically with progressive clinical deterioration. Notice the dense contrast enhancement and the well formed butterfly lesion in E,F. The lesions are surrounded with hypointense edema with positive mass effect.

Figure 31. MRI T1 postcontrast coronal scan of a patient with central lymphoma showing periventricular fungation (perivascular satellitosis). Notice the dense contrast enhancement and the well formed butterfly lesions. The lesions are surrounded with hypointense edema with positive mass effect.

Figure 32. MRI T1 postcontrast showing the characteristic periventricular fungation (perivascular satellitosis), left MRI image is one week earlier than the right image, notice the observable periventricular spread of lymphoma in such a short time.
Figure 33. Perivascular satellitosis, postcontrast CT scan showing a thalamic lymphoma (left image) that started to fungate centrifugally outward on follow up CT scan (middle image) forming later on the characteristic butterfly lesion (right image), these changes occurred over 2 weeks of the patient hospitalization.

Low signal intensity in a nonhemorrhagic tumor on T2-weighted images can be due to high cellularity, a high nuclear-to-cytoplasmic ratio, or minimal extracellular fluid. Primary tumors that are commonly lower in signal intensity on T2-weighted images include primitive neuroectodermal tumors (e.g., medulloblastoma, neuroblastoma) and lymphoma. Metastases from a systemic mucinous adenocarcinoma primary can also exhibit low signal intensity on T2-weighted images.

On MR images, the signal intensity on T1-weighted images can vary; however, similar to other lesions that are hyperdense on unenhanced CT studies, primary CNS lymphoma tends to be hypointense or isointense to gray matter on T2-weighted images. Surrounding edema and mass effect ranges from minimal to marked. Enhancement is the norm on MR imaging; it may be homogeneous, heterogeneous or ringlike. (51) In a patient with AIDS and an enhancing mass lesion, the primary differential diagnostic consideration is toxoplasmosis. Although lymphoma is statistically more common, primary CNS lymphoma cannot be reliably distinguished from toxoplasmosis with conventional CT or MR imaging. A variety of techniques, including thallium-201 SPECT, fluorodeoxyglucose PET, and MR spectroscopy, have been advocated to distinguish between the two diseases.
Figure 34. MRI T2 images A, B and MRI T1 postcontrast image C. A was done 5 days before B. Notice the progressive increase in size of the central lymphoma over a short period of time, also notice that the central lymphoma is markedly hypointense on the MRI T2 image (B), the central lymphoma showed marked and dense contrast enhancement. The surrounding edema is marked in this patient (the edema is hyperintense on the T2 images and hypointense on the T1 image).
Figure 35. MRI T1 precontrast image (A) and postcontrast T1 images (B,C) and MRI T2 images (D,E) in a patient with a butterfly infratentorial lymphoma around the 4th ventricle lymphoma. The lymphoma is hypointense on precontrast T1 image (A) and iso to hypointense on MRI T2 images (D,E), with dense contrast enhancement (B,C), also notice the perilesional edema.

From the radiological point of view, the existence of butterfly lesions and the subependymal disease are the most characteristic radiological criteria of PCNSL. In central lymphomas the thalamus is the most frequently involved site. The subependymal disease (the periventricular lymphomatous sheath) is only demonstrated after contrast injection and commonly takes the shape of a hyperdense (CT scan) or hyperintense (MRI T1) bands that ensheathe the ventricular system.
Figure 36. MRI T1 postcontrast scans showing the periventricular lymphomatous sheath (A,B), the butterfly lesions (C) also notice involvement of the corpus callosum, hypothalamus and the frontal lobes (D,E), in a patient with central lymphoma.

Figure 37. Postcontrast CT scan showing right thalamic and left frontal corticomeningeal lymphoma (A is one month earlier than B). Notice the centripetal inward growth of the left frontal corticomeningeal lymphoma (perivascular satellitosis) on follow up scan, also the thalamic disease increased in size on follow up.
Table 5. The radiological characteristics of primary CNS lymphomas

1. The existence of butterfly lesions
2. The existence of subependymal lymphomatous sheath around the ventricular system, best seen in postcontrast scans
3. The lesions are hypointense on the MRI T2 images
4. The lesions are slightly hyperdense on precontrast CT scans
5. The existence of dense contrast enhancement
6. Perilesional edema is present to a variable degree
7. Lymphomas are characterized by being a very dynamic pathology with rapid increase in size and periventricular fungation over a short period of time during the hospitalization of the patient

PCNSL commonly shows initial good response to steroid. However following histopathological confirmation of PCNSL, whole brain irradiation must be done. The steroid responsiveness of the lesions could be regarded as an initial therapeutic diagnostic test for PCNSL; since complete disappearance of the lesions by steroids is unlikely to occur in other brain tumours. (27)

![Figure 38. Postcontrast CT scan before steroid therapy (A,C) and and after steroid therapy (B,D), notice complete disappearance of the lesions on steroid therapy](image)

- Intravascular lymphomatosis

The intravascular malignant lymphomatosis (IML), also known as angiotropic large cell lymphoma, represents only 3% of the non-Hodgkin lymphomas and affects middle-aged and elderly patients (median 61 years) with a cerebral manifestation in 74% of the individuals. Signs of dementia or disorientation are reported in the literature in 53% and seizures in 25% of patients (52,53). Important MRI findings are the symmetrical findings in the temporal lobes in combination with involvement of the cingulate gyrus which initially might be misdiagnosed as limbic encephalitis. The prognosis of IML is poor with a median survival time of only 6 months after symptom onset. Temporary remission to a
maximum of a few weeks is described in patients who received corticoids or cytostatic drugs (53).

![Image showing intravascular non-Hodgkin's B-cell lymphoma](image-url)

**Figure 29.** 48-year-old man with intravascular non-Hodgkin's B-cell lymphoma who presented with left leg weakness for 1 year. A, Axial FLAIR MR image shows hyperintense deep white matter signal. B, Diffusion-weighted axial MR image shows restricted diffusion of lesion. C, Contrast-enhanced axial T1-weighted MR image shows nodular enhancement.

Intravascular lymphomatosis usually affects the nervous system and skin, although involvement of most organs has been reported. Neurologic sequelae result from vascular occlusion by the lymphoma cells and are typically manifested by one of four syndromes: progressive, multifocal infarcts; paraparesis, pain, and incontinence; subacute encephalopathy; or cranial or peripheral neuropathy. The clinical diagnosis of intravascular lymphomatosis may be difficult, and in most reported cases the diagnosis has been made at autopsy. The prognosis is poor despite aggressive chemotherapy and radiotherapy. (53)

The key microscopic feature of IML is the filling of lumina of small and medium-sized vessels with large atypical lymphoid cells. These cells possess predominantly round nuclei, vesicular chromatin and prominent nucleoli. Mitotic figures are common. Immunohistochemically, these cells are positive for leukocyte common antigen and usually B cell markers, but a few cases of T cell origin have been described. The blood vessels are closed and sometimes thrombosed by tumor cells leading to circulation disturbances resulting in multiple, ischemic microinfarctions as well as small parenchymal hemorrhages. Endothelial proliferation may be present (54). Migration out of the vascular spaces is rarely seen and this is likely due to the lack of surface expression of leukocyte adhesion molecule CD11a/CD18 by the tumor cells (55). Securing the diagnosis by brain biopsy is controversial, however, brain biopsy confirmed the diagnosis in 50% of individuals with brain involvement. While skin biopsy is more convenient, dermal involvement is sufficiently low to miss the diagnosis in 2/3 of all patients (53). Consequently, brain biopsy is recommended as the preferable way to establish this diagnosis.
In conclusion, in a case of dementia, seizures and infarct-like lesions by MRI, the diagnosis of an intravascular malignant lymphomatosis should be considered.

**FINAL COMMENT**

Brain to brain metastasis is far less well studies in literature and constitute the main reason why the prognosis in many primary brain tumors is bad. Perilesional satellitosis, whether through neural structures (intrafascicular satellitosis, Perineuronal satellitosis) or vascular structure (Perivascular/intravascular satellitosis), is very common in diffuse astrocytoma and primary CNS lymphoma, while it is less common in other primary brain tumors like medulloblastoma where CSF seedling and leptomeningeal metastasis are more common. Perilesional satellitosis occur very rapidly in primary CNS lymphoma and can be observed clinically in many patients on follow up neuroimaging studies done over a short period of time where small tumor masses can be seen radiating from the main tumor, the radiating tumor masses rapidly increase in size and number over a short period of time, this is in contrast with diffuse astrocytoma where the tumor spread occur less rapidly and can not be appreciated over a short period of time.

Perivascular/intravascular satellitosis are more common and more characteristic of CNS lymphoma while intrafascicular satellitosis/perineuronal satellitosis are more characteristic of diffuse astrocytoma. Tumor spread alongside blood vessels in the virchow robin spaces probably occur more rapidly, thus explaining the rapid growth of CNS lymphoma compared with diffuse astrocytoma. The virchow robin spaces yield less resistance in the face of the creeping lymphoma cells allowing them to grow rapidly alongside the penetrating arterioles.

This invasive behavior of the individual glioma cells may correspond to the neoplastic cell's reacquisition of primitive migratory behavior during central nervous system development. An integral component of normal neurons is the capability of reaching the appropriate location during normal brain development. Very little is known about the molecular signals that guide migrating neurons to the appropriate place in the cortical plate. In laminar structures such as the cerebral and cerebellar cortices, glial cells of a specialized nature, the Bergmann glia and the radial glia for the cerebellum and cerebral cortex, respectively, are thought to guide young neurons in their radial migratory path during normal brain development. It looks like that during the process of dedifferentiation and malignant transformation of astrocytes, the malignant cells reacquire their primitive migratory behavior. Myelinated fibers, white matter tracts may act as a guide for the malignant cells during their intraaxial dissemination (intrafascicular spread). Very little is known about the molecular signals that trigger this migratory behavior of malignant glioma cells.

Aborting the migratory behavior of malignant astrocytes by neutralizing the molecular signals that trigger their migratory behavior is probably the only hope for patients with diffuse astrocytoma/glioblastoma multiforme. Indeed more research is needed to define the nature of the molecular signals responsible for the relentless perilesional satellitosis of gliomas that ultimately results in wide intraaxial dissemination of the neoplasm, thus making any surgical attempt for radical tumor resection impossible.
Brain to brain metastasis has its impact on neuroimaging in so far as the diagnosis of primary brain tumors is concerned. The neurologist must be aware of the neuroimaging picture of CSF seedling, leptomeningeal metastasis, perilesional satellitosis and subependymal/subpial tumor spread as many primary brain tumors are already disseminated within the CNS when first diagnosed. Failure to appreciate the radiological picture of brain to brain metastasis in primary brain tumors might result in misdiagnosis or at least perplexity regarding the patient's diagnosis. It is not enough to know the MRI picture of a glioblastoma multiforme, but it is mandatory to know what would be the radiological picture if the glioblastoma is already disseminated, thus producing subpial deposits, leptomeningeal or subependymal enhancement and the neurologist must understand the meaning of these radiological findings and their impact on the overall patient management and prognosis. One must be aware of the MRI picture of a main tumor with a rapidly developing small masses radiating from it in primary CNS lymphoma. The prognosis when there is already radiological evidence of dissemination is beyond doubt worse compared with that when radiological evidence of dissemination is absent.
Table 6. Brain to brain metastasis

<table>
<thead>
<tr>
<th>Brain tumor</th>
<th>Perineuronal satellitosis</th>
<th>Intrafascicular satellitosis</th>
<th>Perineural satellitosis</th>
<th>Perivascular/intervascular satellitosis</th>
<th>Drop metastasis, CSF seedling</th>
<th>Subependymal/subpial spread</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse astrocytoma</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>+++</td>
<td>Unknown</td>
</tr>
<tr>
<td>CNS lymphoma</td>
<td>Unknown</td>
<td>Unknown</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ependymomas, pineal region germinomas, CNS teratomas, Melanoma, choroid plexus papilloma, and Primitive Neuroectodermal Tumor.</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>+++</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

References


INTRODUCTION

Hereditary metabolic disorders affect the nervous system on multiple levels, suggesting an inborn error or metabolic defect such as the following:
### Developmental delay
- Episodic alteration in level of consciousness or recurrent neurologic symptoms
- Family history of similar symptoms in a sibling or closely related individual
- Neurologic or developmental regression
- Multisystem involvement (in addition to neurologic systems)
- Presence of a particular neurologic sign

The development of ataxia is a neurologic sign that may provide a clue to the nature of the underlying disorder. Ataxia is defined as an inability to maintain normal posture and smoothness of movement. Interruption of afferent and efferent connections within the spinocerebellar system results in a broad-based gait (ataxic gait), scanning dysarthria, explosive speech, intention tremor, dysdiadochokinesia, dysmetria, and abnormalities of eye movements. Other neurologic symptoms and signs such as seizures and movement disorders may accompany ataxia. Consequently, many variations are encountered in the clinical phenotype, ranging from findings of pure cerebellar dysfunction to mixed patterns of involvement reflecting extrapyramidal, brainstem, and cerebral cortical involvement.

A wide range of molecular defects have been identified in which the spinocerebellar pathways are involved. However, the pathologic responses within the system are limited, resulting in a great deal of overlap in the clinical presentation. The disorders under consideration have a heritable basis; most follow an autosomal-dominant or autosomal-recessive pattern of inheritance and have an identified biochemical defect. This group of disorders is expanding constantly as the genetic defects underlying many of the recessively inherited ataxias are unraveled. For example, the molecular mechanism underlying Friedreich ataxia is due to a triplet repeat expansion, affecting the production of a protein called frataxin. The biochemical defect now is believed to result in impaired mitochondrial function.

### PATHOPHYSIOLOGY

The spinocerebellar pathways principally are involved in most genetic ataxia syndromes. Lesions of the midline cerebellar vermis produce truncal and gait ataxia, while involvement of the lateral cerebellar hemispheres produces a limb ataxia. Other features of cerebellar involvement include scanning dysarthria, dysmetria, abnormalities of eye movements, and dysdiadochokinesia.

The pathologic bases of many clinically recognized phenotypes show considerable overlap. However, the genetic molecular and biochemical causes for these disorders are often distinct. The phenotypes may present with pure ataxia or involve multiple levels of the nervous system (including dementia, seizures, disturbance in proprioceptive function, movement disorders, and polymyoclonus).
Thus classification of these disorders is a daunting task, and no single method is entirely successful. In today’s molecular era, identification of genetic mutations has been instrumental in classifying these disorders, with the phenotype playing a secondary role.

**GENETIC-BIOCHEMICAL BASIS FOR CLASSIFICATION**

Early attempts to classify inherited ataxias were based on anatomic localization of pathologic changes (eg, spinocerebellar, pure cerebellar ataxias). In 1993, Harding introduced another classification in which the ataxias were placed into 3 categories, congenital, inherited metabolic syndromes with known biochemical defects, and degenerative ataxias of unknown cause. The last category was subdivided further into early onset (<20 y) and late-onset (>20 y) subtypes.

This article outlines inherited ataxias with a known biochemical defect and uses biochemical defects as an anchor with which to classify these various disorders. The molecular genetic explanations for the autosomal-dominant spinocerebellar ataxias rapidly are being unraveled, although the precise pathogenesis is not clearly understood in many of these disorders. Although ataxia is a prominent feature of all these disorders, the presentation can be variable (static vs progressive, intermittent vs chronic, early vs delayed). The mode of inheritance also varies. Autosomal-dominant, recessive, and nonmendelian inheritance patterns have been described. Nonmendelian inheritance patterns have become increasingly significant in the understanding of the biology of human diseases. The term refers to disorders of inheritance for which the rules of mendelian genetics do not apply. Disorders of triplet repeat expansion and certain mitochondrial defects are examples.

- **Triplet repeat expansions**

  This new class of mutation is characterized by dynamic expansion of tandem nucleotide repeats in the human genome. These stretches of repeats tend to be inherently unstable, and this instability favors expansion. When the length of the repeat expansion exceeds the range in the general population, a symptomatic state may result.

  These mutations help explain clinical observations of increasing severity and earlier age of onset in successive generations in many of the dominantly inherited disorders—a phenomenon termed "genetic anticipation." Such dynamic mutations form the basis of an increasing list of inherited neurologic disorders that includes mental retardation (fragile X syndrome), myotonic dystrophy, oculopharyngeal muscular dystrophy, Friedreich ataxia, Huntington disease, and the dominantly inherited cerebellar ataxias.

- **Mitochondrial DNA defects**

  Since mitochondria were established to carry their own functional genome, a new mechanism of genetic nonmendelian inheritance, maternal inheritance, was discovered. All the mitochondria in the newly formed zygote are derived from the ovum (ie, maternally derived). Mitochondrial DNA is more vulnerable to mutations in the oxidizing environment
of mitochondria; its repair mechanisms are poor compared to nuclear DNA. Mutations in mitochondria accumulate in cells until a threshold is reached. Eventually, the proportion of mutant mitochondria exceeds wild type, resulting in the manifestation of impaired cell function.

The process of uneven replicative segregation ensures different proportions of mutant and wild types in different tissues, a condition termed heteroplasmny. Mild to moderately deleterious mutations can persist and be transferred to offspring.

The differential segregation and production of reactive oxygen species can vary among tissues and organ systems in affected individuals, giving rise to varying phenotypes. Postmitotic cells such as neurons appear to carry higher ratios of mutant mitochondrial DNA, thereby partially explaining the neurologic involvement in many mitochondrial disorders.

- Classification

In this chapter, the disorders are classified as follows:

- **Acute intermittent ataxia**
- **Ataxias with polymyoclonus and seizures**
- **Ataxias with spinocerebellar dysfunction**
- **Progressive ataxias plus (ie, prominent cerebellar dysfunction with additional neurologic signs)**

**ACUTE INTERMITTENT ATAXIAS**

- **Maple Syrup Urine Disease (Intermittent Form)**

A delayed presentation of this autosomal-recessive form of a branched chain aminoacidopathy may occur at any age from infancy to adulthood.

  - **Clinical features**
    - Characteristic urine odor
    - Intermittent bouts of ataxia and neurologic obtundation progressing to coma
    - Possibly mental retardation and motor delay in intermediate form
  
  - **Biochemical abnormalities**
    - Elevation of branched-chain amino acids and branched-chain keto acids in the urine, plasma, and cerebrospinal fluid (CSF)
    - Metabolic acidosis, ketonemia, and ketonuria; occasional hypoglycemia and hypoalaninemia
    - L-allo-isoleucine in body fluids (pathognomonic)
Treatment

- Treatment includes restriction of dietary protein intake and supplementation of branched-chain amino acid-free synthetic formula to meet protein and other dietary needs.

- Begin thiamine supplementation in thiamine-responsive individuals (5-20 mg/kg/d, not to exceed 100 mg/d) immediately. In adults, 100 mg may be administered immediately in the acute situation, followed by further supplementation of 50-100 mg/d until adequate oral intake and a stable clinical state are achieved.

Episodic Ataxia 1

Episodic ataxia 1 (EA1) is a rare autosomal-dominant disorder and represents a channelopathy. It is caused by point mutations that affect the human voltage-gated potassium channel gene on band 12p13.

- Clinical features
  - Continuous myokymia between attacks
  - Duration of seconds to minutes
  - Partial epilepsy (some individuals in affected families)
  - Sudden episodes of ataxia precipitated by movement, startle, or emotion

- Laboratory features
  - Electroencephalography (EEG) may show continuous rhythmic muscle discharge artifact, which may become more prominent with hyperventilation.
  - Electromyography is the only helpful investigation; it usually demonstrates continuous motor unit activity in all patients.

- Treatment
  - Partial responses to acetazolamide, carbamazepine, phenytoin, and phenobarbital have been reported.

Episodic Ataxia 2

Episodic ataxia 2 (EA2) is an autosomal-dominant disorder that has been associated with mutations that affect the calcium channel (CACNA1A) gene at the 19p13 locus. It is allelic to familial hemiplegic migraine and spinocerebellar ataxia type 6 (SCA6), wherein mutations affecting the same gene have been described.

- Clinical features
  - Headache (in some families)
  - Intermittent midline cerebellar dysfunction characterized by bouts of ataxia, nystagmus, dysarthria, and vertigo
  - Absence of myokymia
  - Provoking factors - Stress, exercise, and fatigue, among others

- Investigation
- No specific diagnostic test is available.
  - Treatment
    - Some patients with EA2 may respond to acetazolamide.
- Hartnup Disease

This autosomal-recessive disorder is caused by defective intestinal transport and renal tubular reabsorption of neutral amino acids (primarily tryptophan). The reduced availability of tryptophan may lead to a secondary deficiency of the vitamin niacin (nicotinic acid). The gene locus is 11q13. Incidence based on neonatal screening data is estimated at 1 in 30,000.

  - Clinical features
    - Intermittent ataxia and other cerebellar signs
    - Neuropsychiatric dysfunction ranging from emotional lability to frank psychosis
    - Pellagralike skin rash induced by exposure to sunlight
    - Normal intelligence and no abnormal neurologic signs in most patients with the biochemical phenotype
  - Laboratory features
    - Excessive excretion of monoamino-monocarboxylic amino acids in urine
    - Urinary indoxyl derivatives (5-hydroxyindoleacetic acid) also excreted in urine; may be demonstrated following an oral tryptophan load
  - Treatment
    - Treatment includes a high-protein diet. Niacin supplementation reverses the skin and neuropsychiatric manifestations. A tendency exists for spontaneous improvement.

Pyruvate Dehydrogenase Deficiency

Pyruvate dehydrogenase (PDH) deficiency is an X-linked recessive disorder that affects a mitochondrial multienzyme complex, which in turn inhibits the conversion of pyruvate to acetyl-CoA.

The enzymatic complex consists of 3 enzymes. The pyruvate dehydrogenase has 4 subunits, with the E1 alpha1 subunit most often affected. Inheritance is X linked.

Clinical features

- Many present in early infancy with a catastrophic neurologic picture of hypotonia, lactic acidosis, and seizures (associated with cerebral malformations)
- Benign late-infantile variant also known to occur
- Episodic ataxia
• Normal mental and motor development
• Postexercise fatigue
• Transient paraparesis

Laboratory investigations

• Serum and CSF lactic acidosis (characteristic)
• Reduced PDH activity in muscle biopsy
• Multiple areas of necrosis in the gray matter, white matter, and basal ganglia on imaging studies in prenatal and early infantile form
• Limited information concerning late benign presentations of this disorder

Postmortem and autopsy in one affected male who died when aged 50 years showed findings of cerebellar degeneration and lesions around the third ventricle and cerebral aqueduct. This case suggests findings that are consistent with Leigh disease and Wernicke encephalopathy.

Treatment

Thiamine supplementation in high doses (5-20 mg/kg/d, not to exceed 100 mg/d in acute stage) may be effective in the thiamine-responsive form of the disease. Ketogenic diet has been effective in some patients. Treatment of lactic acidosis by dichloroacetate also may be helpful.

• Administer 2 doses of dichloroacetate (50 mg/kg body weight) separated by 2 hours.
• If the level does not drop 20% below baseline after 6 hours, the patient is considered a nonresponder.
• For a partial response to less than 20% of baseline levels but above 5 mmol/L, 2 additional doses may be tried.
• Published open trials on the drug indicated improved survival (with reduced morbidity) in responders. However, questions remain regarding the efficacy of this treatment.

Pyruvate Carboxylase Deficiency

This most common disorder of pyruvate metabolism is an autosomal-recessive inherited deficiency of pyruvate carboxylase. Identified mutations affect the gene locus on chromosome 11 (11q13.4-q13.5). It usually presents in the neonatal period with severe lactic acidosis or in early infancy with features similar to PDH deficiency with psychomotor retardation, hypotonia, and seizures. A benign variant with intermittent ataxia and normal development also has been reported.

Laboratory features

• Lactic acidosis (elevated plasma lactate)
- Reported abnormality on ultrastructural examination of skeletal muscle in the neonatal form
- Subsarcolemmal aggregation of lipid droplets, glycogen granules, and pleomorphic mitochondria is found.
- Although nonspecific, these findings in combination with age of onset, clinical features, and lactic acidosis are often helpful in diagnosis.
- Cystic periventricular white matter changes also reported in the neonatal form on magnetic resonance imaging (MRI)
- Can be confirmed by assay for enzyme activity in cultured fibroblasts

**Treatment**

Options are limited to symptomatic treatment of lactic acidosis and are similar to those employed for the treatment of PDH deficiency. Biotin and aspartate have been used in selected patients.

**Fatty Acid Oxidation Defects**

Recessively inherited defects that affect mitochondrial beta-oxidation can result in intermittent episodes of neurologic symptoms (eg, weakness, ataxia, coma) in affected individuals. Examples of such defects are as follows:

- Carnitine palmitoyltransferase-1 deficiency
- Long-chain acyl-CoA dehydrogenase deficiency
- Medium-chain acyl-CoA dehydrogenase deficiency
- Multiple-acyl-CoA dehydrogenase deficiency (glutaric aciduria Type II)
- Primary systemic carnitine deficiency
- Short-chain 3-hydroxyacyl-CoA dehydrogenase deficiency
- Short-chain acyl-CoA dehydrogenase deficiency
- Trifunctional enzyme deficiency
- Very long-chain acyl-CoA dehydrogenase deficiency

**Clinical features**

- Episodic vomiting
- Intermittent bouts of weakness, lethargy, ataxia, and coma
- Neurologic symptoms induced by fasting

**Laboratory features**

- Hypoglycemia with minimal-to-absent ketonemia and ketonuria
- Mild lactic acidosis, hyperammonemia
- Reduced plasma carnitine levels (free and total) in many fatty acid oxidation disorders
- Specific enzyme assays on cultured skin fibroblasts
Increased dicarboxylic aciduria (suberic, sebacic, adipic acids) upon urinary organic acid analysis

Treatment

- Avoidance of prolonged fasting
- Carnitine supplementation in doses of 50-100 mg/kg/d
- Adequate caloric intake through intravenous glucose or nasogastric cornstarch-based formula
- Substitution of dietary fat with medium-chain triglycerides (may be helpful in bypassing metabolic block in these disorders)

Urea Cycle Defects

Defects of each of the 5 enzymes of the urea cycle and 1 of its activators have been described. Most present with hyperammonemic coma in the neonatal period. Partial deficiencies can result in delayed presentation or intermittent symptoms during periods of decompensation.

The 5 urea cycle enzymes are as follows:

- Carbamyl phosphate synthetase
- Ornithine transcarbamylase (X-linked inheritance)
- Argininosuccinate synthetase
- Argininosuccinate lyase
- Arginase

Four of the 5 enzyme deficiencies (excepting ornithine transcarbamylase) are inherited as autosomal-recessive defects.

Clinical features

- Delayed presentations of partial enzyme deficiencies in children and adults include the following:
- Behavioral abnormalities such as self-abusive behavior
- Episodic hyperammonemia
- Intermittent ataxia and spasticity
- Protein intolerance with intermittent vomiting
- In adults, migrainelike episodes, confusional states, visual impairment, hallucinations, and neuropsychiatric symptoms are reported.
- Clinical symptoms may first present in ornithine transcarbamylase heterozygotes during pregnancy.
- Examination findings may demonstrate hyperactive deep tendon reflexes, papilledema, and decerebrate or decorticate posturing.
- The clinical picture in cases of argininemia may mimic spastic diplegic cerebral palsy.
Laboratory features

- Abnormalities in plasma amino acids
- Elevated glutamine and alanine in blood and CSF
- Indication of precise urea cycle enzyme deficiency possible by presence or absence of citrulline, argininosuccinic acid in plasma, and orotic acid in urine
- Elevated plasma ammonium (ionized form at physiologic pH)
- Enzyme assays on liver biopsies and DNA analysis (can be confirmatory)
- Respiratory alkalosis

Treatment

- Reduction of dietary protein intake with special dietary formulas
- Supplementation of arginine and/or citrulline (depending on site of urea cycle defect)
- Aggressive treatment of hyperammonemic coma using alternative pathway activation (eg, via sodium benzoate, phenylbutyrate)
- Orthotopic liver transplant (another therapeutic option)

Table 1. Intermittent Ataxias

<table>
<thead>
<tr>
<th>Autosomal-Dominant/Recessive Ataxias</th>
<th>Neurologic Phenotype</th>
<th>Genetic-Biochemical Defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maple syrup urine disease</td>
<td>Intermittent ataxia</td>
<td>AR*, 19q13.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Mutations affecting the E1-alpha subunit of branched-chain alpha-keto dehydrogenase complex that catalyzes the conversion of alpha-keto acids to acyl-CoA and carbon dioxide</td>
</tr>
<tr>
<td>Episodic ataxia (EA-1)</td>
<td>Intermittent ataxia</td>
<td>AD†, 12p13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Missense point mutations affecting the voltage-gated potassium channel (KCNA1)</td>
</tr>
<tr>
<td>Condition</td>
<td>Presentation</td>
<td>Inheritance</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>--------------</td>
<td>-------------</td>
</tr>
</tbody>
</table>
| Episodic ataxia (EA-2)                         | Intermittent ataxia | AD, 19p13   | • Point mutations or deletions also allelic with SCA-6 and hemiplegic migraine  
• Altered calcium channel function |
| Hartnup disease                                | Intermittent ataxia | AR, 11q13   | • Abnormality in the intestinal and renal transport of neutral alpha amino acids |
| Pyruvate dehydrogenase deficiency              | Intermittent ataxia Lactic acidosis | X-linked recessive (Xp22.2-p22.1) | • Defective E1 component of the PDH complex |
| Pyruvate carboxylase deficiency                | Intermittent ataxia Lactic acidosis | AR 11q13.4-q13.5 | |
| Defects of mitochondrial fatty acid beta oxidation | Intermittent ataxia Lactic acidosis | AR | • Multiple defects affecting different acyl-CoA dehydrogenases |
| Late-onset urea cycle defects                  | Intermittent ataxia Episodic encephalopathy | AR, X-linked inheritance for OTC‡ | • 7q21.3-q22 (argininosuccinate lyase)  
• 2q33-q36 (carbamoyl phosphate synthetase I)  
• 9q34 (argininosuccinate |
ATAXIAS WITH SPINOCEBELLAR DYSFUNCTION

The following disorders are dominantly or recessively inherited. They present primarily with ataxia and cerebellar dysfunction, which are chronic and may be progressive with or without the presence of other neurologic abnormalities. This group of disorders is large; many have been associated with molecular genetic abnormalities, linking them to identifiable biochemical defects.

DNA-based laboratory testing is available for many of these disorders. SCA 1, 2, 3, 6, and 7 and dentatorubropallidoluysian atrophy (DRPLA) are caused by dynamic mutations that affect tandem triplet nucleotide repeats. Table 3 summarizes the salient phenotypic features and the degree of triplet repeat expansions necessary to produce pathologic symptoms. Such expansions code for polyglutamine tracts, which are responsible for progressive neuronal degeneration.

Autosomal-Dominant Cerebellar Ataxias

The nomenclature for the autosomal dominant hereditary ataxias has varied over the years. Terms no longer used to refer to SCA1 include Marie's ataxia, atypical Friedreich's ataxia, and olivopontocerebellar atrophy. At least 12 forms of dominantly inherited spinocerebellar ataxias have been described and labeled sequentially from SCA1 to SCA12. The position 9 has been reserved for a hitherto unknown variety.
A great degree of overlap in phenotype is present, with the major group of symptoms related to cerebellar and spinocerebellar pathway dysfunction. Other than a few specific distinguishing features described in Table 3, clinical and neuroimaging studies are nonspecific. Most of the triplet expansions affect CAG repeats; in the SCA8 form, a CTG expansion is involved.

Table 3. Progressive Ataxias With Spinocerebellar Dysfunction

<table>
<thead>
<tr>
<th>Autosomal-Dominant Ataxias</th>
<th>Neurologic Phenotype*</th>
<th>Genetic-Biochemical Defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinocerebellar ataxia (SCA-1)</td>
<td>Peripheral neuropathy, pyramidal signs</td>
<td>6p23 Ataxin-1, CAG expansion 39-83 (6-36 normal range)</td>
</tr>
<tr>
<td>Spinocerebellar ataxia (SCA-2)</td>
<td>Abnormal ocular saccades, hyporeflexia, dementia, peripheral neuropathy</td>
<td>12q24.1 Ataxin-2, CAG expansion 34-400 (15-31 normal range)</td>
</tr>
<tr>
<td>Spinocerebellar ataxia (SCA-3)</td>
<td>Pyramidal, extrapyramidal, and ocular movement abnormalities</td>
<td>14q24.3-q32.2 CAG expansion 55-86 (12-40 normal range)</td>
</tr>
<tr>
<td>Spinocerebellar ataxia (SCA-4)</td>
<td>Amyotrophy and sensory neuropathy</td>
<td>16q22.1</td>
</tr>
<tr>
<td>Spinocerebellar ataxia (SCA-5)</td>
<td>Sensory axonopathy</td>
<td>Myokymia, nystagmus, and altered vibration sense</td>
</tr>
<tr>
<td>Spinocerebellar ataxia (SCA-6)</td>
<td>Slowly progressive ataxia</td>
<td>19p13 CAG expansion 20-33 (4-16 normal range) with altered alpha1A subunit of the voltage-dependent calcium channel (CACLNIA4)</td>
</tr>
<tr>
<td>Spinocerebellar ataxia (SCA-7)</td>
<td>Visual loss retinopathy</td>
<td>3p21.1-p12 Ataxin-7, CAG expansion 37 to greater than 300 (4-19 normal range)</td>
</tr>
<tr>
<td>Spinocerebellar ataxia (SCA-8)</td>
<td>Hyperreflexia Impaired vibration sense</td>
<td>13q21 CTG expansion 100-250 (16-34 normal range)</td>
</tr>
<tr>
<td>Spinocerebellar ataxia (SCA-10)</td>
<td>Ataxia, nystagmus, and seizures</td>
<td>22q13 (genetic anticipation in families suggests triplet expansion)</td>
</tr>
<tr>
<td>Spinocerebellar ataxia (SCA-11)</td>
<td>Mild disorder ataxia</td>
<td>15q14-q21.3 Mutation not identified</td>
</tr>
<tr>
<td>Spinocerebellar ataxia (SCA-12)</td>
<td>Pure spinocerebellar ataxia</td>
<td>5q31-q33 Protein phosphatase PPP2R2B gene, CAG expansion 66-78 (6-26 normal range)</td>
</tr>
<tr>
<td>Dentatorubropallidoluysian ataxia</td>
<td>Progressive ataxia</td>
<td>12p13.31</td>
</tr>
</tbody>
</table>
atrophy (DRPLA) | plus chorea, seizures, myoclonus, and dementia | Triplet repeat expansion leading to altered protein product Atrophin-1 with toxic gain of function

*Gait ataxia is a constant feature*

Spinocerebellar ataxia (SCA-1) (Olivopontocerebellar atrophy)

Clinical features include the following:

- Onset in the fourth decade
- Gain of function mutation, resulting in a protein (ataxin-1)
- Gait ataxia, dysarthria, dysmetria, nystagmus, muscle wasting, and dystonia in late stages of the disease

Figure 2. Olivopontocerebellar degeneration. A, The axial T1-weighted scan at the level of the fourth ventricle demonstrates loss of the normal olivary bulge bilaterally (arrows) and atrophy of the middle cerebellar peduncles. Pontine and cerebellar atrophy is noted on additional axial (B) and sagittal (C) T1-weighted scans.
Olivopontocerebellar atrophy (olivopontocerebellar degeneration, olivopontine cerebellar degeneration, spinocerebellar degeneration type I, spinocerebellar ataxia type I) is an autosomal dominant inherited degenerative disorder of the central nervous system that predominantly involves neurons in the cerebellum, inferior olives in the brain stem, and tracts in the spinal cord. The condition results from CAG trinucleotide repeats within the ATX1 gene that encodes for the ataxin. Normal individuals contain 19-36 of the CAG repeats within the gene; affected persons have 40-81 CAG repeats. The disease is manifest by ataxia, an intention tremor, rigidity, loss of deep tendon reflexes, and a loss of vibration and pain sensation. Alpha synuclein is present in neuroglia and neurons of persons with olivopontocerebellar atrophy. The pons becomes markedly atrophic. Several genetically distinct types of olivopontocerebellar atrophy are recognized (olivopontocerebellar atrophy type I, olivopontocerebellar atrophy type II, olivopontocerebellar atrophy type III, and olivopontocerebellar atrophy type IV). Nystagmus occurs in these disorders and other ophthalmic manifestations, such as retinal degeneration and progressive ophthalmoplegia occur in some of these conditions, such as olivopontocerebellar atrophy type III.
Spinocerebellar ataxia (SCA-2)

Clinical features include the following:

- Age of onset - 2-65 years
- Ataxia, facial fasciculation, lid retraction, reduced ocular saccadic velocity
- SCA 2 protein product termed ataxin 2

Spinocerebellar ataxia (SCA-3)

The disorder is allelic to Machado-Joseph disease, which affects individuals of Portuguese-Azorean descent.

Clinical features include the following:

- Age of onset - After the fourth decade
- Ataxia, pyramidal and extrapyramidal signs, amyotrophy, facial and lingual fasciculations, ophthalmoplegia, and exophthalmos
- Protein product termed ataxin 3

Spinocerebellar ataxia (SCA-4)

This disorder is linked tightly to 16q22.1 locus. Molecular basis has not yet been delineated.

Clinical features include the following:

- Late onset ataxia, sensory axonopathy
- Symptoms beginning in second to fourth decade
- Pathologic examination findings demonstrating degeneration of cerebellar Purkinje cells, dorsal root sensory ganglion neurons, and ascending posterior columns

Spinocerebellar ataxia (SCA-5)

Gene locus is the 5 cM candidate region on chromosome 11 in open reading frame of unknown gene. No expansion has been detected yet.

Clinical features include the following:

- Cerebellar ataxia, facial myokymia, impaired vibration sense; very slow progression
- Age of onset variable, with a mean age of 37 years (10-68 y)
- First family described descending from Abraham Lincoln's grandparents; second family described in northeastern France
Spinocerebellar ataxia (SCA-6)

Gene locus is the triplet expansion repeat affecting the 19p13 locus. The size of the expansion in affected individuals is 21-27. The mutation affects the calcium channel \textit{CACNL1A}.

Clinical features include the following:

- Ataxia, nystagmus, dysarthria, and loss of vibration and joint position sense
- Pathologic examination showing loss of Purkinje cells, granule cells, neurons of the inferior olive nucleus, and dentate nucleus
- Progressive pancerebellar dysfunction without involvement of cognitive, pyramidal, or extrapyramidal function
- Slow progression over 20-30 years
- Symptoms beginning in the fourth or fifth decade

Spinocerebellar ataxia (SCA-7)


Clinical features include the following:

- Ophthalmoplegia, dysarthria, pyramidal and extrapyramidal signs, and impaired vibration sense
- Visual loss due to macular retinal degeneration (unique finding in this disorder)

Spinocerebellar ataxia (SCA-8)

This disorder is linked to an untranslated CTG expansion on 13q21.

Clinical features include the following:

- Onset of symptoms ranging from age 18-65 years, with a mean of 39 years
- Dysarthria and gait instability (commonly initial symptoms)
- Examination findings including spastic dysarthria, nystagmus, limb spasticity, limb and gait ataxia, and diminished vibration perception
- Progression generally slow

Spinocerebellar ataxia (SCA-10)

Gene locus is 8.8 cM candidate region on chromosome 22q13-ter.

Clinical features include the following:

- Onset in third to fifth decade
• Pure cerebellar ataxia, nystagmus, dysarthria, dysphagia, hypotonia, generalized and/or complex partial epilepsy

Spinocerebellar ataxia (SCA-11)

Linkage is established to 15q14-q21.3.

Clinical features include the following:

• Mild disorder, with pure ataxia as a major feature
• Normal life span with mean age of onset of 30 years (15-70 y)
• Retained capacity for ambulation

Spinocerebellar ataxia (SCA-12)

• Gene locus is a CAG expansion with a range of 66-78 repeats at 5q31-q33 locus. This expansion codes for a brain-specific regulatory subunit of the protein phosphatase PP2A.

Clinical features include the following:

• Tremor in early stages
• Later development of a pure spinocerebellar ataxia

Dentatorubropallidoluysian atrophy

DRPLA is another triplet-repeat neurodegenerative disorder with dominant inheritance and genetic anticipation. The size of the expansion in affected individuals varies from 49-75 repeats. The mutation is believed to affect a protein product "atrophin-1," resulting in a toxic gain of function for the altered protein; the protein includes a serine repeat, a region of alternating acidic and basic amino acids, and the variable polyglutamine repeat.

The condition is allelic to the Haw River syndrome reported in African Americans. Pathologic features include nerve cell loss and gliosis affecting the dentate nucleus, red nucleus, pallidum, and subthalamic nucleus of Luys. The age of onset varies. It has been reported in Japan and Europe.

Clinical features include ataxia, dementia, polymyoclonus, and chorea. No specific findings are reported on imaging studies. Molecular genetic confirmation by DNA analysis is possible. No treatment is available.

Laboratory features

Imaging studies demonstrate spinocerebellar atrophy and varying degrees of multisystem atrophy.
Diagnosis rests on molecular DNA confirmation of expansion of the number of CAG repeats. Molecular genetic testing is available for SCA types 1, 2, 3, 6, 7, and DRPLA.

### Table 2. Progressive Ataxias With Spinocerebellar Dysfunction

<table>
<thead>
<tr>
<th>SCA SYNDROMES: TESTING</th>
<th>1° Testing</th>
<th>2° Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical sign</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellar ataxia, Pure</td>
<td>SCA6, SCA5</td>
<td>SCA11, SCA14, SCA15, SCA16, SCA22</td>
</tr>
<tr>
<td>Spasticity</td>
<td>SCA3</td>
<td>SCA1, SCA7</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>SCA3, SCA4, SCA18, SCA25</td>
<td>SCA1</td>
</tr>
<tr>
<td><strong>Cortical disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td>SCA17, DRPLA</td>
<td>SCA2, SCA13, SCA19, SCA21</td>
</tr>
<tr>
<td>Psychosis</td>
<td>DRPLA, SCA17</td>
<td>SCA3, SCA-FGF14 (Episodic)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>SCA10, DRPLA</td>
<td>SCA17</td>
</tr>
<tr>
<td><strong>Movement disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chorea</td>
<td>DRPLA, SCA17</td>
<td>SCA1 (Late stage)</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>DRPLA</td>
<td>SCA2, SCA19</td>
</tr>
<tr>
<td>Tremor</td>
<td>SCA2, SCA8, SCA12</td>
<td>SCA16, SCA21, SCA-FGF14</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>SCA3, SCA12</td>
<td>SCA2, SCA21</td>
</tr>
<tr>
<td>Dystonia</td>
<td>SCA3</td>
<td>SCA17</td>
</tr>
<tr>
<td><strong>Ocular disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ophthalmoplegia</td>
<td>SCA3</td>
<td></td>
</tr>
</tbody>
</table>
Autosomal-Recessive Cerebellar Ataxias

- **Friedreich Ataxia**

The prototype disorder of familial spinocerebellar degeneration, FRDA was the first identified recessively inherited condition with a mutation involving a triplet repeat expansion.

Ninety-six percent of patients with FRDA1 are homozygous for a GAA expansion in intron 1 of the X25 gene.

The number of GAA repeats ranges from 7-38 in normal alleles and from 66 to greater than 1700 triplets in disease-causing alleles. The remaining cases are compound heterozygotes for a GAA expansion and a frataxin point mutation. Most affected individuals carry more than 600 repeats.

The DNA-based test for FRDA1 evaluates genomic DNA for the presence of this GAA trinucleotide repeat expansion in the X25 gene.

- **The mutation leads to formation of the abnormal protein termed frataxin.**
  - The cells carrying this mutation appear to be sensitive to oxidative stress.
  - Apparently this disease has more than 1 locus.
  - Great phenotype variance exists among affected individuals, even within the same family; the types have been divided arbitrarily into late-onset FRDA (LOFA onset, 25-39 y) and very-late-onset FRDA (VLOFA, onset >40 y). Deep tendon reflexes are retained and progression is very slow, particularly in Acadians.
  - These variants have been found to have generally shorter GAA expansions (<600) in at least 1 of the X25 alleles.
  - Other postulated mechanisms to account for the differences include tissue-specific variability in triplet expansion size secondary to mitotic instability, *cis*-acting sequence alterations, and other genetic or environmental modifiers.

- **Clinical features**
  - Variable age of onset when younger than 20 years
• Neurologic - Cerebellar ataxia, dysarthria, nystagmus, uncoordinated limb movements, hypoactive knee and ankle deep tendon reflexes, Babinski sign, impaired position sense, and impaired vibratory sense
• Cardiac - Symmetric, concentric, hypertrophic cardiomyopathy; congestive heart failure; and subaortic stenosis
• Skeletal - Pes cavus, scoliosis, and hammer toe
• Metabolic - Abnormal glucose tolerance test, diabetes mellitus, and diabetic ketosis

• **Laboratory features**
  - Abnormal electrocardiogram
  - Abnormal echocardiogram
  - Abnormal motor and sensory nerve conduction
  - MRI - Cerebellar atrophy and a thin spinal cord
  - Evidence of iron accumulation within mitochondria of FRDA fibroblasts subjected to oxidative stress, resulting in impaired respiratory function

• **Treatment**
  - No specific treatment other than symptomatic and supportive care is available.

• **More details about Friedreich Ataxia**

The major pathophysiologic finding in FA is a "dying back phenomena" of axons, beginning in the periphery with ultimate loss of neurons and a secondary gliosis. The primary sites of these changes are the spinal cord and spinal roots. There is a loss of large myelinated axons in peripheral nerves, which increases with age and disease duration. Unmyelinated fibers in sensory roots and peripheral sensory nerves are spared.

![Figure 5. Myelin staining is often used to demonstrate areas of axonal loss, as loss of myelin is much easier to appreciate than axonal loss. In Fredreich ataxia, degeneration can be identified in the spineal cerebellar tracts laterally and the ascending sensory tracts medially.](image)

The posterior columns, corticospinal, ventral, and lateral spinocerebellar tracts all show demyelination and depletion of large myelinated nerve fibers to differing extents. This is accompanied by a fibrous gliosis that does not replace the bulk of the lost fibers. Overall,
the spinal cord becomes thin and the anteroposterior (AP) and transverse diameters of the thoracic cord are reduced. The dorsal spinal ganglia show shrinkage and eventual disappearance of neurons associated with proliferation of capsular cells. The posterior column degeneration accounts for the loss of position and vibration sense and the sensory ataxia. The loss of large neurons in the sensory ganglia causes extinction of tendon reflexes.

Large neurons of the dorsal root ganglia, especially lumbosacral, and nerve cells in Clarke's column are reduced in number. The posterior roots become thin. The dentate nuclei exhibit mild to moderate neuronal loss and the middle and superior cerebellar peduncles are reduced in size. There is patchy loss of Purkinje cells in the superior vermis of the cerebellum and of neurons in corresponding portions of the inferior olivary nuclei. There are mild degenerative changes in the pontine and medullary nuclei and optic tracts. The cerebellar ataxia is explained by loss of the lateral and ventral spinocerebellar tracts, involvement of Clarke's column, the dentate nucleus, superior vermis, and dentatorubral pathways.

The corticospinal tracts are relatively spared down to the level of the cervicomedullary junction. Beyond this point, the corticospinal tracts are severely degenerated, which becomes progressively more severe moving down the spinal cord. This explains the common finding of bilateral extensor plantar responses and weakness late in the disease. Loss of cells in the nuclei of cranial nerves VIII, X, and XII results in facial weakness, speech, and swallowing difficulty.

Myocardial muscle fibers also show degeneration and are replaced by macrophages and fibroblasts. Essentially, chronic interstitial myocarditis occurs with hypertrophy of cardiac muscle fibers; fibers become hypertrophied and lose their striations. This is followed by swelling and vacuolation and finally interstitial fibrosis. The nuclei appear hyperchromatic and occasionally vacuolated. The cytoplasm appears granular with frequent lipofuscin depositions. Kyphoscoliosis is likely, secondary to spinal muscular imbalance.

Figure 6. Friedreich Ataxia
Histologic Findings in Friedreich ataxia

A cross-section through the lower cervical cord clearly shows loss of myelinated fibers of the dorsal columns and the corticospinal tracts (Weil stain). Milder involvement of spinocerebellar tracts is also present. The affected tracts show compact fibrillary gliosis (hematoxylin and eosin [H&E]) but no breakdown products or macrophages, reflecting the very slow rate of degeneration and death of fibers. The dorsal spinal ganglia show shrinkage and eventual disappearance of neurons associated with proliferation of capsular cells (H&E). The posterior roots are nearly devoid of large myelinated fibers. Within the thoracic spinal cord, degeneration and loss of cells of the Clarke column is apparent.

Figure 7. Friedreich Ataxia, Spinal cord

Neuroimaging in Friedreich ataxia

In Friedreich ataxia MRI examination shows cervical cord atrophy, thinning with reduced anteroposterior diameter. A hyperintense line on the posterior portion of cord is commonly seen, which represents loss of myelinated fibers and gliosis. The thinned spinal cord is seen lying on the posterior wall of spinal canal with increased signal intensity in its posterior and lateral compartments.
Figure 8. MRI of the brain in a case with Friedreich ataxia showing normal findings

Figure 9. MRI T2 (A,B) and MRI T1 (C) in a case with Friedreich's ataxia showing marked atrophy of the uppermost part of the cervical spinal cord

Figure 10. MRI T1 (A) and MRI T2 (B) in a case with Friedreich's ataxia showing marked atrophy of the uppermost part of the cervical spinal cord
Figure 11. MRI T2 images in a case with Friedreich's ataxia showing cervical cord atrophy, thinning with reduced anteroposterior diameter. Notice the hyperintense line in posterior portion of cord. The thinned spinal cord is seen lying on the posterior wall of spinal canal with increased signal intensity in its posterior and lateral compartments. The anterior subarachnoid space is enlarged. The intramedullary signal changes reflect loss of myelinated fibers and gliosis.

The decreased anteroposterior diameter of the spinal cord at the upper cervical region confirms that atrophy of the upper cervical part of the spinal cord is a characteristic feature of Friedreich’s ataxia, as opposed to other forms of corticocerebellar and cerebellar-brainstem atrophy. This had been indicated on the basis of subjective evaluation in two previous studies.

No direct pathologic correlation of the intramedullary signal abnormalities is available. However, the sensitivity of MR imaging to degeneration of white matter tracts in the brain and spinal cord after stroke or in degenerative diseases of the CNS - that is manifested on the MRI T2 images as hyperintense lines- has been cited in several reports [1-5]. Because of the substantial similarities between the intramedullary signal abnormality pattern that is found in patients with Friedreich and the distribution of demyelination and gliosis of white matter tracts in the histopathologic pictures of the spinal cord in cases of Friedreich’s ataxia, we think it reasonable to assume that the MR appearance could reflect these pathologic findings. Obviously, the intramedullary signal abnormality pattern is not exclusive to Friedreich’s ataxia and can be observed in subacute combined degeneration, tabes dorsalis, wallerian degeneration, and AIDS myelopathy. In these conditions, however, associated clinical and laboratory findings usually allow the correct diagnosis. [22-25]
Detection of signal changes in the white matter tracts of the spinal cord of patients with Friedreich’s ataxia could be an index of severity or progression of the disease and in this respect it is more useful than cord atrophy. The association between the extent of intramedullary signal changes and the chronicity and severity of disease is well known by the author and was reported by others [22-25]. Although this analysis could be informative, it requires quantitation of the signal changes in the white matter tracts and evaluation of the thoracolumbar spine. Noteworthy is the fact that intramedullary signal changes are only in patients with Friedreich’s ataxia. No such findings were seen in any of the patients with corticocerebellar or cerebellar-brainstem atrophy in the author experience and by others [22-25]. Thus, it appears that evaluation of the cervical spinal cord for intramedullary signal changes might be useful for differential diagnosis in patients with progressive ataxia of uncertain clinical type.

In a broad sense, MR examination of the cervical spinal cord is more informative than examination of the brain in patients with Friedreich’s ataxia. Although spinal cord atrophy and intramedullary signal changes theoretically could be searched for in the thoracic spinal cord of patients with Friedreich’s’ ataxia, focusing on the cervical spinal cord is recommended because it usually allows concurrent evaluation of the brainstem and the cerebellum. This may help in the differential diagnosis with corticocerebellar and cerebellar-brainstem atrophies.

In conclusion, MR imaging of the cervical spinal cord can show thinning of the cord and intramedullary signal changes consistent with degeneration of white matter tracts in the
lateral and posterior columns of patients with Friedreich’s ataxia. These MR findings might be helpful for differential diagnosis in patients with progressive ataxia of uncertain clinical type.

- **Abetalipoproteinemia**

This rare autosomal-recessive disorder is characterized by low levels of low-density lipoproteins (LDLs) and very low-density lipoproteins (VLDLs).

It features defective assembly and secretion of apolipoprotein B (Apo-B)–containing lipoproteins by the intestines and the liver.

Mutations appear to affect the microsomal triglyceride transfer protein (*MTP*) gene, which results in dysfunction.

  - **Clinical features**
    - Areflexia, proprioceptive dysfunction, loss of reflexes, and Babinski sign (prominent findings)
    - By 5-10 years, gait disturbances and cerebellar signs
    - Malabsorptive state in the early years with steatorrhea and abdominal distension
    - Pes cavus and scoliosis present in most patients
    - Pigmentary retinopathy
  - **Laboratory features**
    - Acanthocytosis on peripheral blood smears (constant finding)
    - Decreased serum cholesterol
    - Increased high-density lipoprotein cholesterol levels
    - Low levels of LDL and VLDL
    - Low triglyceride levels
  - **Treatment**
    - High-dose supplementation of vitamin E has a beneficial effect on neurologic symptoms.
    - Administer other fat-soluble vitamins (D, A, K).

- **Hypobetalipoproteinemia**

This autosomal-dominant disorder is clinically indistinguishable from abetalipoproteinemia.

It is caused by mutations that affect the *Apo-B* gene, which affects turnover of apolipoprotein B.

Neurologic and nonneurologic manifestations are similar in homozygotes. Heterozygotes, on occasion, also may be affected.
• **Ataxia With Selective Vitamin E Deficiency**

This is a rare autosomal-recessive disorder resulting from a mutation that affects the gene for alpha-tocopherol transfer protein.

  o **Clinical features**

It is phenotypically similar to Friedreich ataxia (FRDA), with head titubation (28%), spinocerebellar ataxia, areflexia, and proprioception loss.

Skin is affected by xanthelasmata and tendon xanthomas.

Onset varies from ages 2-52 years and usually occurs when younger than 20 years; it slowly progresses over decades.

  o **Laboratory features**

Measurements include low-to-absent serum vitamin E and high serum cholesterol, triglyceride, and beta-lipoprotein.

  o **Treatment**

Treatment consists of vitamin E supplementation. A dose of 400-1200 IU/d improves neurologic function. This should be maintained for life.

**ATAXIAS WITH PROGRESSIVE CEREBELLAR DYSFUNCTION PLUS SYSTEMIC FEATURES**

These disorders present with progressive ataxia combined with other neurologic dysfunction and systemic features that depend on the underlying pathology. The clinical features may include a varying combination of cognitive delay or decline, abnormalities of muscle tone, seizures, and movement disorders. The mode of inheritance varies and includes both mendelian and nonmendelian patterns. Many of the disorders discussed involve defects in DNA repair that involve a complex sequence of events. In disorders involving these pathways, multiple gene defects are involved.

Complementation analysis helps determine if pathogenic mutations are in the same or different genes.

  • Cell fusion of 2 different (diploid) cell lines from affected individuals (eg, from xeroderma pigmentosum) is attempted; DNA repair mechanisms then are studied in the new cell line.
  • If the DNA repair defect is corrected in a tetraploid cell line, the mutations complement, and the 2 cell lines are said to define 2 separate complementation groups.
Cockayne Syndrome

Autosomal-dominant (CSB) and recessive (CKN1) forms have been reported. Defective repair of transcriptionally active DNA is the underlying basis of the disorder. Cultured skin fibroblasts from these patients display abnormal UV sensitivity.

Clinical features

- Blindness, cataracts, and pigmentary retinopathy
- No increase in incidence of malignancy in these patients
- Microcephaly
- Neurologic features including ataxia, pyramidal and extrapyramidal dysfunction, and seizures
- Photosensitivity of skin
- Systemic hypertension, sexual infantilism, renal and hepatic dysfunction
- Wizened facies (similar to progeria)

Laboratory features

Calcification of basal ganglia is found on CT scan, and white matter changes are found on MRI.

Treatment

No treatment is available; early death in the second or third decade is usual.

Xeroderma Pigmentosum

This genetically heterogeneous disorder is due to a defect in DNA excision repair following UV exposure.

The condition differs from Cockayne syndrome because of the presence of skin tumors, absence of intracranial calcifications, and a different molecular defect.

Clinical features

- Ataxia, chorea, and axonal polyneuropathy
- Cutaneous photosensitivity and multiple cancers
- Mental and motor retardation
- Microcephaly
- Sensorineural deafness

Treatment

No treatment is available.
Ataxia Telangiectasia

This progressive, recessively inherited ataxia presents in early childhood.

It is more common in certain ethnic populations, including in those of Amish, Mennonite, Costa Rican, Polish, British, Italian, Turkish, Iranian, and Israeli descent.

A defective truncated protein (possibly phosphatidylinositol-3 kinase) results from mutations that affect the ATM gene locus.

The disease begins when patients are aged 1-3 years.

Clinical features

- Choreoathetosis
- Cutaneous and bulbar telangiectasia
- Immunodeficiency and increased susceptibility to infections
- Oculomotor apraxia
- Progressive ataxia and slurred speech
- Susceptibility to cancer (eg, leukemia, lymphoma)

Laboratory features

Molecular genetic testing is performed for mutations affecting the ATM gene locus (11q22.3). For those patients in whom mutations cannot be identified, other supportive laboratory evidence must be sought.

- Elevated (>10 ng/mL) serum alpha-fetoprotein in 90-95% of patients
- Abnormality in colony survival assay, the ability of colony formation of a lymphoblastoid cell line following irradiation
- Karyotyping abnormalities involving 7-14 chromosomal translocation in 5-15% of cells after phytohemagglutinin stimulation of lymphocytes in peripheral blood
- Breakpoints involved in translocation at the 14q11 and 14q32 sites

Treatment

No treatment is available other than supportive care and careful management of complications with modified chemotherapy.

Refsum Disease

This autosomal-recessive disorder is associated with impaired oxidation of phytanic acid. Elevated phytanic acid levels in the nervous system are associated with neurotoxicity.

Clinical features
Onset in the second to third decade of life
Cerebellar ataxia (may be superimposed in some patients)
Early presentation of night blindness and pigmentary degeneration of the retina
Polyneuropathy with elevated CSF protein
Sensorineural deafness
Skin (ichthyosis) and cardiac abnormalities (arrhythmia)

Laboratory features

- Cultured fibroblasts show reduced ability to oxidize phytanic acid.
- Elevated phytanic acid levels in the plasma and urine are diagnostic.

Treatment

Refsum disease has a relapsing-remitting course. Drastic reduction in dietary phytanic acid (supplemented by plasmapheresis) at onset can ameliorate the neuropathy and possibly other clinical abnormalities.

Cerebrotendinous Xanthomatosis

This autosomal-recessive disorder is caused by a defect in bile acid synthesis. Cholestanol accumulates in the tissues, including the nervous system. The defect is due to deficiency of hepatic sterol 27-hydroxylase, a mitochondrial enzyme.

Clinical features

- Palatal myoclonus, seizures
- Peripheral neuropathy
- Progressive ataxia with mental decline
- Pseudobulbar palsy
- Tendon xanthomas, cataracts

Laboratory features

- Elevated cholestanol and apolipoprotein B in CSF
- Low plasma cholesterol; elevated plasma cholestanol
- Low-to-absent chenodeoxycholic acid in the bile

Treatment

Lifelong oral administration of chenodeoxycholic acid (750 mg/d) is effective if initiated early. HMG-CoA reductase inhibitor also can be added to inhibit cholesterol biosynthesis.
Biotinidase Deficiency

Because of the lack of free biotin, biotinidase deficiency results in dysfunction of 3 mitochondrial carboxylases. It is recessively inherited, and the underlying defect involves mutations of the 3p25 locus for biotinidase.

Clinical features

- Delayed presentation (second year of life)
- Intermittent ataxia, sensorineural hearing loss
- Myoclonic seizures, developmental delay
- Skin rashes, alopecia

Laboratory features

- Can be demonstrated by assay in serum leukocytes or cultured fibroblasts
- Hyperammonemia
- Hypoglycemia
- Metabolic acidosis, lactic acidosis
- Possible intermittent organic aciduria (excess excretion of metabolites such as hydroxyisovaleric acid, methylcrotonylglycine, hydroxypropionate, and methylcitrate in the urine) as demonstrated by mass spectrometry

Treatment

- Biotin 5-20 mg/d PO is remarkably effective in reversing neurologic and cutaneous symptoms.
- Hearing and visual dysfunction may be resistant to treatment.

Late-Onset Sphingolipidoses

These complex biochemical defects are related to specific deficiencies of lysosomal enzymes (see Table 4). The brain and other tissues such as the liver store abnormal sphingolipids. The presentation is a combination of cognitive deterioration, seizures, and gait abnormalities due to a combination of pyramidal features (spasticity), cerebellar dysfunction (ataxia), extrapyramidal features (eg, dystonia), choreoathetosis, and ophthalmologic abnormalities.

Ataxia almost never is the sole clinical symptom. As these disorders are progressive, symptoms and signs can be seen in combination. The disorders are autosomal recessive. Skin examination under electron microscope is an effective screening tool. Definitive diagnosis can be established by lysosomal enzyme assay in leukocytes or cultured skin fibroblasts.
**L-2-hydroxyglutaricaciduria**

This autosomal-recessive inherited defect is characterized by excessive excretion of L-2-hydroxyglutaric acid in the urine. The precise molecular basis not well established.

**Clinical features**

- Presence of cognitive delay and epileptic seizures
- Age of onset of 6-20 years
- Progressive ataxia, dysarthria, and extrapyramidal dysfunction
- Added features of short stature and macrocrania

**Laboratory findings**

- Elevated 2-hydroxyglutaric acid in plasma, urine, and CSF
- Elevated lysine in plasma and CSF

**Treatment**

No treatment is available.

**Carbohydrate Deficient Glycoprotein Syndrome**

Carbohydrate deficient glycoprotein syndrome (CDG) is a new class of disorders that results from abnormalities of carbohydrate-deficient glycoproteins, particularly transferrin. The disorder has been reported from Scandinavian countries as well as other European countries. All are autosomal-recessive conditions; several clinical and biochemical types have been characterized. CDG is caused by mutations affecting the enzyme phosphomannomutase; the gene locus is located on subband 16p13.3.

**Clinical features**

- Stage of ataxia; mental deficiency during infantile and childhood stage
- Delayed development, failure to thrive, hypotonia, and multisystem organ failure
- Dysmorphic facial features, including prominent ears and nose
- Fat pads over buttocks, abnormal patches of skin over thighs, and inverted nipples (considered characteristic clinical features)
- In the teenage years, evident lower limb atrophy and peripheral neuropathy
- Presents in infancy (first year)
- Severe mental retardation and hypogonadism recognized in later years

**Laboratory features**

- Decreased serum glycoproteins
- MRI showing striking pontocerebellar atrophy
- Reduced thyroxine-binding globulin levels
Reduced N-acetylglucosaminyltransferase
Sialic acid, galactose, and N-acetylglucosamine deficiency in total serum glycoproteins
Synthesized proteins with fewer attached carbohydrate moieties than normal glycoproteins.
When an electric field is applied to serum, proteins tend to separate based on charge.
Sialotransferrins, a specific class of glycoproteins, behave differently in serum from patients with CDG than in serum from individuals without CDG; patients with CDG have less sialic acid, a negatively charged sugar.
The pattern of separation during electrophoresis is considered diagnostic for this disorder.

Treatment

No treatment is available other than supportive care.

Leukoencephalopathy With Vanishing White Matter

Leukoencephalopathy with vanishing white matter (VEM) is a recently described disease entity presenting with leukoencephalopathy of unknown origin. The disorder has an autosomal-recessive inheritance with an age-dependent penetrance.

The gene is located on band 3q27; the disease gene, its function, and mutations causing the disease remain to be identified.

Clinical features

- Cerebellar ataxia and spasticity are prominent.
- Chronic progressive neurologic deterioration and episodic exacerbation follow in late infancy or early childhood. Episodes of deterioration follow minor infection and head trauma, leading to periods of lethargy or coma.
- Cognitive ability may show decline but is relatively preserved compared to the severity of motor deficit.
- Initial motor and mental development is normal or mildly delayed.
- Optic atrophy and epilepsy may be additional features.

Laboratory features

- Cerebellar atrophy varies from mild to severe and primarily involves the vermis.
- Elevated CSF glycine is a marker for this disorder.
- MRI indicates symmetric involvement of the cerebral hemispheric white matter, which acquires a signal intensity close to or the same as CSF on proton density, T2-weighted, T1-weighted, and fluid-attenuated inversion recovery images.
- Magnetic resonance spectroscopy shows a significant decrease to near absence of normal signals from the white matter, except for lactate and glucose (the signals of
which become more prominent with disappearance of other normal signals). Signals over the cortex remain relatively normal.

- Pathologic studies confirm white matter rarefaction and loss of myelinated white fibers. Microcystic changes are reported in the periventricular white matter.

**Treatment**

No effective treatment is known to halt progression of the disorder, although symptomatic and supportive measures can improve the quality of life.

**Succinic-Semialdehyde Dehydrogenase Deficiency**

Succinic-semialdehyde dehydrogenase deficiency (SSADH) is a recessively inherited disorder affecting the aminobutyric acid (GABA) degradation pathway. Although it is characterized by excretion of large amounts of 4-hydroxybutyric acid in the urine, phenotype varies widely.

**Clinical features**

- Ataxia
- Hypotonia
- Nonspecific neurologic features such as cerebral palsy and developmental delay
- Psychomotor retardation, language delay

**Laboratory features**

- Elevated 4-hydroxybutyric acid in plasma, urine, and CSF
- High free GABA in CSF
- Cerebellar atrophy on MRI

**Treatment**

- L-carnitine supplementation has been tried with improvement in muscle tone.
- Vigabatrin, an inhibitor of GABA transaminase, has proven effective in low doses of 25 mg/kg/d.

**Neuropathy, Ataxia and Retinitis Pigmentosa, and Peripheral Neuropathy Syndrome**

Neuropathy, ataxia and retinitis pigmentosa, and peripheral neuropathy (NARP) syndrome is a mitochondrial disorder that displays maternal inheritance. Affected individuals present with features of cerebellar ataxia, seizures, cognitive impairment, and peripheral neuropathy. The condition carries a variable phenotype and also may occur sporadically. The underlying defect involves a mitochondrial ATP synthase gene (subunit 6) affecting nucleotide 8993, mutations of which also can result in the Leigh syndrome phenotype. The diagnosis can be confirmed by mitochondrial DNA mutation analysis.
• **Leigh Disease**

This disorder has a distinct neuropathologic picture, a highly variable clinical presentation, and multiple biochemical and molecular genetic defects. Autosomal-recessive inheritance and maternal inheritance (mutations in mitochondrial DNA) patterns exist.

  o **Clinical features**
    • Clinical features include protean manifestations due to multifocal lesions in the brain stem, thalamus, and cerebellum; the most important of these are as follows:
      ▪ Oculomotor - Nuclear or supranuclear ophthalmoplegia; central nystagmus with rotary and horizontal components
      ▪ Relapsing-remitting course, rarely progressively fatal
      ▪ Respiratory - Characterized by unexplained hyperventilation, apnea, and irregular respiration (air hunger)
      ▪ Truncal ataxia, incoordination, and intention tremor evident as child begins to walk
  
  o **Laboratory features**
    • Characteristic lesions, which are symmetric, can be demonstrated in the thalamus, putamen, and globus pallidus on T2-weighted MRI sequences. The lesions also are distributed in the brain stem and cerebellum.
    ▪ Lactate and pyruvate are elevated in the CSF.
    ▪ Perform enzyme function assays on cultured fibroblasts, muscle, or liver tissue. Frequently, more than one of these tissues should be assayed because of the lack of correlation between enzyme activities in muscle and skin.
    ▪ Hyperammonemia, hypoglycemia, and organic aciduria are not present.
    ▪ Multiple mitochondrial enzymes have been demonstrated to be affected in this disorder, particularly the pyruvate dehydrogenase (PDH) complex, cytochrome c oxidase, and the mitochondrial ATPase 6 gene.
    ▪ Neuropathologic lesions show incomplete necrosis and spongiform changes in the neuropil with relative preservation of the neurons, resulting in a “spongiosis.”
    ▪ Vascular proliferation also occurs, and white matter changes can be seen.
  
  o **Treatment**
    • No treatment is known to actually benefit patients. Vitamin B supplementation has been administered without documented benefit.
Recently, the ketogenic diet has been reported to be useful in treating patients with pyruvate dehydrogenase complex deficiency.

### Table 4. Ataxias With Progressive Cerebellar Dysfunction Plus Systemic Features

<table>
<thead>
<tr>
<th>Autosomal-Dominant/Recessive Ataxias</th>
<th>Neurologic Phenotype</th>
<th>Genetic-Biochemical Defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cockayne syndrome (CSB)</td>
<td>Progressive ataxia plus</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>AD*, 10q11-q21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• DNA excision-repair cross-complementing (ERCC6) gene defect</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Xeroderma pigmentosum</th>
<th>Progressive ataxia plus</th>
<th>AR†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>• Genetically heterogeneous with several identified complementation groups</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Mutations resulting in either defective damage specific DNA-binding protein or defective excision repair</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Neurologic manifestations beginning in childhood relating to complementation Gp. A 9q34 locus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Other complementation groups involved - 2q21 (B &amp; CS); 3p25.1 (C); 19q13.2(D); Unknown (E); 16p13 (F); 13q32-33 (G &amp; CS)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ataxia telangiectasia</th>
<th>Progressive ataxia plus</th>
<th>AR, 11q22-q23</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>• Mutation resulting in truncated protein and dominant negative defect</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recessive Metabolic Ataxias</th>
<th>Neurologic Phenotype</th>
<th>Genetic-Biochemical Defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refsum disease</td>
<td>Progressive ataxia plus</td>
<td>AR, 10pter-p11.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Mutations affecting gene coding for phytanoyl-CoA hydroxylase</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cerebrotendinous xanthomatosis</th>
<th>Chronic progressive ataxia</th>
<th>AR, 2q3-pter</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>• Defective mitochondrial cytochrome-</td>
</tr>
<tr>
<td>Condition</td>
<td>Description</td>
<td>Genetics</td>
</tr>
<tr>
<td>-----------</td>
<td>-------------</td>
<td>----------</td>
</tr>
<tr>
<td>Biotinidase deficiency</td>
<td>Progressive ataxia plus</td>
<td>AR, 3q25</td>
</tr>
<tr>
<td>Late infantile and juvenile sphingolipidoses</td>
<td>Progressive ataxia plus seizures, psychomotor regression, spasticity, extrapyramidal features, supranuclear gaze palsies</td>
<td>AR</td>
</tr>
<tr>
<td>L-2 Hydroxyglutaric acidemia</td>
<td>Chronic progressive ataxia</td>
<td>AR</td>
</tr>
<tr>
<td>Carbohydrate-deficient glycoprotein syndrome</td>
<td>Progressive ataxia plus</td>
<td>AR, 6p13.3-p13.2</td>
</tr>
<tr>
<td>Leukoencephalopathy with</td>
<td>Progressive ataxia, spasticity</td>
<td>AR, 3q27</td>
</tr>
<tr>
<td>Disorder</td>
<td>Clinical Features</td>
<td>genetics</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>-------------------------------------------</td>
<td>------------------------------------</td>
</tr>
<tr>
<td>vanishing white matter</td>
<td>optic atrophy, seizures</td>
<td></td>
</tr>
<tr>
<td>Succinic-semialdehyde dehydrogenase deficiency</td>
<td>Progressive ataxia plus</td>
<td>AR, 6p22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Accumulation of 4-hydroxybutyric acid in plasma and urine</td>
</tr>
<tr>
<td>NARP syndrome</td>
<td>Progressive ataxia plus</td>
<td>• Maternal inheritance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Mitochondrial ATP-6 NARP 8993 mutation, causing base substitution T-to-G or T-to-C (AMA 370) at nucleotide position 8993</td>
</tr>
<tr>
<td>Leigh disease</td>
<td>Progressive ataxia plus lactic acidosis</td>
<td>AR/maternal inheritance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Multiple biochemical and molecular defects underlying condition (eg, PDH complex deficiency, cytochrome oxidase C deficiency, mitochondrial ATPase 6)</td>
</tr>
</tbody>
</table>

*AD - Autosomal dominant
†AR - Autosomal recessive

**ATAXIA WITH PROGRESSIVE MYOCLONIC EPILEPSIES**

The progressive myoclonic epilepsies (PMEs) constitute a group of seizure disorders with phenotypic features of myoclonic and other generalized seizures, ataxia, and cognitive defects. These features occur in variable combinations that progress over time. These disorders are often difficult to distinguish on purely clinical grounds.

- **Unverricht-Lundborg Disease**

Heinrich Unverricht (September 18, 1853 - April 22, 1912) was a German internist who was a native of Breslau. In 1877 he obtained his doctorate from the University of Breslau, where he was a student of Michael Anton Biermer (1827-1892). Later he was a professor at Jena (1886) and Dorpat (1888), where he resigned in 1892 for political reasons, and became director of the city hospital at Magdeburg-Sudenburg.

Heinrich Unverricht is most remembered for his research of epilepsy, especially his work with progressive myoclonus epilepsies (PME). In 1891 he described a form of PME that was later come to be known by the eponymous label "Unverricht-Lundborg disease". Equally notable, however, following Wagner (1863) and Virchow's (1866) initial clinical descriptions, in 1891 he developed the concept of an intimate connection between rash and muscle weakness that defined a new disorder: "...it seems to me that the skin appearance
plays such an important role in the disease picture that the designation Polymyositis is not completely accurate. In our case, the partnership of the skin and muscle disease allows us to use the elocution Dermatomyositis. Unverricht published over fifty medical works, including Studien über die Lungenentzündung, his prize-winning doctorate thesis on pneumonia.

PME of the Unverricht-Lundborg type (EPM1) is autosomal recessive with an approximate age of onset of 10 years. EPM1 mostly has been reported in a genetically homogeneous population, permitting studies using linkage disequilibrium to narrow the gene defect to a small region of subband 21q22.3. The gene CST6 codes for a protein called cystatin B, a noncaspase cysteine protease inhibitor. Cystatin B mRNA was reduced markedly in EPM1 patients. The mutation results from an unstable dodecamer repeat expansion in the promoter region of the CST6 gene.

Figure 13. **Heinrich Unverricht**

- **Clinical features**
  - Ataxia developing late in the disease course
  - Mild mental deterioration
  - Progressive disability from stimulus-sensitive myoclonus and generalized tonic-clonic (GTC) seizures
- **Laboratory features**
  - EEG is nonspecific, showing background slowing and paroxysmal bursts of generalized spike-wave abnormalities.
  - Giant somatosensory evoked potentials can be elicited.
- **Treatment**

\(N\)-acetylcysteine has been found effective in an open trial in 4 patients. A marked decrease in myoclonus and some normalization of somatosensory evoked potentials with \(N\)-acetylcysteine treatment has been documented.
Phenytoin aggravates symptoms.
Piracetam has been useful in the treatment of myoclonus.

Lafora Body Disease

PME of the Lafora type (EPM2/MELF) resembles EPM1 clinically. EPM2 is linked to 6q24, where the gene EPM2A encodes a protein tyrosine phosphatase termed laforin. Phosphatases are involved in many aspects of neuronal function, including glycogen metabolism and regulation of ionic channels and synaptic transmission.

Figure 14. Lafora bodies

- Clinical features
  - Ataxia
  - Progressively worsening myoclonic and occipital seizures with visual signs
  - Presentation in late childhood or adolescence, leading to a fatal outcome within a decade
- Laboratory features
MRI shows cerebellar atrophy. Periodic acid-Schiff–positive cytoplasmic inclusion bodies are found in the brain, muscle, liver, and skin. These findings are considered diagnostic.

Treatment

The disorder is fatal. Symptomatic treatment for seizures and myoclonus may be tried.

- Neuronal Ceroid Lipofuscinosis

Neuronal ceroid lipofuscinosis (NCL) describes autosomal-recessive disorders in which characteristic storage material is identified within neurons, resulting in their degeneration. NCLs are a group of progressive neurodegenerative disorders that share several clinical features, particularly the presence of seizures and progressive dementia.

Several genetically distinct subgroups have been determined based on age at presentation. Each subgroup has a characteristic ultrastructural appearance of the intracellular lipopigment.

The gene for the classic late infantile form (LINCL CLN2) maps to band 11p15.

Mutations in the gene encoding a pepstatin-insensitive lysosomal peptidase have been identified in patients with CLN2, and assays of this enzyme have been demonstrated as deficient in CLN2 autopsy specimens.

- Clinical features
  - Ataxia
  - Dementia
  - Myoclonic seizures, atypical absence seizures, GTC seizures, other seizure types
  - Visual impairment

- Laboratory features
  - CT scan and MRI show predominantly cerebellar atrophy.
  - Electron microscopic examination of skin or conjunctival biopsy shows typical intralysosomal curvilinear inclusions.
  - Giant visual evoked potentials and large somatosensory visual evoked potentials can be elicited.
  - The diagnosis can be suspected on the basis of abnormal driving responses on the EEG to photic stimulation (high-amplitude spike at low rates of stimulation).
Treatment

The disorder is progressive and fatal. No treatment is available, although symptomatic treatment and supportive measures may help improve the quality of life.

Figure 15. Neuronal ceroid lipofuscinosis (NCL). (A) Axial T2-weighted MR image of patient with infantile NCL reveals dark, atrophied thalami (arrow), diffuse volume loss, ventriculomegaly, and significant delay in myelin maturation. (B) Axial T2-weighted image of patient with juvenile variant demonstrates atrophied thalami and loss of signal within the periventricular white matter and the posterior limb of internal capsule (arrow).

Figure 16. Magnetic resonance imaging study of the brain in a patient with neuronal ceroid lipofuscinosis showing cerebellar atrophy on sagittal view
Myoclonic epilepsy with ragged red fibers (MERRF) is the prototype disorder in which epilepsy results from deficient mitochondrial energy production. An A-to-G transition mutation at nucleotide pair 8344 in human mitochondrial DNA has been identified in most patients. The mutation creates a specific restriction site on the tRNA_Lys gene, producing defects in complex I and IV enzymes of the oxidative phosphorylation system. Myriad cell functions are involved in the control of excitability and are energy dependent. Thus deficient energy production or utilization can lead to neurologic dysfunction in a variety of ways.

- Clinical features
  - Ataxia
  - Impaired deep sensations (similar to FRDA)
  - Myopathy
  - Sensorineural deafness
  - Short stature
  - Myoclonic and GTC seizures often photosensitive and exaggerated by voluntary movements

- Laboratory features
  - CT scan may show basal ganglia calcification.
  - Ragged red fibers in muscle biopsy specimens result from the subsarcolemmal aggregation of mitochondria.
  - EEG shows paroxysmal irregular generalized spike wave complexes with background abnormalities.
  - Lactic acidosis is present.
  - Mutation analysis can be performed to demonstrate mtDNA mutation.

- Treatment
  - No specific treatment measures exist. Treat seizures symptomatically.
Table 5. Progressive myoclonic Epilepsy

<table>
<thead>
<tr>
<th>Progressive Myoclonic Epilepsies</th>
<th>Neurologic Phenotype</th>
<th>Genetic-Biochemical Defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unverricht-Lundborg syndrome</td>
<td>Myoclonus, ataxia, and seizures</td>
<td>AR*, 21q22.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Mutations involving dodecamer repeat expansions affecting the gene for cystatin B</td>
</tr>
<tr>
<td>Lafora body disease</td>
<td>Myoclonus, ataxia, and seizures</td>
<td>AR, 6q24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Mutation affecting gene for a protein tyrosine phosphatase (laforin), which may disrupt glycogen metabolism</td>
</tr>
<tr>
<td>MERRF</td>
<td>Myoclonus and ataxia</td>
<td>Maternal inheritance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• mtDNA mutations affecting tRNA_{Lys} defective oxidative phosphorylation</td>
</tr>
<tr>
<td>Late infantile neuronal ceroid lipofuscinosis</td>
<td>Myoclonus, ataxia, and seizures</td>
<td>AR, 11p15.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Gene coding for lysosomal pepstatin insensitive protease</td>
</tr>
</tbody>
</table>

*AR - Autosomal recessive

**CONCLUSIONS**

- Biochemical defects that affect myriad pathways can result in disorders with ataxia as the sole presentation or part of a more generalized syndrome.
- Most biochemical defects have a genetic basis, and both traditional mendelian and nontraditional inheritance mechanisms are involved.
- When approaching the child or adult with ataxia, the differential diagnosis always must include biochemical defects.
The age of onset, mode of presentation, family history, and presence or absence of other neurologic signs are involved heavily in determining the screening and specific tests in the evaluation (see Picture 1).

Many of these neurodegenerative conditions are progressive, with no treatment currently available. Other specific defects such as ataxia with selective vitamin deficiency are eminently treatable, and still others such as urea cycle defects may have treatment that prolongs life and reduces morbidity.

Advances in the field of molecular genetics have improved the understanding of these diseases. New techniques will guide the way for future therapeutic advances.

References

INTRODUCTION

Multiple system atrophy (multisystem atrophy) is a rare neurological disorder characterized by a combination of parkinsonism, cerebellar and pyramidal signs, and autonomic dysfunction. The term "Multiple System Atrophy" is synonymous with striatonigral degeneration (SND) when Parkinsonism predominates, olivopontocerebellar atrophy (OPCA) when cerebellar signs predominate, and Shy-Drager syndrome when autonomic failure is dominant.
Clinical feature of MSA

<table>
<thead>
<tr>
<th>Name</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Striatonigral degeneration</td>
<td>Predominating Parkinson’s-like symptoms</td>
</tr>
<tr>
<td>Shy-Drager syndrome</td>
<td>Characterized by Parkinsonism plus a more pronounced failure of the autonomic nervous system</td>
</tr>
<tr>
<td>Sporadic Olivopontocerebellar atrophy (OPCA)</td>
<td>Characterized by progressive ataxia (an inability to coordinate voluntary muscular movements) of the gait and arms and dysarthria (difficulty in articulating words)</td>
</tr>
</tbody>
</table>

The classical presentation of MSA are atypical parkinsonism with early autonomic dysfunction and cerebellar signs that usually manifests in middle age and progresses relentlessly with a mean survival of 6 to 9 years. Initial L-dopa response occurs in a third of patients, however 90% of them are unresponsive on long-term follow-up. Orofacial dystonia is a feature observed in more than half of all MSA patients and may occur spontaneously or more usually as a complication of L-dopa therapy. Disproportionate anterocollis is another characteristic feature seen in MSA. Early urinary incontinence and syncope are characteristic for MSA and contrast with the later autonomic involvement often seen in Parkinson disease (PD). Early erectile dysfunction is also common and urinary retention can rarely be an early symptom. There are two subtypes of MSA: parkinsonian (MSA-P) and cerebellar (MSA-C) subtypes. Neuropathologically, all subtypes of MSA are collectively characterized by the finding of a-synuclein glial cytoplasmic inclusions in the striatum and cerebellum (GCIs).

The clinical differential diagnoses for this patient would include the following: other atypical parkinsonian syndromes, adult-onset cerebellar ataxia that can be hereditary despite a negative family history (eg, Friedreich ataxia), spinocerebellar ataxia, Fragile X tremor ataxia syndrome (FXTA) syndrome, and autoimmune conditions in association with Anti-GAD in celiac disease, anti-Yo and anti-Hu in paraneoplastic syndromes. Toxic and metabolic conditions (eg, hypothyroidism, alcohol-related cerebellar degeneration) should also be considered, as some of these are potentially reversible.

The most common first sign of MSA is the appearance of an "akinetic-rigid syndrome" (i.e. slowness of initiation of movement resembling Parkinson’s disease) found in 62% at first presentation. Other common signs at onset include problems with balance (found in 22%), followed by genito-urinary problems (9%). For men, the first sign can be erectile dysfunction (unable to achieve or sustain an erection). Both men and women often experience problems with their bladders including urgency, frequency, incomplete bladder emptying or an inability to pass urine (retention). About 1 in 5 MSA patients will suffer a fall in their first year of disease.

As the disease progresses three groups of symptoms predominate. These are:

1-Parkinsonism (slow, stiff movement, writing becomes small and spidery). The parkinsonian subtype of MSA (MSA-P) or striatonigral degeneration
2-Cerebellar dysfunction (difficulty coordinating movement and balance). The Cerebellar subtype of MSA (MSA-C) or olivopontocerebellar atrophy.

3-Autonomic dysfunction. The autonomic subtype of MSA or Shy-Drager syndrome (impaired automatic body functions) including:

- Postural or orthostatic hypotension, resulting in dizziness or fainting upon standing up
- Urinary incontinence
- Impotence
- Constipation
- Dry mouth and skin
- Trouble regulating body temperature due to abnormal sweating abnormal breathing during sleep

The concept of multiple system atrophy (MSA) as a unitary diagnosis encompassing several clinical syndromes has a long history (see Table 1). In 1996 and 1998, the Consensus Committees representing the American Autonomic Society and the American Academy of Neurology defined MSA as a sporadic, progressive, neurodegenerative disease of undetermined etiology, characterized by extrapyramidal, pyramidal, cerebellar, and autonomic dysfunction in any combination.

MSA can be classified as possible, probable, or definite based on the features and criteria in the 3 clinical domains of (1) autonomic and/or urinary dysfunction, (2) parkinsonism, and (3) cerebellar dysfunction (Table 2, Table 3, Table 4, Table 5, Table 6). Possible MSA can be diagnosed when one criterion and two features separate from other clinical domains are found. The diagnosis of probable MSA requires the criterion of autonomic and/or urinary dysfunction and the presence of poorly levodopa-responsive parkinsonism or cerebellar ataxia. Only pathologic findings can confirm the diagnosis of definite MSA.
Figure 1. Bilateral putaminal degeneration is typically seen in striatonigral degeneration

When autonomic failure predominates, MSA sometimes is termed Shy-Drager syndrome. When extrapyramidal features predominate, the term striatonigral degeneration or MSA-P sometimes is used. When cerebellar features predominate, MSA sometimes is termed sporadic olivopontocerebellar atrophy or MSA-C.
Figure 2. Olivopontocerebellar atrophy: As the name implies, atrophic features can be seen within the medullary olives, the basis pontis, and the cerebellar cortex.

The clinical and diagnostic distinctions between MSA and pure autonomic dysfunction are reviewed in Table 7.
<table>
<thead>
<tr>
<th>Period</th>
<th>Authors</th>
<th>Terms</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1900</td>
<td>Dejerine and Thomas</td>
<td>OPCA</td>
<td>Introduction of term olivopontocerebellar atrophy (OPCA)</td>
</tr>
<tr>
<td>1925</td>
<td>Bradbury and Eggleston</td>
<td>OH</td>
<td>Introduction of autonomic failure as clinical syndrome (orthostatic hypotension [OH])</td>
</tr>
<tr>
<td>1960</td>
<td>Shy and Drager</td>
<td>SDS</td>
<td>Origin of term Shy-Drager syndrome (SDS) as neuropathologic entity with parkinsonism and autonomic failure with OH</td>
</tr>
<tr>
<td>1960</td>
<td>Van der Eecken et al</td>
<td>SND</td>
<td>Description of striatonigral degeneration (SND)</td>
</tr>
<tr>
<td>1969</td>
<td>Graham and Oppenheimer</td>
<td>MSA is OPCA, SDS, and SND</td>
<td>SDS, SND, and OPCA coexist and represent single disease; introduction of term MSA</td>
</tr>
<tr>
<td>1989</td>
<td>Papp et al, Matsuo et al</td>
<td>GCIs</td>
<td>Discovery of glial cytoplasmic inclusions (GCIs) as hallmark of MSA</td>
</tr>
<tr>
<td>1996-1999</td>
<td>Consensus Committees</td>
<td>MSA</td>
<td>Definition of MSA based on clinical domains and features and neuropathology</td>
</tr>
<tr>
<td>Clinical Domain,*</td>
<td>Feature (Characteristic of the Disease)</td>
<td>Criterion (Defining Feature)</td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>----------------------------------------</td>
<td>------------------------------</td>
<td></td>
</tr>
<tr>
<td>Autonomic and urinary dysfunction</td>
<td>Orthostatic hypotension Decrease of 20 Hg systolic and Decrease of 10 Hg diastolic within 3 min of standing Urinary incontinence or incomplete bladder emptying</td>
<td>Orthostatic hypotension Decrease of 20 Hg systolic and Decrease of 5 Hg diastolic within 3 min of standing and/or Urinary incontinence as persistent, involuntary, partial or total bladder emptying, accompanied by erectile dysfunction in men</td>
<td></td>
</tr>
<tr>
<td>Parkinsonism, 87%</td>
<td>Bradykinesia - Slowness of voluntary movement with progressive reduction in speed and amplitude during repetitive actions Rigidity Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction Tremor - Postural, resting, or both</td>
<td>Bradykinesia plus At least one parkinsonian feature</td>
<td></td>
</tr>
<tr>
<td>Cerebellar dysfunction, 54%</td>
<td>Gait ataxia - Wide-based stance with steps of irregular length and direction Ataxic dysarthria Limb ataxia Sustained gaze-evoked nystagmus</td>
<td>Gait ataxia plus At least one cerebellar feature</td>
<td></td>
</tr>
<tr>
<td>Corticospinal tract dysfunction, 49%</td>
<td>Extensor plantar response with hyperreflexia (pyramidal sign)</td>
<td>Not used as criterion in defining diagnosis of MSA</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Clinical Domains and Features in Diagnosis of MSA*
Table 3. Exclusion Criteria for Diagnosis of MSA*

<table>
<thead>
<tr>
<th>History</th>
<th>Symptomatic onset younger than age 30 years. Family history of similar disorder. Systemic diseases or other identifiable causes for features listed in Table 2. Hallucinations unrelated to medication.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Examination</td>
<td><em>Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition</em> criteria for dementia. Prominent slowing of vertical saccades or vertical supranuclear gaze palsy. Evidence of focal cortical dysfunction such as aphasia, alien limb syndrome, and parietal dysfunction.</td>
</tr>
<tr>
<td>Laboratory Investigation</td>
<td>Metabolic, molecular genetic, and imaging evidence of alternative cause of features listed in Table 2.</td>
</tr>
</tbody>
</table>

*Adapted from Gilman et al [81,19,20,21]*

Table 4. Diagnostic Categories of MSA*

<table>
<thead>
<tr>
<th>Possible MSA</th>
<th>One criterion plus Two features from separate other domains. When criterion is parkinsonism, a poor levodopa response qualifies as one feature (hence only one additional feature required).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable MSA</td>
<td>Criterion for autonomic failure and urinary dysfunction plus Poorly levodopa-responsive parkinsonism or cerebellar dysfunction</td>
</tr>
<tr>
<td>Definitive MSA</td>
<td>Pathologically confirmed by presence of high density of GCIs in association with degenerative changes in nigrostriatal and olivopontocerebellar pathways</td>
</tr>
</tbody>
</table>

*Features and criteria for each clinical domain are shown in Table 2 (adapted from Gilman et al [18,19,20,21]).

MSA is characterized by progressive loss of neuronal and oligodendroglial cells in numerous sites in the central nervous system (CNS). The etiology of the cell loss is still unknown.
unknown. Autoimmune mechanisms and toxic agents have been suggested as potential causes of MSA, but evidence for these etiologies is weak. No evidence of a genetic etiology has been found. The clinical symptoms of MSA correlate with cell loss in different CNS sites (Table 5).

Initially, researchers assumed that MSA was caused by gray matter damage. The discovery of oligodendroglial cytoplasmic inclusions (GCIs, Table 8) indicates that damage is primarily in the white matter. These chronic alterations in glial cells may impair trophic function between oligodendrocytes and axons and cause secondary neuronal damage. Whether the inclusions represent the primary lesion or are nonspecific secondary markers of cellular injury remains unknown. In addition to the GCIs, extensive myelin degeneration occurs in the brain. Changes in myelin may play an important role in the pathogenesis of MSA.

Table 5. Clinicopathologic Correlations*

<table>
<thead>
<tr>
<th>Clinical Symptom</th>
<th>Pathologic Findings; Location of Damage or Cell Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthostatic hypotension</td>
<td>Primary preganglionic damage of intermediolateral cell columns</td>
</tr>
<tr>
<td>Urinary incontinence (not retention)</td>
<td>Preganglionic cell loss in spinal cord (intermediolateral cell columns) Related to detrusor hyperreflexia caused mainly by loss of inhibitory input to pontine micturition center (rather than to external urethral sphincter denervation alone)</td>
</tr>
<tr>
<td>Urinary retention caused by detrusor atonia</td>
<td>Sacral intermediolateral cell columns</td>
</tr>
<tr>
<td>Cerebellar ataxia</td>
<td>Cell loss in inferior olives, pontine nuclei, and cerebellar cortex</td>
</tr>
<tr>
<td>Pyramidal signs</td>
<td>Pyramidal tract demyelination</td>
</tr>
<tr>
<td>Presence of extensor plantar response</td>
<td>Pyramidal tract lesion</td>
</tr>
<tr>
<td>Hyperreflexia</td>
<td>Pyramidal tract lesion</td>
</tr>
<tr>
<td>Motor abnormalities</td>
<td>GCIs in cortical motor areas or basal ganglia</td>
</tr>
<tr>
<td>Akinesia</td>
<td>Putamen, globus pallidus</td>
</tr>
<tr>
<td>Rigidity</td>
<td>Putaminal (not nigral) damage</td>
</tr>
<tr>
<td>Limb and gait ataxia</td>
<td>Inferior olives, basis pontis</td>
</tr>
<tr>
<td>---------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>Decreased or absent</td>
<td>Striatal cell loss</td>
</tr>
<tr>
<td>levodopa responsiveness</td>
<td>Loss of D1 and D2 receptors in striatum or impaired functional coupling of D1 and D2 receptors</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>Inferior olives, pontine nuclei</td>
</tr>
<tr>
<td>Dysartrhia</td>
<td>Pontine nuclei</td>
</tr>
<tr>
<td>Laryngeal stridor</td>
<td>Severe cell loss in nucleus ambiguus or Biochemical defect causing atrophy of posterior cricoarytenoid muscles</td>
</tr>
</tbody>
</table>

*Adapted from Wenning et al [64]*

The prevalence of MSA in the population may be 2-15 per 100,000. An estimated 25,000-100,000 Americans suffer from MSA. Most patients do not receive the correct diagnosis during their lifetime because of the difficulty in differentiating MSA from other disorders (e.g., Parkinson disease, pure autonomic failure, other rare movement disorders); therefore, a much higher prevalence can be assumed. Patients with MSA have a poor prognosis. The disease progresses rapidly. Patients survive an average of 9.5 years after the onset of the illness. Bronchopneumonia (48%) and sudden death (21%) are common terminal conditions.

MSA has been encountered in Caucasian, African, and Asian populations. The disease can be found more often in males than in females. Female-to-male ratios of occurrence from 1:3 to 1:9 are reported. Earlier and easier diagnosis of impotence may lead to the predominance of males diagnosed with MSA. The mean age at onset in MSA is 52.5-55 years. The disease progresses over intervals of 1-18 years. Median survival times of 6.2-9.5 years from the first symptoms have been reported in the last 2 decades. Older age of onset was associated with shorter survival duration. The overall nigrostriatal cell loss correlated with severity of disease at the time of death. The cause of multisystem atrophy is unknown. Environmental toxins or a history of trauma have been suggested, but evidence is slight.

- **Clinical picture**
  - **History**

Most patients with MSA develop the disease when older than 40 years and experience fast progression. Usually autonomic and/or urinary dysfunction develops first. Patients with MSA may have parkinsonian symptoms with poor or nonsustained response to levodopa therapy. Motor impairment can be caused by cerebellar dysfunction. Corticospinal tract dysfunction also can occur but is not often a major symptomatic feature of MSA. An
overview of the clinical domains, with their features, is given in Table 2. More details are described in the next sections.

- **Physical Examination**
  - **Autonomic and/or urinary dysfunction**
    - Autonomic symptoms are the initial feature in 41-74% of patients with MSA but ultimately develop in 97%. Genitourinary dysfunction is the most frequent initial complaint in women, and erectile dysfunction is the most frequent initial complaint in men.
    - Orthostatic hypotension, defined as a reduction of systolic blood pressure (BP) of at least 20 mm Hg or of diastolic BP of at least 10 mm Hg within 3 minutes of standing, is common and present in at least 68% of patients. Associated symptoms include the following:
      - Light-headedness
      - Dizziness
      - Dimming of vision
      - Head, neck, or shoulder pain
      - Altered mentation
      - Weakness, especially of legs
      - Fatigue
      - Yawning
      - Slurred speech
      - Syncope
    - Occasionally, patients have few symptoms. In 51% of patients with MSA, syncope was reported at least once. In 18% of patients with severe hypotension, more than one syncopal episode was documented. Because of dysautonomia-mediated baroreflex impairment and consequent debuffering, patients respond in an exaggerated fashion to drugs that raise or lower blood pressure.
    - Patients also are susceptible to postprandial hypotension. Approximately 60% of patients with MSA suffer from orthostatic hypotension and supine hypertension. The supine hypertension is sometimes severe (190/110 mm Hg) and complicates the treatment of orthostatic hypotension in these patients.
    - Orthostatic hypotension must be distinguished from postural tachycardia syndrome, defined as an increase in heart rate of greater than 40 bpm and maintained blood pressure.
  - **Parkinsonism**
    - Parkinsonism can be the initial feature in 46% of patients and ultimately develops in 91% of patients.
    - Although akinesia and rigidity predominate, tremor is present at rest in 29% of patients; however, a classic pill-rolling parkinsonian rest tremor is recorded in only 8-9% of patients. Patients with MSA have a poor response to levodopa.
    - Some patients (28-29%) have a good or even excellent levodopa response early in their disease. However, only 13% maintained this response.
Patients with early onset (younger than 49 y) MSA tended to have a good levodopa response.

- Patients sometimes complain of stiffness, clumsiness, or a change in handwriting at the onset of MSA.

  - **Cerebellar dysfunction**
    - Cerebellar symptoms or signs were the only initial feature in 5% of patients.
    - MSA of the cerebellar type (MSA-C) most commonly presents with gait and limb ataxia. Tremor, pyramidal signs, and myoclonus are less common in the MSA-C type.

  - **Other symptoms based on mixed dysfunction**
    - When the disorder presents with nonautonomic features, imbalance caused by cerebellar or extrapyramidal abnormalities is the most common feature.
    - With involvement of cerebellar, extrapyramidal, and pyramidal systems, the movement disorder usually constitutes the most profound disability.
    - Vocal cord paralysis may lead to hoarseness and stridor.
    - A neurogenic and obstructive mixed form of sleep apnea can occur.

### Table 6. Differential Diagnosis in MSA and Parkinson Disease

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MSA</th>
<th>Parkinson Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response to chronic levodopa therapy</td>
<td>Poor or unsustained motor response because of loss of postsynaptic dopamine receptors</td>
<td>Good response</td>
</tr>
<tr>
<td>Effects on nigrostriatal transmission</td>
<td>Both presynaptic and postsynaptic; dopaminergic cell bodies in substantia nigra and their terminals in striatum and their striatal target cells have reduced dopamine receptors</td>
<td>Presynaptic</td>
</tr>
<tr>
<td>Symmetry of movement disorder</td>
<td>Asymmetric?</td>
<td>Asymmetry is characteristic</td>
</tr>
<tr>
<td>Progression of symptoms</td>
<td>Rapid</td>
<td>Slow</td>
</tr>
<tr>
<td>Instability and falling</td>
<td>Early</td>
<td>Late</td>
</tr>
<tr>
<td>Progress of disability</td>
<td>Disabled faster; 40% of patients in wheelchair within 5 years</td>
<td>Slower</td>
</tr>
<tr>
<td>Lewy bodies (hyaline eosinophilic cytoplasmic)</td>
<td>Not present*</td>
<td>Primarily in substantia nigra</td>
</tr>
</tbody>
</table>
neuronal inclusions) | Glial inclusions; argyrophilic cellular inclusions in oligodendrocytes | Absent

Cytoplasmic inclusions (immunocytochemical reaction with antibodies to anti-alpha-synuclein) | Cold hands and decrease of warm-up after coldpack stimulus | Normal

Thermoregulation, skin perfusion | Decreased in putamen and caudate | Decreased in putamen, but much smaller decrease in caudate

Caudate-putamen index of dopamine uptake (PET) | No release; dysfunction of hypothalamic-pituitary pathway (alpha2-adrenoceptor-hypothalamic deficit) | Increase of growth hormone; intact function

Pakiam et al reported that diffuse Lewy body disease may present with parkinsonism and prominent autonomic dysfunction, fulfilling proposed criteria for the striatonigral form of MSA.

Table 7. Differential Diagnosis in MSA and Pure Autonomic Failure

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MSA</th>
<th>Pure Autonomic Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS involvement</td>
<td>Multiple involvement</td>
<td>Unaffected</td>
</tr>
<tr>
<td>Site of lesion</td>
<td>Mainly preganglionic, central; degeneration of intermediolateral cell columns; ganglionic neurons relatively intact</td>
<td>Mainly postganglionic; loss of ganglionic neurons</td>
</tr>
<tr>
<td>Progression</td>
<td>Fast; median survival 6.5-9.5 y</td>
<td>Slow; some survive more than 10-15 y</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Poor</td>
<td>Good</td>
</tr>
<tr>
<td>Extrapyramidal involvement</td>
<td>Common</td>
<td>Not present</td>
</tr>
<tr>
<td>Cerebellar involvement</td>
<td>Common</td>
<td>Not present</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>Uncommon</td>
<td>Absent, except constipation</td>
</tr>
</tbody>
</table>
Plasma supine norepinephrine level | Normal | Reduced
---|---|---
Antidiuretic hormone (ADH) response to tilt | Impaired because of catecholaminergic denervation of hypothalamus (but normal ADH response to osmotic stimuli) | Maintained
Adrenocorticotropic hormone and beta-endorphin response to hypoglycemia | Impaired because of central cholinergic dysfunction or dysfunction of adrenergic input to paraventricular nucleus | Normal
Growth hormone release with clonidine IV injection | No release; dysfunction of hypothalamic-pituitary pathway (alpha2-adrenoceptor-hypothalamic deficit) | Increase of growth hormone; intact function
Substance P, catecholamine, 5-HT, and acetylcholine markers in cerebrospinal fluid | Decreased levels |  
Lewy bodies | Mostly absent | Present in autonomic neurons
BP response to oral water intake | Increased | Increased but variable
BP response to ganglionic blockade | Profound decrease | Modest decrease

**MSA and Parkinson disease**
- Parkinsonian symptoms can occur frequently in MSA. Approximately 10% of patients diagnosed in life as having Parkinson disease (PD) are found at autopsy to have MSA.
- Clinical differentiation of PD and MSA is extremely difficult. MSA is suggested when (1) disability progresses rapidly, (2) patients are poorly responsive to levodopa, (3) autonomic features such as urinary retention or incontinence or orthostatic hypotension are pronounced, and (4) rigidity and bradykinesia are out of proportion to tremor. Some distinctive features are outlined in Table 6.
- Wenning et al [64] developed a predictive model based on established pathologic data from patients with MSA and PD. The new model contains the following features: poor response to levodopa, autonomic features, speech
or bulbar dysfunction, absence of dementia, absence of levodopa-induced confusion, and falls.

- **MSA and pure autonomic failure**
  - Patients with MSA who present with only autonomic and urinary dysfunction can be diagnosed incorrectly as having pure autonomic failure (PAF).
  - Bradbury and Eggleston first described PAF as “idiopathic hypotension” in 1925, but today’s criteria imply autonomic nervous system failure in the absence of extrapyramidal, pyramidal, or cerebellar abnormalities. MSA is quite distinct from PAF.
  - The sympathetic and parasympathetic systems are impaired centrally in MSA, whereas the involvement is peripheral in PAF.
  - The progression of MSA is much faster than in PAF, and the prognosis is poor.
  - Lewy bodies are common in PAF at many sites, even occasionally in the heart, but they are not present in MSA. (Exception: In 1999, Pakiam et al demonstrated one case in which diffuse Lewy body disease presented with parkinsonism and prominent autonomic dysfunction, fulfilling proposed criteria for the striatonigral form of MSA.)
  - Instead of Lewy bodies, patients with MSA have oligodendroglial cytoplasmic inclusions.
  - A low plasma norepinephrine (NE) usually indicates PAF.
  - Vasopressor response to tilt also can assist in making the diagnosis.
  - A summary of distinctive features is presented in Table 7. Early in the disease’s process (ie, in the first 1-2 y) this distinction may be difficult, but it is usually evident during follow-up care.

- **MSA and progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome)**
  - Progressive supranuclear palsy (PSP), also known as the Steele-Richardson-Olszewski syndrome, is characterized by neuronal degeneration and neurofibrillary tangles affecting the pons and mid brain.
  - The clinical picture of PSP may be similar to that of MSA.
  - Analysis of the horizontal and vertical eye movements may help to distinguish between PSP and MSA.
    - Patients with PSP demonstrate slowing of saccades, which is not the situation in MSA.
    - The trajectories of saccades made to diagonal target jumps is deviated toward the horizontal plane; because of the vertical hypometria, this is more pronounced in patients with PSP than in those with MSA.
  - The patient with PSP may be prone to falls because of impaired downward gaze.
  - PSP subjects demonstrated different responses to pharmacologic and physiologic stimuli in autonomic function tests.
  - Cardiovascular autonomic dysfunction should be an exclusionary feature in the diagnosis of PSP.
• **MSA and corticobasal ganglionic degeneration**
  - Corticobasal ganglionic degeneration is characterized pathologically by enlarged achromatic neurons in cortical areas and nigral and striatal neuronal degeneration.
  - The onset typically is unilateral, with marked rigidity-dystonia on the involved arm, which differs from MSA.
  - Cortical signs of apraxia, alien limb phenomena, cortical sensory loss, and cortical reflex myoclonus are helpful to distinguish between corticobasal ganglionic degeneration and MSA.

• **MSA and cerebrovascular syndromes**
  - Cerebrovascular syndromes (eg, multi-infarct lesions in the brain) may demonstrate features similar to those of MSA.
  - Dementia is not common in MSA.
  - Brain imaging (MRI) helps to exclude cerebrovascular diseases.

**INVESTIGATIONAL STUDIES**

**Lab Studies:**

- The diagnosis of MSA is based mainly on clinical features (see Table 2, Table 3, Table 4). Definite MSA can be established only on postmortem examination. The following laboratory tests can assist in the diagnostic process:
  - Blood status - Normal supine NE level; low upright NE level
  - Response to levodopa - Poor or no response

**Imaging Studies:**

- **Iodine I 123 metaiodobenzylguanidine (MIBG) scintigraphy**
  - Scintigraphy with I 123 MIBG appears to be a useful tool for differentiation between PD and MSA early after onset of autonomic dysfunction.
  - Patients with PD have significantly lower cardiac uptake of I 123 MIBG than patients with MSA and controls.

- **Neuroimaging to exclude other conditions - Magnetic resonance imaging (MRI) and proton magnetic resonance**
  - Brain imaging may be normal in MSA. OPCA, cerebellar atrophy, and the putaminal lesion of striatonigral degeneration often are detected by MR techniques.
  - The slit hyperintensity of the lateral margin of the putamen in T2-weighted MRI is a characteristic finding in patients with MSA involving the extrapyramidal system.
  - MRI can help to exclude cerebrovascular diseases, such as multi-infarct syndromes.
  - Expected findings are as follows:
    - Atrophy of cerebellum and brain stem in OPCA and SND
    - No vascular damage
    - No multi-infarct pattern in brain
- No other lesions
- Hyperintensity in pons, peduncles, and cerebellum on T2-weighted and proton density sequences
- Slitlike hyperintensity on T2-weighted and proton density sequences

- **Positron emission tomography**
  - For differentiation between MSA and PD, fluoride F 18 fluordeoxyglucose dopa positron emission tomography (PET) imaging can be used.
  - The caudate-putamen index, which is calculated by a formula based on the difference in the uptakes in the caudate and putamen divided by the caudate uptake, is lower in patients with MSA than in patients with PD.
  - Expected findings are as follows:
    - Reduced putaminal F 18 fluordeoxyglucose
    - Reduced $[{11}C]$raclopride and $[{11}C]$diprenorphine
    - Reduced cerebellar glucose metabolism in OPCA

**NEUROIMAGING IN MULTISYSTEM ATROPHY**

- **Cerebral involvement in MSA**

Drug-unresponsive patients with Parkinsonian symptomatology are often classified as multiple system atrophies (MSA) or Parkinson's Plus disorders. There are three pathologic entities that are generally classified as part of the MSA grouping: (1) olivopontocerebellar atrophy (OPCA), (2) striatonigral degeneration (SND), and (3) Shy-Drager syndrome. Generalized cortical atrophy is often observed with SND, while generalized cerebellar atrophy often dominates in Shy-Drager syndrome and OPCA. Pontine atrophy is markedly prominent in OPCA so that the anterior pons has a wedge-shape. Because of the pontine and medullary atrophy, the ascending and descending white matter tracts within the brain stem can often be clearly delineated. Prominent signal hypointensity on T2-weighted images may be visualized in the putamen (and often caudate nucleus) in approximately 85% of individuals suffering from a MSA. In addition to exhibiting lower signal intensity on the T2-weighted images as compared to the globus pallidus, the putamen may also have an atrophic appearance. Pathologic confirmation of such changes has been obtained using the Perls' stain for ferric iron at postmortem examination. (See Figure 1)
Figure 3. Striatonigral degeneration (SND) versus Parkinson's disease (PD). A, SND (drug unresponsive) has hypointensity in the caudate and putamen equal to the globus pallidus; B, PD (drug responsive) exhibits the normal pattern of lower signal in the globus pallidus. C, Multiple system atrophy (striatonigral degeneration). Putaminal hypointensity extending to the globus pallidus and generalized atrophy on T2-weighted images.

Figure 4. MRI T2 images, left normal image, right patient with multisystem atrophy, notice the putaminal signal attenuation
Figure 5. Striatonigral degeneration (SND) versus Parkinson's disease (PD). A, SND (drug unresponsive) has hypointensity in the caudate and putamen equal to the globus pallidus; B, PD (drug responsive) exhibits the normal pattern of lower signal in the globus pallidus. C, Multiple system atrophy (striatonigral degeneration). Putaminal hypointensity and generalized atrophy on T2-weighted images.

The low-signal intensity abnormalities in the basal ganglia are most likely related to abnormal iron accumulation. The ferritin may be a primary manifestation of the Parkinsonian syndrome, causing dysfunction of the putamen, or is more likely a secondary effect of the chronic degenerative change in the putamen. Such changes are best seen using a high-field strength (1.5 Tesla or 3 Tesla) MR image system with T2-weighted spin-echo images (long TR, long TE). It is important to remember that when a high field system is used to obtain fast spin-echo images, there is less susceptibility effect; therefore, the signal hypointensity in both normal and abnormal structures is not clearly seen.

Figure 6. Multiple system atrophy (olivopontocerebellar atrophy). A, Cerebellar and brainstem atrophy on T1-weighted images; B, putaminal hypointensity on T2-weighted image.
Table 4. Differences between the idiopathic parkinson disease and multisystem atrophy

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>IDIOPATHIC PARKINSON DISEASE</th>
<th>PARKINSON</th>
<th>MULTISYSTEM ATROPHY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical picture</td>
<td>Unilateral or predominately unilateral tremors is the presenting clinical picture</td>
<td></td>
<td>Bilateral presentation, rapid progression, pyramidal, cerebellar, orthostatic hypotension, gaze palsy, dementia, or sphincter troubles are commonly the presenting clinical picture</td>
</tr>
<tr>
<td>Levodopa-responsiveness</td>
<td>Responsive in a sustained or a fluctuant pattern</td>
<td></td>
<td>Levodopa-resistant</td>
</tr>
<tr>
<td>The nigral pattern of involvement</td>
<td>Invariably present</td>
<td></td>
<td>Never present</td>
</tr>
<tr>
<td>Putaminal involvement without concomitant nigral involvement</td>
<td>Never present</td>
<td></td>
<td>Invariably present</td>
</tr>
<tr>
<td>Putaminal atrophy</td>
<td>Not a feature</td>
<td></td>
<td>Invariably present</td>
</tr>
<tr>
<td>Caudate nucleus involvement</td>
<td>Invariably absent</td>
<td></td>
<td>Present in 85% of cases</td>
</tr>
</tbody>
</table>

Brain stem imaging in MSA with olivopontocerebellar atrophy

Neuroimaging is not included in the consensus diagnostic criteria of MSA. Nevertheless, typical neurologic findings can assist in differentiating MSA from other causes of parkinsonism and cerebellar ataxia. The “hot-cross bun” sign observed in this case is characterized by cruciform signal hyperintensity on T2-weighted images in mid pons, which resembles a hot-cross bun, traditionally baked on the last Thursday before Easter. This finding is thought to correspond to the loss of pontine neurons and myelinated transverse cerebellar fibers with preservation of the corticospinal tracts. However, this sign is not specific to MSA and has been reported in other conditions such as spinocerebellar ataxia (SCA).

The more common typical radiological findings in MSA include atrophy of the cerebellum, most prominently in the vermis, middle cerebellar peduncles, pons, and lower brainstem. In addition to putaminal atrophy, a characteristic hypointense signal in T2 with hyperintense rim, corresponding to reactive gliosis and astrogliosis, can be observed in the external putamen, and is termed “slit-like void sign”. This combination of hypointense and hyperintense putaminal signal change is specific for MSA and its finding can be used to differentiate MSA from PSP and PD. Hypointensity alone without hyperintense rim is a sensitive radiological feature but nonspecific for MSA.
Figure 7. A hot cross bun, or cross-bun, is a type of sweet spiced bun made with currants or raisins and leavened with yeast. It has a cross marked on the top which might be effected in one of a variety of ways including: pastry, flour and water mixture, rice paper, icing, or intersecting cuts.

Figure 8. A case with multisystem atrophy. (A) Axial T2-weighted MR imaging demonstrates cruciform hyperintense signal changes in mid pons, the so-called “hot-cross bun sign” (B) Axial T2-weighted MR imaging demonstrates hypointensity in association with hyperintense rim in the external putamen, which is termed “slit-like void sign.”
Figure 9. A case with multisystem atrophy C (Olivopontocerebellar atrophy). (A) Axial T2-weighted MR imaging demonstrates cruciform hyperintense signal changes in mid pons, the so-called “hot-cross bun sign” . (B) MRI T2 image showing bilateral basal ganglionic hypointensity.
In addition to putaminal atrophy, a characteristic hypointense signal in T2 with hyperintense rim, corresponding to reactive gliosis and astrogliosis, can be observed in the external putamen, and is termed “slit-like void sign”. This combination of hypointense and hyperintense putaminal signal change is specific for MSA and its finding can be used to differentiate MSA from PSP and PD. Hypointensity alone without hyperintense rim is a sensitive radiological feature but nonspecific for MSA.

Other Tests:

- Autonomic function testing - Evaluation of the distribution and severity of parasympathetic and sympathetic function
  - Diminished respiratory sinus arrhythmia
  - Abnormal response to Valsalva maneuver (no BP recovery in late phase II and/or no overshoot in phase IV)
  - Diminished response to isometric exercise (handgrip)
  - Diminished response to cold pressor stimuli
- Sphincter electromyography (EMG) - Hyperreflexia of detrusor

Histologic Findings: Neuropathologic changes consist of a high density of Glial cytoplasmic inclusions (GCIs) in association with degenerative changes in some or all of the following structures (an overview of clinicopathological correlation is shown in Table 5):

- Putamen
- Caudate nucleus
- Globus pallidus
- Thalamus
- Subthalamic nucleus
- Substantia nigra
- Locus ceruleus
- Dorsal vagal nucleus

www.yassermetwally.com
- Vestibular nuclei
- Pontine nuclei
- Inferior olives
- Pontine nuclei
- Cerebellar Purkinje cells
- Autonomic nuclei of the brain stem
- Intermediolateral cell columns
- Anterior horn cells
- Onuf nuclei in the spinal cord and pyramidal tracts

Figure 11. A case with multisystem atrophy showing degenerative changes in Putamen, Caudate nucleus, Globus pallidus, Thalamus, Subthalamic nucleus, Substantia nigra, Locus ceruleus, Dorsal vagal nucleus, Vestibular nuclei, Pontine nuclei, Inferior olives, Pontine nuclei, Cerebellar Purkinje cells, Autonomic nuclei of the brain stem, Intermediolateral cell columns, Anterior horn cells, Onuf nuclei in the spinal cord and pyramidal tracts
Glial cytoplasmic inclusions

Glial cytoplasmic inclusions (GCIs) can be stained by Gallyas silver technique and are a hallmark of MSA. They are sickle-shaped to flame-shaped to ovoid, occasionally superficially resembling neurofibrillary tangles. Glial cytoplasmic inclusions (GCIs) are loosely aggregated filaments with cross-sectional diameters of 20-30 nm. These filaments often entrap cytoplasmic organelles (eg, mitochondria, secretory vesicles), have no limiting membrane, and are reported to have tubular profiles and electrondense granules along much of their lengths. Glial cytoplasmic inclusions (GCIs) are ubiquitin-positive, tau-positive, and alpha-synuclein-positive oligodendroglial inclusions. They are different from Lewy bodies and neurofibrillary structures in Alzheimer disease (Table 8).

Table 8. Differences Between GCIs in MSA and Other Pathologic Inclusions and Structures

<table>
<thead>
<tr>
<th>Shape</th>
<th>Glial Cytoplasmic Inclusions in MSA</th>
<th>Lewy Bodies in Parkinson Disease</th>
<th>Neurofibrillary Pathology in Alzheimer Disease</th>
<th>Gial Lesions in Corticobasal and Progressive Supranuclear Palsy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sickle-shaped to flame-shaped to ovoid, neurofibrillary tangles (shape varies)</td>
<td>Target-shaped inclusions</td>
<td>Tangles</td>
<td>Tufted astrocytes; coiled bodies</td>
</tr>
<tr>
<td>Membrane</td>
<td>No limiting membrane; tubular profiles and electrondense granules</td>
<td>Membrane exists</td>
<td>Membrane exists</td>
<td>Membrane exists</td>
</tr>
<tr>
<td>Ultrastructure</td>
<td>Loosely aggregated filaments</td>
<td></td>
<td></td>
<td>Astrocytic plaques</td>
</tr>
<tr>
<td>ICC*</td>
<td>Ubiquitin positive, Alpha-B-crystallin (synuclein) positive, Alpha-tubulin and beta-tubulin positive, Tau-protein positive</td>
<td>Hyaline eosinophilic cytoplasmic neuronal inclusions; ubiquitin</td>
<td></td>
<td>Absence from phosphorylated tau</td>
</tr>
<tr>
<td>Localization</td>
<td>In oligodendroglial cells and neurons</td>
<td>In neuronal cells and oligodendroglial cells</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Immunocytochemistry

Medical Care: The cause of MSA remains unknown, and no current therapy can reverse or halt progression of the disease. The extrapyramidal and cerebellar aspects of the disease are debilitating and difficult to treat, but the earliest symptom that brings patients to
medical attention usually is orthostatic hypotension. Orthostatic hypotension leads to curtailing of physical activity, with all the attendant problems of deconditioning that occur in consequence. Without an adequate upright blood pressure, keeping patients active and on an exercise regimen is extremely difficult; therefore, management of orthostatic hypotension is one of the major tasks in the treatment of patients with MSA.

- **Nonpharmacologic management in MSA**
  - Orthostatic hypotension: Mechanical maneuvers such as leg-crossing, squatting, abdominal compression, bending forward, and placing one foot on a chair can be effective to prevent episodes of orthostatic hypotension. A tight-waisted external support garment improves venous return and preload to the heart during standing but loses effectiveness if worn while the patient is supine. Increased salt and fluid intake and tilted sleeping with the head elevated increase the circulatory plasma volume.
  - Postprandial hypotension: Small and more frequent meals prevent blood pressure drop after eating. Intake of water half an hour before meals or drinking coffee can counteract postprandial hypotension.
  - Supine hypertension: Patients should not lie down during the day. Tilted sleeping with the head elevated is helpful to lower supine hypertension during the night, to decrease nocturia, and to prevent orthostatic hypotension in the morning.
  - Urinary incontinence: Intermittent self-catheterization or suprapubic or urethral catheterization can improve symptoms of urinary incontinence.
  - Constipation: A high-fiber diet, bulk laxative, lactulose, and suppositories can prevent constipation.
  - Stridor: Speech therapy often is useful to improve swallowing and communication.
  - Deconditioning: Physical therapy and an aquatic exercise program (hypotension does not occur while patients are in water) prevent physical deconditioning of the patient unless the movement disorder aspect of the illness so impairs balance that this is not advisable.

- **Pharmacologic management in MSA**: Please see Medication for a discussion of pharmacologic management.

**Surgical Care**: The following surgical care may be necessary:

- An atrial pacemaker rarely benefits patients but may be tried in patients with profound bradycardia to prevent orthostatic hypotension.
- Consider tracheostomy with the utmost care for intermittent respiratory stridor.
- Cricopharyngeal myotomy or gastrostomy has been employed in patients with severe dysphagia, but the value is uncertain.

**Consultations**: Physical therapy, occupational therapy, speech therapy, and social work are of considerable practical value.

**Diet**: An essentially normal diet is recommended, with the following guidelines:
• Increased salt and fluid intake maintains plasma volume.
• Frequent and small meals may help those for whom postprandial hypotension is a significant problem.
• High-fiber diet, bulk laxative, and suppositories prevent constipation.

**Activity:** Exercise of muscles of the lower extremities and abdomen, water aerobics at hip level (not swimming, as it causes polyuria), and postural training, in combination with drug therapy, are useful.

---

**MEDICATION**

Drug therapy is directed mainly toward alleviation of symptoms of the movement disorder and orthostatic hypotension. Medical therapy can be also applied for urinary incontinence, constipation, and erectile dysfunction.

**Medical therapy of movement disorder**

The movement disorder component of MSA usually is treated with levodopa, dopaminergic agonists, anticholinergic agents, or amantadine, but results are rarely as favorable in MSA as in classical PD.

**Drug Category:** *Antiparkinson agents* - Patients with MSA may have an initial response to levodopa. This response usually diminishes over time. Withdrawal of levodopa can cause the patient’s condition to deteriorate, but this is much more prominent in PD than in MSA. In modern practice, levodopa is administered in combination with a dopa decarboxylase inhibitor.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Levodopa/Carbidopa (Sinemet)- Combination of levodopa plus dopa decarboxylase inhibitor. If levodopa administered alone, is largely decarboxylated by intestinal mucosa or other peripheral sites that are rich in MAO, so that relatively little reaches cerebral circulation and CNS.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Dose</td>
<td>25/100 mg PO hs; increase at intervals of 3-7 days to total daily dose of 100 mg levodopa, or until adverse effects occur</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>Not established</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity; narrow-angle glaucoma; malignant melanoma; undiagnosed skin lesions</td>
</tr>
<tr>
<td>Interactions</td>
<td>Hydantoins, pyridoxine, phenothiazines, and hypotensive agents may decrease effects; antacids and MAOIs increase toxicity</td>
</tr>
</tbody>
</table>
Precautions

Certain adverse CNS effects (eg, dyskinesias) may occur at lower dosages and earlier in therapy with SR form; caution in patients with history of myocardial infarction, arrhythmias, asthma, or peptic ulcer disease; sudden discontinuation of levodopa may cause worsening of Parkinson disease; high-protein diets should be distributed throughout day to avoid fluctuations in levodopa absorption.

**Drug Category: Dopaminergic agonists** - These agents are an alternative to levodopa therapy in the late phase of the movement disorder. They act selectively on different subtypes of dopamine receptors throughout the brain. The mechanism is independent of the functional capacities of the nigrostriatal neurons and may be more effective.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Pergolide (Permax)- Believed to exert therapeutic effect by directly stimulating postsynaptic dopamine receptors in nigrostriatal system. Agonist of both D1 and D2 striatal dopamine receptors.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Dose</td>
<td>0.75-3 mg PO qd</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>Not established</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity</td>
</tr>
<tr>
<td>Interactions</td>
<td>Dopamine antagonists such as neuroleptics, phenothiazines, butyrophenones, thioxanthines, or metoclopramide may diminish effectiveness Because pergolide mesylate is more than 90% bound to plasma proteins, exercise caution if pergolide is coadministered with other drugs known to affect protein binding</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>C - Safety for use during pregnancy has not been established.</td>
</tr>
<tr>
<td>Precautions</td>
<td>Orthostatic hypotension may occur; may induce hallucinosis or confusion; may induce pleuropulmonary and retroperitoneal fibrosis, erythromyalgias, and digital vasospasm</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Bromocriptine (Parlodel)- Strong agonist of D2 and partial agonist of D1 striatal dopamine receptors.</td>
</tr>
</tbody>
</table>
**Drug Category:** Anticholinergic agents (Muscarinic receptor agonists) - These agents were used widely prior to the discovery of levodopa.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Trihexyphenidyl (Artane)- Anticholinergic receptor agent affecting structures in neostriatum.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Dose</td>
<td>2-4 mg PO tid</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>Not established</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity; glaucoma; peptic ulcers; pyloric or duodenal obstruction; stenosing prostatic hypertrophy or bladder neck obstructions; achalasia; toxic megacolon</td>
</tr>
<tr>
<td>Interactions</td>
<td>Amantadine may increase anticholinergic side effects that disappear when dose reduced; haloperidol may result in worsening of schizophrenic symptoms; may decrease haloperidol serum concentrations; may reduce pharmacologic/therapeutic actions of phenothiazines</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>C - Safety for use during pregnancy has not been established.</td>
</tr>
<tr>
<td>Precautions</td>
<td>Dose adjustment may be required in elderly patients; caution in patients with tachycardia, cardiac hypotension, prostatic hypertrophy, arrhythmias, hypertension, or any tendency toward urinary retention, liver or kidney disorders, or obstructive disease of GI or GU tract; if dry mouth severe and impairs swallowing or speaking, or if loss of appetite and weight, reduce dosage or discontinue medication temporarily</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Benztrapine mesylate (Cogentin)- Anticholinergic receptor agent affecting structures in neostriatum.</td>
</tr>
<tr>
<td>---------------------------</td>
<td>---------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Adult Dose</td>
<td>2-4 mg PO tid</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>Not established</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity; angle-closure glaucoma; stenosing peptic ulcers; prostatic hypertrophy; bladder neck obstructions; myasthenia gravis; pyloric or duodenal obstruction; achalasia (megaesophagus); megacolon</td>
</tr>
<tr>
<td>Interactions</td>
<td>Decreases effects of levodopa; increases effects of narcotic analgesics, phenothiazines, quinidine, TCAs, and anticholinergics</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>C - Safety for use during pregnancy has not been established.</td>
</tr>
<tr>
<td>Precautions</td>
<td>May exacerbate hypertension, tachycardia, cardiac arrhythmias, liver or kidney disorders, hypotension, prostatic hypertrophy, urinary retention, and obstructive disease of GI/GU tract; in extrapyramidal reactions resulting from phenothiazine treatment in psychiatric patients, toxic psychosis may occur</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Diphenhydramine hydrochloride (Benadryl)- Affects structures in neostriatum.</td>
</tr>
<tr>
<td>Adult Dose</td>
<td>25-50 mg PO tid/qid</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>Not established</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity; MAOIs</td>
</tr>
<tr>
<td>Interactions</td>
<td>Potentiates effect of CNS depressants; because of alcohol content, do not give syrup dosage form to patient taking medications that can cause disulfiramlike reactions</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>C - Safety for use during pregnancy has not been established.</td>
</tr>
<tr>
<td>Precautions</td>
<td>May exacerbate angle-closure glaucoma, hyperthyroidism, peptic ulcer, or urinary tract obstruction; xerostomia may occur</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Amantadine (Symmetrel)- Suggested mechanisms are alteration of dopamine release or reuptake and actions at glutamate receptors.</td>
</tr>
<tr>
<td>Adult Dose</td>
<td>100 mg PO bid</td>
</tr>
</tbody>
</table>
**Pediatric Dose**
Not established

**Contraindications**
Documented hypersensitivity

**Interactions**
Drugs with anticholinergic or CNS stimulant activity increase toxicity; hydrochlorothiazide plus triamterene may increase plasma concentrations

**Pregnancy**
C - Safety for use during pregnancy has not been established.

**Precautions**
Caution in liver disease, uncontrolled psychosis, eczematoid dermatitis, seizures, and those receiving CNS stimulant drugs; reduce dose in renal disease when treating Parkinson disease; do not discontinue this medication abruptly

---

**Drug Category: Urinary agents**
- When urinary incontinence is caused by detrusor hyperreflexia, peripherally acting anticholinergic agents such as oxybutynin chloride (Ditropan), tolterodine (Detrol), or propantheline (Pro-Banthine) can be applied.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Oxybutynin chloride (Ditropan)- Tertiary amine muscarinic receptor antagonist. Nonspecific relaxant on smooth muscles.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Dose</td>
<td>5-10 mg PO hs</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>Not established</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity; glaucoma; partial or complete GI obstruction; myasthenia gravis; ulcerative colitis; toxic megacolon</td>
</tr>
<tr>
<td>Interactions</td>
<td>CNS effects increase when administered concurrently with other CNS depressants</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>B - Usually safe but benefits must outweigh the risks.</td>
</tr>
<tr>
<td>Precautions</td>
<td>Caution in urinary tract obstruction, reflux esophagitis, and heart disease; may worsen constipation</td>
</tr>
</tbody>
</table>

| Drug Name | Tolterodine (Detrol)- Competitive muscarinic receptor antagonist for overactive bladder. However, differs from other anticholinergic types in that it has selectivity for urinary bladder over salivary glands. Exhibits high specificity for muscarinic receptors, has minimal activity or affinity for other neurotransmitter receptors and other potential targets, such as calcium channels. |

www.yassermetwally.com
### Drug Category: Gastroprokinetic agents

If a special bulk-forming diet fails, lactulose occasionally is helpful. Rarely, cisapride (Propulsid) may promote bowel movements.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Erythromycin (E.E.S., E-Mycin)- Macrolide antibiotic that duplicates action of motilin and is responsible for migrating motor complex activity, by binding to and activating motilin receptors. IV administration of this drug enhances emptying rate of both liquids and solids. Effect can be seen with oral erythromycin. Enteric-coated form may be tolerated better by patient.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Dose</td>
<td>250 mg PO 30 min ac initially</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Propantheline (Pro-banthine)- Blocks action of acetylcholine at postganglionic parasympathetic receptor sites.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Dose</td>
<td>15-30 mg PO hs</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>Not established</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity; ulcerative colitis; narrow-angle glaucoma; obstructive disease of GI or urinary tract</td>
</tr>
<tr>
<td>Interactions</td>
<td>Antacids decrease effects; disopyramide, tricyclic antidepressants, phenothiazines, corticosteroids, and bretylium increase toxicity</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>C - Safety for use during pregnancy has not been established.</td>
</tr>
<tr>
<td>Precautions</td>
<td>Caution in renal or hepatic disease; may worsen constipation</td>
</tr>
</tbody>
</table>
Drug Category: *Agents for erectile dysfunction* - MSA patients may respond to yohimbine with BP elevation; occasionally, male erectile dysfunction improves. Yohimbine (Yohimex, Yocon) should be given 5.6 mg 1-3 times daily. The effect of Viagra has not been determined in patients with autonomic failure. Other approaches include mechanical devices, pumps, penile prostheses, or implants.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Yohimbine (Yohimex)- Blockade of alpha2-receptors in pontomedullary region of CNS increases sympathetic outflow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Dose</td>
<td>2.7 -5.4 mg PO bid with breakfast and lunch</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>Not established</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity</td>
</tr>
<tr>
<td>Interactions</td>
<td>Increases toxicity of antidepressants</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>C - Safety for use during pregnancy has not been established.</td>
</tr>
<tr>
<td>Precautions</td>
<td>Adverse effects include anxiety, tremor, palpitation, diarrhea, supine hypertension; not for use in cardio-renal patients</td>
</tr>
</tbody>
</table>

Drug Category: *Medical therapy of hypotension* - Many agents have been advocated for the management of orthostatic hypotension. Some of the more widely used approaches are shown in Table 9. However, drug therapy of orthostatic hypotension is limited by supine hypertension, which is found in about 60% of patients with MSA.
Table 9. Drugs for Orthostatic Hypotension in MSA

<table>
<thead>
<tr>
<th>Group</th>
<th>Drug</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fludrocortisone</td>
<td>Mineralocorticoid Sodium retention, primarily in extravascular compartment, causes tissue edema to venous capacitance bed in lower extremity. In presence of this edema, venous bed accommodates lesser volume of blood on assumption of upright posture (high doses, late effect). Increase of sensitivity to NE (already during small doses)</td>
</tr>
<tr>
<td></td>
<td>Florinef</td>
<td>Alpha1-adrenoreceptor agonist acts directly on vasculature Causes venous and arteriolar vasoconstriction</td>
</tr>
<tr>
<td></td>
<td>Midodrine</td>
<td>Increases sensitivity to pressor effects of angiotensin II Increases plasma endothelin level, enhances renal tubular reabsorption Increases cytosolic free calcium in vascular smooth muscle Increases intravascular volume</td>
</tr>
<tr>
<td></td>
<td>Phenylpropanolamine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ephedrine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dihydroxyphenylserine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epoetin alfa</td>
<td>Increases sensitivity to pressor effects of angiotensin II Increases plasma endothelin level, enhances renal tubular reabsorption Increases cytosolic free calcium in vascular smooth muscle Increases intravascular volume</td>
</tr>
<tr>
<td></td>
<td>Indomethacin</td>
<td>Inhibition of vasodilator prostaglandins has been proposed but not proven</td>
</tr>
<tr>
<td></td>
<td>Ibuprofen</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diphenhydramine</td>
<td>Reduce vasodilatation caused by histamine release</td>
</tr>
<tr>
<td></td>
<td>Cimetidine</td>
<td>Reduce splanchnic capacitance</td>
</tr>
<tr>
<td></td>
<td>Somatostatin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Octreotide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Desmopressin (DDAVP)</td>
<td>Vasopressin analogues No effect on V1 receptors, which are responsible for vasopressin-induced vasoconstriction Acts on V2 receptors on renal tubuli, which are responsible for antidiuretic effect Prevents nocturnal diuresis, raises BP in morning</td>
</tr>
<tr>
<td></td>
<td>Yohimbine</td>
<td>Alpha2-adrenoreceptor antagonist, sympathomimetic</td>
</tr>
<tr>
<td></td>
<td>Caffeine</td>
<td>Adenosine receptor antagonist, sympathomimetic</td>
</tr>
</tbody>
</table>

**Fludrocortisone:** The mainstay of therapy for the past 40 years has been fludrocortisone. Fludrocortisone is a powerful mineralocorticoid largely devoid of glucocorticoid effect when administered in low to moderate doses. With institution of fludrocortisone, blood volume is raised initially, although it tends to return toward normal after the first week of therapy. Most patients continuing to take fludrocortisone will experience weight gain, usually 5-8 pounds, associated with mild ankle edema. The weight gain comes on gradually.
over a period of 2 weeks and is due to sodium retention, primarily in the extravascular compartment. Surprisingly, much of the value of fludrocortisone is dependent upon the support provided by tissue edema to the venous capacitance bed in the lower extremities. In the presence of this edema, the venous bed accommodates a lesser volume of blood on assumption of the upright posture. This in turn improves blood return to the heart and therefore the patient's functional capacity. In addition to this direct effect of extravascular fluid accumulation, increases of about 50% in alpha1-adrenoreceptor sensitivity elicited by the mineralocorticoid are documented. During fludrocortisone therapy, the renin-angiotensin system is suppressed, as might be expected.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Fludrocortisone (Florinef acetate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brief Discussion</td>
<td>Mineralocorticoid</td>
</tr>
<tr>
<td></td>
<td>Sodium retention primarily in extravascular compartment causes tissue edema to venous capacitance bed in lower extremities. In presence of this edema, venous bed accommodates lesser volume of blood on assumption of upright posture (ie, high doses, late effect). Increase of sensitivity to norepinephrine (already during small doses)</td>
</tr>
<tr>
<td>Adult Dose</td>
<td>2.5 mg PO tid, increasing to 10 mg tid</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Supine hypertension (ie, systolic BP 200 mm Hg)</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>Hypokalemia, hypomagnesemia, gain of weight, supine hypertension</td>
</tr>
</tbody>
</table>

**Limitations of fludrocortisone:** The disadvantages of fludrocortisone include the potential for hypokalemia, hypomagnesemia, and excessive fluid accumulation with excessive BP elevation in the supine posture. Unfortunately, most patients with MSA have supine hypertension, even when receiving no therapy, and this limits the degree to which upright BP can be increased with fludrocortisone. Supine hypertension is believed to probably increase the risk of hemorrhage in MSA, but reliable studies on this question are lacking.

**Midodrine and short-acting sympathomimetics:** Midodrine, a prodrug with alpha1-adrenoreceptor agonist activity, also is used widely to treat orthostatic hypotension in MSA. Midodrine acts directly on the vasculature to elicit increased BP and avoids the electrolyte abnormalities associated with fludrocortisone. However, supine hypertension remains a significant problem and limits the degree to which the functional capacity of the patient with MSA may be enhanced. A variety of other sympathomimetic amines, such as phenylpropanolamine, ephedrine, and dihydroxy-phenylserine, also have been employed in MSA and share with midodrine the possible complication of excessive supine hypertension. The advantage of these short-acting pressor agents is that they can be given during the day while asking the patient not to lie down for the next 3-4 h. A late afternoon dose should be avoided if possible.
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Midodrine (Pro-Amatine)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brief Discussion</strong></td>
<td>Alpha1-adrenoreceptor agonist acts directly on vasculature Causes venous and arteriolar vasoconstriction</td>
</tr>
<tr>
<td><strong>Adult Dose</strong></td>
<td>10 mg PO tid</td>
</tr>
<tr>
<td><strong>Contraindication</strong></td>
<td>Supine hypertension (ie, systolic BP 200 mm Hg)</td>
</tr>
<tr>
<td><strong>Adverse Effects</strong></td>
<td>Scalp pruritus, tachyphylaxis, increased urinary sodium loss</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Phenylpropanolamine (Propagest)</td>
</tr>
<tr>
<td><strong>Brief Discussion</strong></td>
<td>Sympathomimetic Acts directly to release noradrenaline</td>
</tr>
<tr>
<td><strong>Adult Dose</strong></td>
<td>12.5-25 mg PO bid with 12 oz of water</td>
</tr>
<tr>
<td><strong>Adverse Effects</strong></td>
<td>Reduced appetite, nervousness, tachycardia, supine hypertension, tachyphylaxis</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Ephedrine (Ephedrine sulfate)</td>
</tr>
<tr>
<td><strong>Brief Discussion</strong></td>
<td>Sympathomimetic Alpha- and beta-adrenergic agonist; peripheral vasoconstrictor</td>
</tr>
<tr>
<td><strong>Adult Dose</strong></td>
<td>Starting: 25 mg PO tid</td>
</tr>
<tr>
<td><strong>Contraindication</strong></td>
<td>Sitting hypertension (systolic BP 200 mm Hg)</td>
</tr>
<tr>
<td><strong>Adverse Effects</strong></td>
<td>Nervousness, tachycardia, supine hypertension, tachyphylaxis</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Dihydroxyphenylserine (L-DOPS)</td>
</tr>
<tr>
<td><strong>Brief Discussion</strong></td>
<td>Sympathomimetic Direct synthesis of NE from this drug in absence of dopamine beta-hydroxylase</td>
</tr>
<tr>
<td><strong>Adult Dose</strong></td>
<td>250-500 mg PO bid</td>
</tr>
<tr>
<td><strong>Precautions</strong></td>
<td>Dopamine beta-hydroxylase deficiency</td>
</tr>
</tbody>
</table>

**Recombinant erythropoietin:** Recently, recombinant erythropoietin has been shown to increase the functional capacity of patients with MSA, particularly those who have the characteristic mild anemia associated with this disease. Up to 38% of patients with severe autonomic failure are anemic. Lack of sympathetic stimulation may lead to a decrease of erythropoietin production and development of anemia. Sympathetic impairment and low plasma norepinephrine levels have been found to correlate with severity of anemia. Therapy with recombinant erythropoietin, even low doses (25-50 units/kg body weight SC three times a week) has successfully corrected anemia and improved upright BP.
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Erythropoietin (Epoetin alfa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brief Discussion</td>
<td>Recombinant erythropoietin</td>
</tr>
<tr>
<td></td>
<td>Increases sensitivity to pressor effects of angiotensin II</td>
</tr>
<tr>
<td></td>
<td>Increases plasma endothelin level</td>
</tr>
<tr>
<td></td>
<td>Enhances renal tubular reabsorption</td>
</tr>
<tr>
<td></td>
<td>Increases cytosolic free calcium in vascular smooth muscle, and increases intravascular volume</td>
</tr>
<tr>
<td>Adult Dose</td>
<td>25-50 units/kg body wt SC 3 times a week</td>
</tr>
<tr>
<td>Side Effects</td>
<td>Supine hypertension</td>
</tr>
<tr>
<td>Precautions</td>
<td>Iron supplementation often needed</td>
</tr>
</tbody>
</table>

**Other agents:** Other classes of drugs now less often employed include nonsteroidal anti-inflammatory agents, antihistamines, somatostatin analogues, caffeine, and yohimbine.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Indomethacin (Indocin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brief Discussion</td>
<td>Nonsteroidal anti-inflammatory</td>
</tr>
<tr>
<td></td>
<td>Inhibitor of vasodilator prostaglandin synthesis</td>
</tr>
<tr>
<td>Adult Dose</td>
<td>25 mg PO tid with meals; increasing to 50 mg tid</td>
</tr>
<tr>
<td>Contraindication</td>
<td>Sitting hypertension (ie, systolic BP 200 mm Hg)</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>Nausea, vomiting, gastric irritation, constipation, rash</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Diphenhydramine (Benadryl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brief Discussion</td>
<td>Antihistamine</td>
</tr>
<tr>
<td></td>
<td>First-generation H1-receptor antagonist with anticholinergic effects</td>
</tr>
<tr>
<td>Adult Dose</td>
<td>25-50 mg PO q4h</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>Sedation, dizziness, tinnitus, lassitude, incoordination, fatigue, blurred vision, diplopia, euphoria, nervousness, insomnia, tremors</td>
</tr>
<tr>
<td></td>
<td>Loss of appetite, nausea, vomiting, epigastric distress, constipation, diarrhea</td>
</tr>
<tr>
<td></td>
<td>Dryness of mouth and respiratory passages, urinary retention, dysuria</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Desmopressin acetate (DDAVP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brief Discussion</td>
<td>Vasopressin analogue</td>
</tr>
<tr>
<td>Adult Dose</td>
<td>2-4 mcg IM given at 8:00 pm as single dose</td>
</tr>
<tr>
<td>Interactions</td>
<td>Hyponatremia</td>
</tr>
<tr>
<td>Precautions</td>
<td>Monitor osmolality and plasma sodium levels on a 6-wk basis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Octreotide (Sandostatin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brief Discussion</td>
<td>Somatostatin analogue</td>
</tr>
<tr>
<td></td>
<td>Inhibits growth hormone release</td>
</tr>
<tr>
<td>Adult Dose</td>
<td>Dosage must be individualized but may be initiated 50 mg bid/tid; increase in 100 mg increments up to 1500 mg/d until desired effect achieved</td>
</tr>
</tbody>
</table>
### Adverse Effects

<table>
<thead>
<tr>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suppression of GI motility, secretion including loose stools. Malabsorption, nausea, flatulence</td>
</tr>
</tbody>
</table>

#### Yohimbine:

Alpha2-receptors have an important role in regulation of the activity of the sympathetic nervous system, both peripherally and centrally. Activation of presynaptic alpha2-receptors inhibit NE from peripheral nerve endings. Activation of alpha2-receptors in the pontomedullary region of the CNS inhibits sympathetic nervous system activity and leads to a fall in BP.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Yohimbine (Yohimex)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brief Discussion</td>
<td>Blockade of alpha2-receptors in pontomedullary region of CNS Increases sympathetic outflow</td>
</tr>
<tr>
<td>Adult Dose</td>
<td>2.7-5.4 mg PO bid with breakfast and lunch</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>Anxiety, tremor, palpitation, diarrhea, supine hypertension</td>
</tr>
</tbody>
</table>

#### Other problems to consider

**Supine hypertension:** With all drugs discussed above, the presence of the characteristic supine hypertension in MSA represents a formidable obstacle. The fact that the supine hypertension is usually present even before pharmacologic intervention has been a paradox. In the presence of true autonomic failure, BP might be expected to be low in the supine posture rather than high. Yet in patients with autonomic failure, a 20% elevation in peripheral vascular resistance in the supine posture has been documented. The mechanisms responsible for this increased vascular resistance remain unknown. Since plasma renin activity is also low and is usually unresponsive to a variety of stimuli in patients with autonomic failure, that this hormonal system is playing a role in the raised resistance seems unlikely.

Because autonomic failure is present, the mechanisms causing supine hypertension have been assumed to be independent of sympathetic function. Residual autonomic function, however, may be present even in severe autonomic failure. For example, yohimbine, which increases sympathetic tone, has been found to elicit a pressor response in almost all patients with severe autonomic failure. The hypothesis that residual autonomic function might contribute significantly to supine hypertension in patients with autonomic impairment due to either peripheral (pure autonomic failure) or central (MSA) autonomic dysfunction was tested successfully by blocking residual sympathetic traffic (and parasympathetic traffic) with the NN-nicotinic antagonist trimethaphan.

**Medical/Legal Pitfalls:**

MSA is a difficult diagnosis (especially early in the clinical course) and commonly is misdiagnosed by the initial physician caregivers. The most common initial diagnosis is idiopathic Parkinson disease. As the disease progresses, the risk of falls increases. Proper gait instruction and precautions are critical in the prevention of falls and resultant injury.
Incidence of medication-related adverse effects is increased, especially as the number of medications and the dosage of individual medications increase.

References


The brain is a seemingly nonsegmented organ that is, however, formed in a segmented fashion by the overlap of genes that define anatomic and probably functional components of the brain. Other genes and their encoded proteins regulate the processes of cell proliferation and migration; many of these genes have been identified based upon discoveries of human and mouse disease-causing genes.

Human brain developmental disorders represent clinical challenges for the diagnosing clinician as well as for the treating physician. Some disorders represent well-defined
clinical and genetic entities for which there are specific tests; others have ill-defined genetic causes, while others can have both genetic and destructive causes. In most cases the recognition of a disorder of brain development portends certain developmental disabilities and often seizure disorders that can be very difficult to treat. In addition, it now bears upon the treating physician to recognize the genetic causes, and to properly advise patients and their families of the risks of recurrence or refer them to the proper specialist who can do so. The genetics of some of these disorders are not all well defined at present, and the recognition of some disorders is variable; what is known is presented herein.

The genetics and signaling utilized in brain development is briefly reviewed to provide the framework for the understanding of human brain developmental disorders. The well-defined genetic disorders of brain development are discussed, and a brief suggested algorithm for evaluation and for counseling of patients is provided.

**BRAIN DEVELOPMENT**

- **Overview**

General mechanisms tend to recur in all phases of brain development, and these include induction, cell proliferation, cell fate determination (differentiation), cell process formation and targeting (synapse formation), and cell movement (migration). Induction is the process by which one group of cells or tissue determines the fate of another by the release of soluble factors or inducers. Cell fate or differentiation is dependent upon this process of induction, and probably can best be understood as the initiation of a genetic program by the recognition of an inducing molecule and/or expression of a transcriptional regulator. In general, it is rare that a cell in the nervous system is born and differentiates in the same location that it finally resides. Rather, cells migrate over long distances to reach their final locations. Similarly, cells in the nervous system must extend processes over long distances to reach their synaptic targets.

- **Neural tube formation**

The human brain is formed from the neuroectoderm, a placode of cells that are induced to differentiate from the surrounding ectoderm by the presence of the notochord at about 18 days gestation. Candidate inducing factors include the retinoids, follistatin, and Noggin [1-4]. The neuroectoderm develops folds in the lateral aspects that begin to approximate in the region of the future medulla and fuse at 22 days gestation. This closure is known as neurulation, and results in the formation of a tube termed the neural tube [5]. The anterior neural tube closes by about 24 days gestation and serves as the foundation for further brain development; the posterior neural tube closes by about 26 days gestation and serves as the foundation for further spinal cord development. Defects in the closure of the neural tube lead to encephaloceles or myelomeningocele.
• **Nervous system segmentation**

At the rostral end of the newly closed neural tube flexures delineate the primary vesicles, which are designated as the hindbrain (rhombencephalon), mesencephalon, and forebrain (prosencephalon). The primary vesicles can be further subdivided into secondary vesicles that will form adult brain structures. The hindbrain can be divided into the metencephalon and myelencephalon, which will become the pons, cerebellum, and medulla oblongata of the adult. The mesencephalon will be the midbrain, and the prosencephalon divides into the telencephalon (two telencephalic vesicles) and diencephalon. The telencephalic vesicles will become the cerebral hemispheres; the diencephalon will become the thalamus and hypothalamus.

Regional specification of the developing telencephalon is an important step in brain development, and is likely under control of a number of genes that encode transcription regulators. In the fruit fly, Drosophila, these genes are involved in segmentation of this animal and define structures such as hair-like spiracles. Not surprisingly, the role of these genes in human brain development differs, yet it appears that the general role of these proteins is that of regional specification of clones of cells destined to form specific brain structures. Homeobox and other transcription genes encode some of these transcriptional regulators and these "turn on" genes by binding to specific DNA sequences, and in so doing initiate genetic programs that lead to cell and tissue differentiation. EMX2, a transcriptional regulator, has a homolog in Drosophila that defines the hair spiracles and has been implicated in human brain malformations.

**DISORDERS OF SEGMENTATION**

• **Schizencephaly**

Schizencephaly (cleft in brain) has been regarded by many as a migration abnormality; however, it is best understood as a disorder of segmentation because one of the genes that is abnormal in the more severe and familial forms is EMX2 [6,7]. Thus, this developmental disorder, at least in the more severe cases, appears to be the result of failure of regional specification of a clone of cells that are destined to be part of the cortex.

Clinically, these patients vary depending upon the size of the defect and upon whether bilateral disease is present [8]. The clefts extend from the pia to the ventricle and are lined with a polymicrogyric gray matter [9]. The pia and ependyma are usually in apposition, especially in severe cases. The defect is termed open-lipped if the cleft walls are separated by cerebrospinal fluid, and closed-lipped if the walls are in contact with one another. Bilateral schizencephaly is associated with mental retardation and spastic cerebral palsy; affected patients often are microcephalic. Seizures almost always accompany severe lesions, especially the open-lipped and bilateral schizencephalies. The exact frequency of seizures in patients with the less severe lesions is uncertain. Most patients in whom schizencephaly is diagnosed undergo neuroimaging because of seizures. Therefore, a bias in favor of a universal occurrence of seizures in this disorder is noted. Hence, patients with
schizencephaly who do not have epilepsy might exist, but the malformation remains undetected because no imaging is performed.

Figure 1. Closed-lip schizencephaly. Sagittal T1-weighted MRI shows gray matter (arrows) extending from cortex to a dimple in the surface of the left lateral ventricle. The lips of the schizencephaly are in apposition, making this a "closed-lip" schizencephaly.

Figure 2. Bilateral open-lip schizencephaly. A,B: Axial T2-weighted images show open-lip schizencephalies in both hemispheres. Both images show vessels in the gray matter-lined clefts and large vessels (arrows) run at the outer surface of the right hemispheric cleft. This does not represent a vascular malformation.

Seizure type and onset may also vary in this disorder. Patients may experience focal or generalized seizures, and some will present with infantile spasms. The onset varies from infancy to the early adult years. Seizures may be easily controlled or may be recalcitrant to standard anticonvulsant therapy.
Figure 3a. MRI T1 (A,B) and CT scan (D) showing open-lip schizencephaly with pachygyria. Notice the associated encephalocele that is sometimes associated with cortical dysplasias.

Figure 3b. Open-lip schizencephaly with cortical dysplasia.

Improvements in neuroimaging have enhanced the recognition of schizencephalic lesions [9-13]. The lesions may occur in isolation or may be associated with other anomalies of brain development such as septo-optic dysplasia [14].

Disorders of segmentation likely represent a heterogeneous set of abnormalities of varying etiologies. One theory holds that an early (first-trimester) destructive event disturbs
subsequent formation of the cortex. Another theory is that segmental failure occurs in the formation of a portion of the germinal matrix or in the migration of primitive neuroblasts. Certainly, the finding of mutations of the EMX2 gene in some patients with the open-lipped form of schizencephaly supports the latter hypothesis.

- **Prosencephalon cleavage**

At about 42 days of gestation, the prosencephalon undergoes a division into two telencephalic vesicles that are destined to become the cerebral hemispheres. The anterior portion of this cleavage is induced by midline facial structures and the presence of the notochord. Abnormalities of this process are thought to result in holoprosencephaly, septo-optic dysplasia, and agenesis of the corpus callosum [I 5]. One of the important molecules responsible for the induction of this cleavage is Sonic hedgehog [16]. This protein is produced by the notochord, ventral forebrain, and the floor plate of the neural tube [17]. It interacts through at least one receptor, PTCH-A human homolog of patched, and alters the expression of transcription factors [18,19]. Furthermore, in an interesting link between these ventral inductive events and segmentation, Sonic hedgehog can alter the expression of the transcriptional regulating genes when applied to proliferating cells at critical times in development [21]. This ties the inductive proteins to the expression of transcriptional regulating genes and gives a hint as to the mechanisms involved in inductive processes.

![Figure 4a. Agenesis of the corpus callosum](image)

Other molecules of interest in this inductive process are the retinoids, which are lipids capable of crossing membranes and that have been shown to exist in posterior to anterior
gradients across embryos [3,20]. Retinoic acid can alter the pattern of transcriptional factors in neuroepithelial cells [3] and can downregulate Sonic hedgehog, perhaps explaining some of the head defects seen in retinoid embryopathy [17,22].

Agenesis of the corpus callosum

<table>
<thead>
<tr>
<th>Etiology</th>
<th>• Both genetic and sporadic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenesis</td>
<td>• Unknown,</td>
</tr>
<tr>
<td>Epidemiology</td>
<td>• Agenesis of the corpus callosum may be part of an extensive malformation complex or the callosum may be partially or completely absent or hypoplastic in an otherwise normal brain.</td>
</tr>
<tr>
<td></td>
<td>• The malformation is relatively rare.</td>
</tr>
<tr>
<td>General Gross Description</td>
<td>• The brain in agenesis of the corpus callosum shows batwing shaped ventricles as well as loss of the corpus callosum and there is no cingulate gyrus.</td>
</tr>
<tr>
<td></td>
<td>• The remainder of the abnormalities depend on what syndrome or other malformations are associated with the defect. In most cases there is a bundle of white matter processes on both cerebral hemispheres in the area where the corpus callosum should be, called the bundle of Probst. In some patients there is a lipoma or other tumor in the area where the corpus callosum should be.</td>
</tr>
<tr>
<td>General Microscopic Description</td>
<td>• None</td>
</tr>
<tr>
<td>Clinical Correlation</td>
<td>• Patients with agenesis of the corpus callosum may be normal or may have neurological abnormalities dependent on the other accompanying malformations.</td>
</tr>
</tbody>
</table>
Holoprosencephaly is a heterogeneous disorder of prosencephalic vesicle cleavage that results from a failure of the prosencephalic vesicle to cleave normally. Three forms of this disorder have been described: alobar, semilobar, and lobar [23,24]. In the alobar form, the telencephalic vesicle completely fails to divide, producing a single horseshoe-shaped ventricle, sometimes with a dorsal cyst, fused thalami, and a malformed cortex. In the semilobar form, the interhemispheric fissure is present posteriorly, but the frontal and, sometimes, parietal lobes, continue across the midline [25]; in some cases just ventral fusion is noted. In the lobar form, only minor changes may be seen: the anterior falx and the septum pellucidum usually are absent, the frontal lobes and horns are hypoplastic, and the genu of the corpus callosum may be abnormal.
Figure 5. This is holoprosencephaly in which there is a single large ventricle with fusion of midline structures, including thalami. The affected fetuses and neonates typically have severe facial defects, such as cyclopia, as well. Underlying chromosomal abnormalities, such as trisomy 13, or maternal diabetes mellitus are possible causes, but some cases are sporadic.

Holoprosencephaly is associated with a spectrum of midline facial defects. These include cyclopia, a supraorbital proboscis, ethmocephali, in which the nose is replaced by a proboscis located above hypoteloric eyes; cebcephaly, in which hypotelorism and a nose with a single nostril are seen; and premaxillary agenesis, with hypotelorism, a flat nose, and a midline cleft lip [26].
Figure 6. (left three images) A,B semilobar holoprosencephaly from the same patient, C a patient with lobar holoprosencephaly. Arrowhead in A points to lack of ventral interhemispheric cleavage. Arrowhead in B points to fused thalami. The septum pellucidum is absent in B. In C notice the horseshoe or mushroom shaped single ventricle designated by *, arrowhead in C points to lack of interhemispheric fissure. (right image) MRI - Holoprosencephaly: This 6-day-old girl presented with laryngeal malacia and a diminished level of arousal. This proton density axial MR image shows an absence of the anterior horns of the lateral ventricles, fused thalami and absence of the corpus callosum anteriorly.

Only children who have the lobar and semilobar forms are known to survive for more than a few months. An infant affected with the severe form is microcephalic, hypotonic, and visually inattentive [25]. In infants with the less severe forms of holoprosencephaly, myoclonic seizures frequently develop and, if the infant survives, autonomic dysfunction, failure to thrive, psychomotor retardation, and atonic or spastic cerebral palsy often are present. Some infants with the lobar form may be only mildly affected and, for example, present as a relatively mild spastic diplegia. Pituitary defects may be associated with these malformations, and may result in neuroendocrine dysfunction [27]. One, therefore, has to wonder how much genetic overlap exists between this condition and septo-optic dysplasia to be described below.

Holoprosencephaly has been associated with maternal diabetes [28], retinoic acid exposure, cytomegalovirus, and rubella [29]. Chromosome abnormalities associated with this disorder include trisomies 13 and 18; duplications of 3p, 13q, and 18q; and deletions in 2p, 7q, 13q, and 18q [30]. Of particular concern to the clinician is the existence of an autosomal
dominant form in which mutations in Sonic Hedgehog lead to variable expression of holoprosencephaly. In the mildest form of this genetic disorder, patients may have a single central incisor, a choroid fissure coloboma, or simply attention deficit disorder; a parent of a child with holoprosencephaly manifesting these features should be considered to be at high risk for recurrence of holoprosencephaly in their children (up to 50% risk) [31,32]. A number of other genes (HPE] (21 q22.3), HPE2 (2p2 1), HPE3 (7q36), HPE4 (18p), ZIC2, SIX3 (2p2l), and PATCHED) have been associated with holoprosencephaly, and although potentially inherited in an autosomal recessive fashion, most occurrence seems to be random [33,34].

- **Septo-optic dysplasia**

Septo-optic dysplasia (de Morsier syndrome) is a disorder characterized by the absence of the septum pellucidum, optic nerve hypoplasia, and hypothalamic dysfunction. It may be associated with agenesis of the corpus callosum. This disorder should be considered in any patient who exhibits at least two of the above abnormalities and perhaps even solely hypothalamic dysfunction [35]. Septo-optic dysplasia also appears to involve prosencephalic cleavage and development of anterior telencephalic structures [36]. About 50% of patients with septo-optic dysplasia have [schizencephaly](#) [14].

![Figure 7. Septo-optic dysplasia associated with schizencephaly. Arrows in A,B point to absent septum pellucidum, arrow in C, and black arrowhead in D point to open lip schizencephaly, white arrow head point to polymicrogyria in D](image)

Patients may present with visual disturbance, seizures, mental retardation, hemiparesis (especially if associated with [schizencephaly](#)), quadriplegia, or hypothalamic dysfunction. Endocrine abnormalities may include growth hormone, thyroid hormone, or antidiuretic hormone function or levels. The consideration of septo-optic dysplasia necessitates an evaluation of the hypothalamic-pituitary axis because as many as 60% of the children with this disorder might exhibit evidence of a disturbance of endocrine function [37].
evaluation can include thyroid function studies and electrolytes; these patients are at high risk for growth retardation.

The recent identification of patients with this condition that harbor mutations in the transcriptional regulator gene HESX1, suggest that the mechanism of this disorder is likely genetic and a patterning or segmental abnormality [38]. Even though the genetic abnormality has been identified for a minority of patients, there exists the possibility that this may not represent an entirely genetic disorder because associations have been made with young maternal age, diabetes, the use of anticonvulsants, phencyclidine, cocaine, and alcohol [39],

**DISORDERS OF CELL PROLIFERATION**

- Normal cell proliferation

Following telencephalic cleavage, a layer of proliferative pseudostratified neuroepithelium lines the ventricles of the telencephalic vesicles. These cells will give rise to the neurons and glia of the mature brain. The generation of the proper complement of cells is a highly ordered process that results in the generation of billions of neurons and glia. Neuroepithelial processes extend from the ventricular surface to the pial surface, and the nuclei of the primitive neuroepithelial cells move from the cortical surface in a premitotic phase to a mitotic phase near the ventricle. Cells divide at the most ventricular aspects of the developing telencephalon, and after division move back toward the pial surface. The pial processes of neuroepithelial cells near the ventricle often will detach from the cortical surface before a new cycle begins.

Neuroepithelial cells divide in so-called proliferative units such that each unit will undergo a specific number of divisions resulting in the appropriate number of cells for the future cortex. Abnormalities in the number of proliferative units or in the total number of divisions can lead to disorders of the brain manifested by abnormal brain size and, therefore, an unusually small or large head circumference. Two such disorders resulting in small head size -radial microbrain and microcephaly vera- are believed to result from abnormalities of this phase of neurodevelopment [40]. Disorders in which too many cells are generated in the proliferative phase result in megalencephaly (large brain) or, if proliferative events go awry on only one side of the developing cortex, hemimegalencephaly.

The genes and molecules involved in regulating the proliferative cycles in human brain formation are likely similar to those involved in other species. This cell cycle in the brain can be divided into a number of distinct phases: mitosis (M), first gap (G1), deoxyribonucleic acid synthesis (S), and second gap (G2) [41]. These phases appear to be regulated by key molecules to check the advancement of proliferation. Some cells enter a resting state (GO) that they maintain throughout life. Others temporarily enter this phase to await a specific signal to proliferate later. Probably the GI-S transition regulation determines the number of cell cycles and, therefore, the complement of cells that will make brain [40]. Cyclins are proteins that appear to be involved in cell cycle control.
proteins are activating subunits of cyclin-dependent kinases. Cyclins D1, D2, D3, C, and E seem to control the key transition of a cell to the GI S interface; this transition is regarded as important because it commits a cell to division [42-44]. Cyclin E seems to be the gatekeeper for this transition, and is essential for movement from the GI to the S phase [42,45].

The number of cells that finally make up the mature nervous system is less than that generated during proliferation. Cells appear not only to be programmed to proliferate during development but to contain programs that lead to cell death [46,47]. The term apoptosis (from the Greek, meaning "a falling off") has been applied to this programmed loss of cells [48].

- **Non-neoplastic proliferative disorders**
  - **Microcephaly**

Although primary microcephaly may be a normal variant, in the classic symptomatic form, clinical and radiologic examinations reveal a receding forehead, flat occiput, early closure of fontanelles, and hair anomalies such as multiple hair whirls and an anterior cowlick. Neuroimaging may show small frontal and occipital lobes, open opercula, and a small cerebellum [24]. The cortex may appear thickened and the white matter reduced. Histologic examination may show a reduction of cell layers in some areas and an increase in others [49].

Neurologic findings also vary. Only mild psychomotor retardation may be noted, sometimes associated with pyramidal signs, or more severe retardation, seizures, and an atonic cerebral palsy might be evidenced. Primary microcephaly is seen in many genetic syndromes and, in its isolated form, may be autosomal recessive, autosomal dominant, or X-linked [50-52]. Microcephaly vera is the term most often applied to this genetic form of microcephaly. Affected children present with a head circumference that is usually more than 4 standard deviations below the mean, hypotonia, and psychomotor retardation. They later show mental retardation, dyspraxias, motor incoordination and, sometimes, seizures. On histologic examination, neurons in layers II and III are depleted [53].

Destructive lesions of the forming brain, such as those caused by teratogens and by infectious agents, also may result in microcephaly. Teratogens of note are alcohol, cocaine, and hyperphenylalaninemia (maternal phenylketonuria) [54]. Intense radiation exposure (such as that from a nuclear explosion) in the first trimester, can cause microcephaly [55]. Microcephaly and intracranial calcifications are likely due to well-recognized in utero infections caused by cytomegalovirus, toxoplasmosis, or the human immunodeficiency virus.

- **Megalencephaly and hemimegalencephaly**

The terms megalencephaly and hemimegalencephaly refer to disorders in which the brain volume is greater than normal (not owing to the abnormal storage of material); usually, the enlarged brain is accompanied by macrocephaly, or a large head. Although considered by
some to be a migration disorder, the increase in brain size in these disorders appears to be attributable to errors in neuroepithelial proliferation, as the microscopic appearance of the brain is that of an increase in number of cells (both neurons and glia) and in cell size [56-59].

Typically, patients are noted to have large heads at birth, and may manifest an accelerated head growth in the first few months of life [60,61]. Children with megalencephaly or hemimegalencephaly may come to medical attention when presenting with seizures, a developmental disorder (mental retardation), hemihypertrophy, or a hemiparesis (opposite the affected hemisphere). Seizures vary both in onset and in type, and usually are the most problematic symptom, sometimes necessitating hemispherectomy or callosotomy [58].

Approximately 50% of patients with linear sebaceous nevus syndrome have hemimegalencephaly [62,63]. Many patients with hypomelanosis of Ito also have hemimegalencephaly [64]. The neuropathologic and clinical pictures of these associations appear to be identical to the isolated hemimegalencephalies.

- **Neoplastic proliferative disorders**

Lesions of proliferation after an abnormal induction event during brain development may be malformative, hamartomatous, neoplastic, or a combination. Malformative disorders consisting of neoplasias on a background of disordered cortex or in association with focal cortical dysplasia include dysembryoplastic neuroepithelial tumor and ganglioglioma. [103,104]

  - **Dysembryoplastic neuroepithelial tumours**

Dysembryoplastic neuroepithelial tumors are supratentorial, predominantly temporal lobe tumors that are typically multinodular with a heterogeneous cell composition, including oligodendrocytes, neurons, astrocytes, and other cells. These lesions are typically fairly well-demarcated, wedge-shaped lesions extending from the cortex to the ventricle. Calcification, enhancement, and peritumoral edema are lacking on neuroimaging studies. These low-attenuation lesions may suggest an infarct on computed tomography (CT), although there is no volume loss over time, and scalloping of the inner table or calvarial bulging suggests slow growth. Lesions are low in signal on T1-weighted images and high in signal on T2-weighted images and often have a multinodular or pseudocystic appearance. There is a spectrum of pathology in dysembryoplastic neuroepithelial tumors. On one end of the spectrum are multinodular lesions with intervening malformed cortex, in which there is some hesitation to use the designation tumor. On the other end are lesions, which are clearly neoplastic and have clinically demonstrated some growth potential. Because the term dysembryoplastic neuroepithelial tumor has only recently been introduced, such malformative and neoplastic lesions were previously labeled as hamartomas, gangliogliomas, or mixed gliomas. [100,101,102]
Gangliogliomas

Gangliogliomas are typically demonstrated within the temporal lobe. In one large series of 51 gangliogliomas, 84% were found in the temporal lobe, 10% were found in the frontal lobe, 2% were found in the occipital lobe, and 4% were found in the posterior fossa. These lesions are typically hypodense (60% to 70%) on CT, with focal calcifications seen in 35% to 40%, contrast enhancement in 45% to 50%, and cysts in nearly 60%. The reported incidence of calcifications demonstrated on imaging in pediatric gangliogliomas is higher, seen in 61% of one series of 42 children. Features on MR imaging are less specific, with solid components isointense on T1-weighted images, bright on proton density images, and slightly less bright on T2-weighted images. Although imaging features are not specific, an enhancing, cystic temporal lobe lesion with focal calcification should suggest the diagnosis of ganglioglioma. The pathologic features that suggest the diagnosis of ganglioglioma include a neoplastic glial and neuronal component and calcification. Because calcifications are often poorly demonstrated on MR imaging and because they increase specificity of imaging findings, documentation of calcium should be sought on CT after MR imaging demonstration of a temporal lobe tumor. [97,98,99]

DISORDERS OF NEURONAL DIFFERENTIATION

- Normal differentiation

At the time of neuronal differentiation the neural tube consists of four consecutive layers: (1) the ventricular zone, the innermost layer, which gives rise to neurons and all of the glia of the central nervous system; (2) the subventricular zone, which is the adjacent, more superficial layer and is the staging area from which postmitotic neurons begin to differentiate and to migrate; (3) the intermediate zone, which is the contiguous, more superficial zone, and which is destined to become the cortical plate and the future cerebral cortex; and (4) the marginal zone, which is the outermost zone and is composed of the cytoplasmic extensions of ventricular neuroblasts, corticopetal fibers, and the terminal processes of radial glia (which, at this time, are completely spanning the neural tube).

Differentiation of neuroepithelial cells begins in the subventricular layer at approximately gestational day 26. The older, larger pyramidal cells are the first cells to be born and probably differentiate early to act as targets in the migration of the nervous system.

- Tuberous sclerosis

Disorders such as tuberous sclerosis, in which both tumor development and areas of cortical dysplasia are seen, might be a differentiation disorder. The brain manifestations of this disorder include hamartomas of the subependymal layer, areas of cortical migration abnormalities (tubers, cortical dysgenesis), and the development of giant-cell astrocytomas in upwards of 5% of affected patients. Two genes for tuberous sclerosis have been identified: TSCI (encodes for Hamartin) has been localized to 9q34 [65], and TSC2 (encodes for Tuberin) has been localized to 16p13.3 [65].
DISORDERS OF MIGRATION

- Normal migration

At the most rostral end of the neural tube in the 40- to 41-day-old fetus, the first mature neurons, Cajal-Retzius cells, begin the complex trip to the cortical surface. Cajal-Retzius cells, subplate neurons, and corticopetal nerve fibers form a preplate [66]. The neurons generated in the proliferative phase of neurodevelopment represent billions of cells poised to begin the trip to the cortical surface and to form the cortical plate. These neurons accomplish this task by attaching to and migrating along radial glial in a process known as radial migration or by somal translocation in a neuronal process [67]. The radial glia...
extend from the ventricle to the cortical surface. In the process of migration, the deepest layer of the cortical plate migrates and deposits before the other layers. Therefore, the first neurons to arrive at the future cortex are layer VI neurons. More superficial layers of cortex then are formed—the neurons of layer V migrate and pass the neurons of layer VI; the same process occurs for layers IV, III, and I. The cortex therefore is formed in an inside-out fashion [67-69].

A possible mode of movement in neuronal migration on glia would be the attachment of the neuroblast to a matrix secreted by either the glia or the neurons. The attachment of the neuron would be through integrin receptors, cytoskeletal-linking membrane-bound recognition sites for adhesion molecules. That attachment serves as a stronghold for the leading process and soma of the migrating neuron. Neuron movement on radial glia involves an extension of a leading process, neural outgrowth having an orderly arrangement of microtubules. Shortening of the leading process owing to depolymerization or shifts of microtubules may result in movement of the soma relative to the attachment points. This theory of movement of neurons also must include a phase of detachment from the matrix at certain sites, so that the neuron can navigate successfully along as much as 6 cm of developing cortex (the maximum estimated distance of radial migration of a neuron in the human). Finally, the movement of cells must stop at the appropriate location, the boundary between layer I and the forming cortical plate. Therefore, some stop signal must be given for the migrating neuron to detach from the radial glia and begin to differentiate into a cortical neuron. Perhaps that signal is REELIN, a protein that is disrupted in the mouse mutant Reeler and is expressed solely in the Cajal Retzius cells at this phase of development [66, 70-73].

- **Migration disorders**

Advanced neuroimaging techniques, particularly magnetic resonance imaging, have allowed the recognition of major migration disorders and of the frequency of more subtle disorders of migration. Some of these disorders are associated with typical clinical features that might alert the clinician to the presence of such malformations even before imaging is obtained. In other disorders, the clinical features are so varied that a strong correlation between imaging and the clinical presentation points to a specific genetic syndrome.

- **Lissencephaly**

Lissencephaly (smooth brain) refers to the external appearance of the cerebral cortex in those disorders in which a neuronal migration aberration leads to a relatively smooth cortical surface. One should not consider only agryia in making this diagnosis, rather, the full spectrum includes agryia and pachygyria. Gyri and sulci do not form in this disorder because the lack of cortical-cortical attractive forces owing to improper axon pathways. At least two types have been identified: classic lissencephaly, and cobblestone lissencephaly. The distinction is based upon the external appearance and upon the underlying histology, and can be made with neuroimaging.
Figure 10. Pachygyric (A), and agyric (B) lissencephalic brain

- **Classic lissencephaly**

Classic lissencephaly may occur in isolation, owing to LIS1 or Doublecortin aberrations or in combination with somatic features and LIS1 deletions in the Miller-Dieker syndrome. The hallmarks on imaging are a lack of opercularization (covering of the sylvian fissure), large ventricles or colpocephaly (dilated posterior horns), and agyria or pachygyria. The corpus callosum is almost always present, and the posterior fossa is usually normal, although a form of lissencephaly does exist that includes cerebellar hypoplasia.

The LIS1 protein forms complexes with other cellular proteins that are crucial for cell division, migration, and intracellular transport. Complete loss of LIS1 is fatal. Deletion of one copy of the gene is causes lissencephaly. The LIS1 gene is found in 17q13.3 location.

Doublecortin (DCX), a gene on Xq22.3-q23 that codes for a microtubule associated protein, is responsible for migration of neurons. Mutation of this gene results in band heterotopia.
LIS1 genetic syndromes

The Miller-Dieker phenotype consists of distinct facial features that include bitemporal hallowing, upturned nares, and a peculiar burying of the upper lip by the lower lip at the corners of the mouth. The lissencephaly is usually more severe than isolated lissencephaly, and the prognosis is worse. Most affected patients die in the first few years of life.

By both molecular and cytogenetic techniques, deletions in the terminal portion of one arm of chromosome 17 can be found in approximately 90% of Miller-Dicker lissencephaly cases [74]. The deletions of the terminal part of chromosome 17 in these cases have included microdeletions [74], ring 17 chromosome [75], pericentric inversions [76], and a partial monosomy of 17p13.3 [77]. The most appropriate genetic test is a fluorescent in situ hybridization (FISH) for LIS1; this test involves marking chromosome 17 at the centromere and LIS1 with fluorescent probes.

The greatest risk to future offspring exists when a parent harbors a balanced translocation involving this region of chromosome 17. In families that are affected in this manner, screening by amniocentesis can be performed in subsequent pregnancies. Therefore, it is recommended that both parents have screening for chromosome 17 rearrangements by FISH for LIS1. Should a translocation be present in a parent, then the LIS1 fluorescence will be on another chromosome.

Figure 11. Classical lissencephaly with patchy agyria/agyria, thick Cortex and band heterotopia
Figure 12. A, Type I lissencephaly, agyria type. Axial T2-weighted image shows a brain with a "figure-8" configuration secondary to the immature Sylvian fissures. A band of neurons (arrows) that was arrested during migration lies between the thin cortex and the lateral ventricles. B, Type 1 lissencephaly, pachygyria type. Axial T2-weighted image is similar to that shown in (A), with the exception that a few broad gyri with shallow sulci are present. C, Type 1 lissencephaly, pachygyria type. Axial T2-weighted image shows broad, flat gyri with shallow sulci throughout the cerebrum.

- Isolated lissencephaly

Classic lissencephaly without somatic or facial features represents a distinct genetic syndrome from Miller-Dieker, but it involves the same gene LIS1. Approximately 40% of patients with isolated lissencephaly have FISH detectable deletions of LIS1, and about 20% of additional patients harbor mutations of this gene [78-80]. The remaining patients may have mutations involving promoter regions of LIS1 or abnormalities of other genes such as Doublecortin or the involvement of other genes that have not been recognized.

The genetic risk of recurrence is highest when rearrangements of chromosome 17 exist in one parent. This is rare in isolated lissencephaly, but could occur. Therefore, it would be prudent to perform FISH for LIS1 in the parents of children with isolated lissencephaly who have FISH proven deletions for the LIS1 region.

The prognosis for this disorder is better than that for Miller-Dieker syndrome, but it is not consistent with long-term survival. These patients typically present in the first few months of life with hypotonia, lack of visual fixation, and often seizures. Patients with lissencephaly will uniformly have seizures and profound mental retardation. Often, seizures are very difficult to control and require multiple anticonvulsant drugs.
o X-linked lissencephaly

The imaging of X-linked lissencephaly looks nearly identical to the images of lissencephaly involving LIS1. Patients have classic lissencephaly, and the neurologic presentation described above. However, the skeletal and other anomalies seen in the Miller-Dieker are not noted in this form of lissencephaly. When viewing the images from patients with lissencephaly owing to abnormalities of LIS1 and of Doublecortin it is apparent that differences in an anterior to posterior gradient of severity exists [81-83]. Doublecortin mutations result in anterior greater than posterior severity, whereas LIS1 mutations result in posterior greater than anterior severity [84].

In addition, X-linked lissencephaly occurs mostly in boys; girls who are heterozygous for Doublecortin mutations have band heterotopia [80,81,85]. Women with band heterotopia have been known to give birth to boys with lissencephaly. In female patients, the less severe phenotype probably is attributed to random lyonization of the X chromosome, such that in a variable number of cells, normal gene expression is seen and, in the remaining cells, the Doublecortin mutation-containing X chromosome is expressed. It is presumed that those cells expressing the abnormal X chromosome will be arrested in the migration to the surface of the brain and reside in a subcortical band.

Figure 13. Gross specimen showing lissencephaly with pachygyria and agyria
When viewing images from patients with this disorder, a thick band of tissue that is isointense with cerebral gray matter is seen within what should be the white matter of the hemispheres. The overlying gyral appearance may vary from normal cortex to a pachygyria. A brain biopsy performed in a patient demonstrated well-preserved lamination in cortical layers I-IV [86]. Layers V-VI were not clearly separated and merged with underlying white matter. Beneath the white matter was a coalescent cluster of large, well-differentiated neurons.
Lissencephaly with cerebellar hypoplasia

The association of lissencephaly with cerebellar hypoplasia represents a distinct malformation from both a genetic and clinical standpoint to those described above. The cerebellar hypoplasia is usually extreme, and the brainstem may be small. Patients may or may not have an associated microcephaly. This disorder is often inherited in an autosomal recessive fashion and may be due to mutations in REELIN in some families [87].
Figure 18. MRI showing a mild form of lissencephaly (pachygyria), the brain have a few broad, flat gyri with thick cortex and separated by shallow sulci (pachygyria). The cerebellum and the brain stem are hypoplastic, the brain volume is also reduced especially the temporal lobes.

- Cobblestone lissencephaly

Cobblestone lissencephalies are disorders in which a smooth configuration of cortex is noted, but the distinction from classic lissencephaly is made based upon the clinical association of eye abnormalities, muscle disease, and progressive hydrocephalus. The term "cobblestone" refers to the appearance of the cortical surface upon pathologic examination. In these disorders, cells pass their stopping point and erupt over the surface of the cortex into the subarachnoid spaces. This results in a cobblestone street appearance to the surface, and therefore, the name.
A, Type II lissencephaly, Cobblestone lissencephaly (Walker-Warburg syndrome). The cortex is lissencephalic and thickened, with an irregular gray matter-white matter junction that probably represents the bundles of disorganized cortex surrounded by fibroglial tissue. The patient has been shunted for hydrocephalus. The brain is hypomyelinated. B, Presumed microcephalia vera. The brain is completely smooth (lissencephaly) with a very thin cortex. No layer of arrested neurons is present in the white matter. C, Presumed radial microbrain. Axial T2-weighted image shows an immature gyral pattern and hypomyelination. Cortical thickness is normal. This patient was profoundly microcephalic (head circumference 19 cm).

The Walker-Warburg, muscle-eye-brain, and HARD +/- syndromes are likely all varying degrees of the same entity. Abnormalities that may or may not be seen in these disorders include muscular dystrophy, ocular anterior chamber abnormalities, retinal dysplasias (evidenced by abnormal electroretinogram and visual evoked responses), hydrocephalus (usually of an obstructive type), and encephaloceles. The Walker-Warburg syndrome might be diagnosed even if the ocular examination and muscle biopsies are normal if on MRI, an abnormal white matter signal and a thickened falx suggest the diagnosis. Neuroimaging of the muscle-eye-brain disorders often reveals focal white matter abnormalities.
Fukuyama muscular dystrophy is distinguished from the Walker Warburg-like syndromes by the severity of the muscular dystrophy [88-91]. This disorder is seen more often in Japan than in the Western hemisphere, probably because it is the result of a founder mutation. Patients typically present with evidence of a neuronal migration defect, hypotonia, and depressed reflexes. Recent identification of Fukutin as the causative gene in this disorder should provide insight into the pathogenesis of the cobblestone lissencephalies [92]. This disorder is inherited as an autosomal recessive disorder.

The cobblestone lissencephalies often have an associated cerebellar and brainstem hypoplasia, and therefore may be difficult to distinguish from lissencephaly with cerebellar hypoplasia described above. The presence of eye abnormalities, elevated CPK, or other evidence for the presence of muscle disease and progressive hydrocephalus distinguish this disorder. These disorders may be inherited in an autosomal recessive manner.
Table 1. The lissencephalies syndromes

<table>
<thead>
<tr>
<th>TYPE</th>
<th>DESCRIPTION</th>
<th>GENE</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIS1 genetic syndromes</td>
<td>The Miller-Dieker phenotype consists of distinct facial features that include bitemporal hallowing, upturned nares, and a peculiar burying of the upper lip by the lower lip at the corners of the mouth. The lissencephaly is usually more severe than isolated lissencephaly, and the prognosis is worse. Most affected patients die in the first few years of life.</td>
<td>By both molecular and cytogenetic techniques, deletions in the terminal portion of one arm of chromosome 17 can be found in approximately 90% of Miller-Dieker lissencephaly cases [74]. The deletions of the terminal part of chromosome 17 in these cases have included microdeletions [74], ring 17 chromosome [75], pericentric inversions [76], and a partial monosomy of 17p13.3 [77]. The most appropriate genetic test is a fluorescent in situ hybridization (FISH) for LIS1; this test involves marking chromosome 17 at the centromere and LIS1 with fluorescent probes.</td>
</tr>
<tr>
<td>Isolated lissencephaly</td>
<td>Classic lissencephaly without somatic or facial features represents a distinct genetic syndrome from Miller-Dieker,</td>
<td>It involves the same gene LIS1. Approximately 40% of patients with isolated lissencephaly have FISH detectable deletions of LIS1, and about 20% of additional patients harbor mutations of this gene [78-80]. The remaining patients may have mutations involving promoter regions of LIS1 or abnormalities of other genes such as Doublecortin or the involvement of other genes that have not been recognized.</td>
</tr>
<tr>
<td>X-linked lissencephaly-subcortical band heterotopia (XLIS-SBH)</td>
<td>• The imaging of X-linked lissencephaly looks nearly identical to the images of lissencephaly involving LIS1. Patients have classic lissencephaly, and the neurologic presentation described above. However, the skeletal and other anomalies seen in the Miller-Dieker are not noted in this form of lissencephaly.</td>
<td>• LIS1 gene mutation results in lissencephaly • Doublecortin gene mutation results in band heterotopia (Doublecortin (DCX), a gene on Xq22.3-q23 that codes for a microtubule associated protein, is responsible for migration neurons. Mutation of this gene results in band heterotopia)</td>
</tr>
</tbody>
</table>
In addition, X-linked lissencephaly occurs mostly in boys; girls who are heterozygous for Doublecortin mutations have band heterotopia [80,81,85].

| Lissencephaly with cerebellar hypoplasia | The association of lissencephaly with cerebellar hypoplasia represents a distinct malformation from both a genetic and clinical standpoint to those described above. The cerebellar hypoplasia is usually extreme, and the brainstem may be small. Patients may or may not have an associated microcephaly. |
| Cobblestone lissencephalies | This disorder is often inherited in an autosomal recessive fashion and may be due to mutations in REELIN in some families [87]. |

Cobblestone lissencephalies are disorders in which a smooth configuration of cortex is noted, but the distinction from classic lissencephaly is made based upon the clinical association of eye abnormalities, muscle disease, and progressive hydrocephalus. The term "cobblestone" refers to the appearance of the cortical surface upon pathologic examination. In these disorders, cells pass their stopping point and erupt over the surface of the cortex into the subarachnoid spaces. This results in a cobblestone street appearance to the surface, and therefore, the name.

- Polymicrogyria

Polymicrogyria (many small gyri) is a disorder often considered to be a neuronal migration disorder, but alternate theories exist regarding its pathogenesis. The microscopic appearance of the lesion is that of too many small abnormal gyri. The gyri may be shallow and separated by shallow sulci, which may be associated with an apparent increased cortical thickness on neuroimaging. The multiple small convolutions may not have intervening sulci, or the sulci may be bridged by fusion of overlying molecular layer, which may give a smooth appearance to the brain's surface. The interface of white matter with gray matter is not distinct and often this observation serves as the confirmation of the presence of polymicrogyria.
Polymicrogyria has also been associated with genetic and chromosomal disorders. It is found in disorders of peroxisomal metabolism such as Zellweger syndrome and neonatal adrenal leukodystrophy. Familial bilateral frontal polymicrogyria and bilateral perisylvian polymicrogyria have been reported. Therefore, if no identifiable cause of the polymicrogyric malformation is found, the recurrence risk may be that of an autosomal recessive disorder. A bilateral parasagittal parieto-occipital polymicrogyria has also been described.

The clinical picture varies depending on the location, extent, and cause of the abnormality. Microcephaly with severe developmental delay and hypertonia may result when
polymicrogyria is diffuse. When polymicrogyria is unilateral, focal deficits might be seen. Epilepsy often is present, characterized by partial complex seizures or partial seizures that secondarily generalize. The age at presentation and severity of seizures depends on the extent of the associated pathology.

![Image of brain with polymicrogyria](image)

**Figure 23.** A, pachygyria with polymicrogyria. B, pachygyria with polymicrogyria, notice the subependymal nodular heterotopia

Bilateral perisylvian dysplasia is a disorder of perisylvian polymicrogyria resulting in an uncovered sylvian fissure on neuroimaging and on sagittal imaging an extension of the sylvian fissure to the top of the convexity. Patients with bilateral perisylvian dysplasia have a pseudobulbar palsy, and often dysphagia can impair proper nutrition. The majority of patients have epilepsy with early onset; infantile spasms are common.
Figure 24. Polymicrogyria with pachygyria

Figure 25. Polymicrogyria. In B the patient also had meningomyelocele, obstructive hydrocephalic and Arnold-Chiari type II malformation

The cause of this syndrome remains unknown, although hints of a genetic mechanism exist. Detailed chromosomal analyses have revealed deletions of chromosomes 1, 2, 6, 21, and 22 [93], and an X-linked form has been also described [94,95]. Monozygotic twins and siblings with this disorder have been described, suggesting a possible autosomal recessive
mechanism. Some speculate that this is a disorder of regional specification, given the bilateral, symmetric nature of the lesions.

- **Heterotopias**

  Heterotopias are collections of normal-appearing neurons in an abnormal location, presumably secondary to a disturbance in migration. The exact mechanism of the migration aberration has not been established, although various hypotheses have been proposed. These include damage to the radial glial fibers, premature transformation of radial glial cells into astrocytes, or a deficiency of specific molecules on the surface of neuroblasts or of the radial glial cells (or the receptors for those molecules) that results in disruption of the normal migration process [96]. Heterotopias often occur as isolated defects that may result in only epilepsy. However, when they are multiple, heterotopias might also be associated with a developmental disorder and cerebral palsy (usually spastic). In addition, if other migration defects such as gyral abnormalities are present, the clinical syndrome may be more profound. Usually, no cause is apparent. Occasionally, heterotopias may be found in a variety of syndromes, including neonatal adrenal leukodystrophy, glutaric aciduria type 2, GMI gangliosidosis, neurocutaneous syndromes, multiple congenital anomaly syndromes, chromosomal abnormalities, and fetal toxic exposures.
Heterotopias may be classified by their location: subpial, within the cerebral white matter, and in the subependymal region. When subependymal, one must consider the X-linked dominant disorder associated with Filamin mutations (Xq28). Leptomeningeal heterotopias
often contain astrocytes mixed with ectopic neurons and may resemble a gliotic scar. They may be related to discontinuities in the external limiting membrane and often are associated with cobblestone lissencephaly. These subarachnoid heterotopias are responsible for the pebbled appearance of the surface of the brain. White matter heterotopias may be focal, subcortical, or diffuse. They may cause distortion of the ventricles and may be associated with diminished white matter in the surrounding area.

Figure 28. MRI showing Subependymal nodular heterotopia

SUMMARY

The progress made in the understanding of the genetics of human brain malformations has lead to insight into the formation of brain and into mechanisms of disease affecting brain. It bears upon neurologists and geneticists to recognize the patterns of diseases of brain formation, to properly diagnose such disorders, to assess the recurrence risk of these malformations, and to guide families with appropriate expectations for outcomes. This article may serve as a guide to neurologists in their approach to these disorders. Because this area is one of rapid progress, the clinician is advised to seek more current information that may be available through on-line databases and other sources.

Table 2. Definition of developmental disorders.

<table>
<thead>
<tr>
<th>Type</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>schizencephaly (disorder of segmentation)</td>
<td>Schizencephaly (cleft in brain) has been regarded by many as a migration abnormality; however, it is best understood as a disorder of segmentation because one of the genes that is abnormal in the more severe and familial forms is EMX2 [6,7]. Thus, this developmental disorder, at least in the more severe cases, appears to be the result of failure of regional specification of a clone of cells that are destined to be part of the cortex.</td>
</tr>
<tr>
<td>Megalencephaly (Non-neoplastic)</td>
<td>The terms megalencephaly and hemimegalencephaly refer to disorders in which the brain volume is greater than normal (not owing to the abnormal storage of material); usually, the enlarged brain is</td>
</tr>
<tr>
<td>Disorder of Neuronal Proliferation</td>
<td>Accompanied by macrocephaly, or a large head.</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>Microcephaly (Non-neoplastic Disorder of Neuronal Proliferation)</td>
<td>The term microcephaly refers to disorders in which the brain volume is smaller than normal.</td>
</tr>
<tr>
<td>Dysembryoplastic Neuroepithelial Tumor and Ganglioglioma</td>
<td>Neoplastic proliferative disorders.</td>
</tr>
<tr>
<td>Lissencephaly (Disorder of Neuronal Migration)</td>
<td>Lissencephaly (smooth brain) refers to the external appearance of the cerebral cortex in those disorders in which a neuronal migration aberration leads to a relatively smooth cortical surface. One should not consider only agyria in making this diagnosis, rather, the full spectrum includes agyria and pachygyria.</td>
</tr>
<tr>
<td>Agyria (Disorder of Neuronal Migration)</td>
<td>Extreme end of lissencephaly (sever lissencephaly) spectrum in which gyri are completely absent and the brain surface is completely smooth.</td>
</tr>
<tr>
<td>Pachygyria (Disorder of Neuronal Migration)</td>
<td>The other end of lissencephaly spectrum (mild lissencephaly), the brain have a few broad, flat gyri separated by shallow sulci (pachygyria). The cortex is thick in pachygyria.</td>
</tr>
<tr>
<td>Polymicrogyria (Disorder of Neuronal Migration)</td>
<td>Polymicrogyria (many small gyri) is a disorder often considered to be a neuronal migration disorder, but alternate theories exist regarding its pathogenesis. The microscopic appearance of the lesion is that of too many small abnormal gyri. The gyri may be shallow and separated by shallow sulci, which may be associated with an apparent increased cortical thickness on neuroimaging. The multiple small convolutions may not have intervening sulci, or the sulci may be bridged by fusion of overlying molecular layer, which may give a smooth appearance to the brain's surface.</td>
</tr>
<tr>
<td>Heterotopias (Disorder of Neuronal Migration)</td>
<td>Heterotopias are collections of normal-appearing neurons in an abnormal location, presumably secondary to a disturbance in migration. Heterotopias may be classified by their location: subpial, within the cerebral white matter, and in the subependymal region.</td>
</tr>
</tbody>
</table>
Tuberous sclerosis (differentiation disorder) | Disorders such as tuberous sclerosis, in which both tumor development and areas of cortical dysplasia are seen, might be a differentiation disorder. The brain manifestations of this disorder include hamartomas of the subependymal layer, areas of cortical migration abnormalities (tubers, cortical dysgenesis), and the development of giant-cell astrocytomas in upwards of 5% of affected patients.

References


[40] Caviness VS, Takahashi T. Proliferative events in the cerebral ventricular zone. Brain Dev 1995;17:159-63.


INTRODUCTION

Behcet’s disease (BD) is an uncommon, relapsing and remitting, multisystem inflammatory disorder characterized by the triad of oral ulceration, genital ulceration, and uveitis. A number of additional features are commonly present, including arthritis, retinal and cutaneous vasculitis, thrombophlebitis, and gastroenteric disorders. The essential lesion is a focus of chronic inflammation, typically in the vicinity of a small blood vessel. Lesions in the CNS resemble those in other organ systems. Characteristically there are multiple small foci of softening that may eventually become confluent. These correspond to myelin loss and, to a lesser degree, drop out of neural elements with replacement by foamy macrophages. The lesions are not fundamentally demyelinative and more closely resemble minute ischemic foci. As in the periphery, lesions tend to occur near blood vessels, but
vasculitis is uncommon. Pathologic findings are most extensive in the midbrain, pons (especially the basis pontis) and the medulla, and there is typically a lesser degree of involvement of the spinal cord, internal capsule, globus pallidus, optic nerves, and hypothalamus. In some cases, the cerebral white matter, cortex, hippocampus, basal ganglia, and thalamus are involved. The cerebellum is usually spared. The meninges are typically thickened and adherent to the brain surface, and acutely there may be considerable meningeal inflammation; hence the common reference to neuro-Behcet's disease as a meningoencephalitis.

In general the most common presentation of parenchymal CNS involvement is a subacute brainstem syndrome with cranial nerve findings, dysarthria, and cerebellar or corticospinal tract signs. More infrequent presentations include a stroke-like presentation (with the acute onset of unilateral neurologic findings and signs of cortical involvement including seizures) and psychiatric features, such as psychosis. Sinus venous thrombosis may evolve relatively slowly and results in intracranial hypertension, resulting headache, vomiting, and bilateral papilledema. Impaired memory (long-term verbal and nonverbal) and visuospatial skills occur frequently in patients with active disease who are taking large doses of steroids. Pure spinal cord or PNS involvement is rarely reported. Impairment of sensation is uncommon. (70)

Between 5% and 20% of patients have neurologic disease. (70) The most common neurologic manifestation of Behcet's disease is a relapsing and remitting, but often progressive, focal meningoencephalitis that most often affects the brainstem. (70) Patients present with a host of cranial nerve and long tract signs and eventually develop spastic quadriparesis and a bulbar or pseudobulbar palsy, frequently with rather dramatic emotional incontinence. (70) Cochlear and vestibular dysfunctions are common. Often there are additional features of impairment in frontal lobe and memory function characteristic of a subcortical dementia. A number of cases of nearly pure subcortical dementia have been reported, but typically long tract signs are prominent, and bulbar involvement eventually develops. Patients may also present initially with features of transverse myelitis, but bulbar signs characteristically appear as the disease progresses. Cerebral cortical involvement is unusual, but seizures and aphasia have been reported. The optic nerves are commonly involved, but symptoms are indistinguishable from those of uveitis, which is usually present in patients with neurologic features. CNS vasculitis is rare, but stroke caused by large artery involvement has been reported. Pseudotumor cerebri is relatively common and almost always caused by venous sinus thrombosis. Cerebral venous thrombosis may affect up to 10% of all patients with Behcet's disease and one third of those with neurologic involvement. CNS involvement generally manifests several years after the onset of systemic Behcet's disease, but occasionally it may be an initial feature and even precede other disease manifestations. As a rule, flares of neurologic disease parallel flares of systemic disease.

Neuro-Behçet's syndrome can be classified as an acute type and as a chronic progressive type (70). It should be pointed out that the two types of neuro-Behçet's syndrome are currently considered to represent different stages rather than independent clinical entities. Acute neuro-Behçet's syndrome is characterized by acute meningoencephalitis with a focal
midbrain pyramidal tract lesions, the lesions are anteriorly located in the cerebral peduncles, bilateral, asymmetrical, extending up and down within the brain stem as a longitudinal linear lesion, and presenting high-intensity areas in the MRI T2-weighted images or the fluid attenuated inversion recovery (FLAIR) images (70). Acute neuro-Behçet's syndrome responds to steroid therapy, and is usually self-limiting.

By contrast, the chronic progressive type of neuro-Behçet's syndrome is characterized by intractable, slowly progressive dementia, ataxia and dysarthria, with persistent elevation of cerebrospinal fluid IL-6 activity (> 20 pg/ml) (70). Most patients with the chronic progressive type of neuro-Behçet's syndrome were HLA-B51-positive, and they had history of attacks of acute type neuro-Behçet's syndrome prior to the development of progressive neurological symptoms (70).

The neurological involvement in Behçet's disease is either caused by primary neural parenchymal lesions (neuro-Behçet's syndrome, or brain stem meningoencephalitis) or is secondary to major vascular involvement. The latter type is rarely complicated with the parenchymal lesions and should be called vascular-Behçet's disease. This vasculo-Behçet's disease type generally has a better prognosis compared with the parenchymal type. (70) Both vascular and parenchymal types can coexist.

- **The typical intra-axial primary parenchymal neuro-Behçet type**

  - It is primary parenchymal neural disease, a focal brain stem meningoencephalitis affecting the midbrain primarily with selective involvement of the corticospinal tract bilaterally. The most common clinical findings are pyramidal signs. Sensory symptoms or signs are much less frequent in neuro-Behçet disease. (73,74) The corticospinal tract lesions extend cephalocaudally in a linear fashion from the mesencephalon down to the pons and less frequently to the medulla and up to the posterior limb of the internal capsule. The cephalocaudal extension of the midbrain corticospinal tract lesions could be either due to wallerian degeneration or extension of vasogenic edema along the myelinated fibers of the corticospinal tract. (70,73,74)

  - The corticospinal tract pathology is manifested by MR imaging as bilateral and asymmetrical longitudinal linear lesions extending from the posterior limb of the internal capsule down to the midbrain, pons and less frequently the medulla. The midbrain is more severely affected. The corticospinal tract linear lesions are hyperintense on the MRI T2 images and hypointense on the MRI T1 images and show contrast enhancement in the acute stage. Contrast enhancement is due to break down of the blood brain barrier and this is in favour of the corticospinal tract MRI signal changes being due to vasogenic edema. (70,73,74)
The atypical intra-axial primary parenchymal neuro-Behçet type

- Parenchymal Behçet disease is seen as a space-occupying lesion or masquerading as a unilateral brain tumor (Fig 10). Differential diagnoses include lymphoma, other types of malignant tumors, and abscess. These atypical manifestations of neuro-Behçet disease may make diagnosis more difficult. In particular, diagnosis is difficult in cases in which the neurologic manifestation does not occur simultaneously with a flare-up of Behçet disease. Steroid administration may be a diagnostic and therapeutic option in uncertain clinical situations.

The extra-axial vascular-Behçet's type

- Involvement of veins and arteries in Behçet's disease is usually called vasculo-Behçet's disease. Venous thrombosis appeared to be the major vascular involvement in 7–33% of patients with Behçet's disease, and represents 85–93% of vascular-Behçet's disease (70). The brain parenchymal involvement seen in the primary neuro-Behçet type is rarely seen in the vascular type of Behçet disease. Parenchymal involvement in the vascular type of Behçet disease is more commonly secondary to venous sinus thrombosis. Deep vein thrombosis or cerebral sinus thrombosis are significantly associated with the male gender and a positive pathergy test (70). Venous thrombosis is a reflection of thrombophilia in vascular Behçet's disease. (70,73,74). To the best of the author's information, cerebral sinovenous thrombosis in the vascular-Behçet type is indistinguishable from sinovenous thrombosis due to any other cause and is only distinct from the viewpoint that it is commonly associated clinically with oro-genital ulcerations. Probably vascular-Behçet syndrome must be put in the differential diagnosis of cases presented with cerebral sinovenous thrombosis of undetermined aetiology.

- The clinical picture of vascular Behçet is different from that of primary neuro-Behçet. The clinical picture of neuro-Behçet is dominated by a mainly motor clinical picture with bilateral pyramidal tract signs, pseudo-bulbar palsy, subcortical dementia, etc. and sensory symptoms are uncommon, while the clinical picture of vascular Behçet is that of acute and chronic cerebral sinovenous thrombosis and its parenchymal complications (headache, seizures, focal sensory and motor deficits, bilateral papilledema, pseudotumor cerebri).

- A number of studies have explored the pathogenesis of thrombophilia in Behçet's disease. Neither deficiency in protein C, in protein S, in factor V Leiden and in antithrombin III nor resistance to activated protein C and anticardiolipin antibody levels seemed to be correlated with vascular thrombosis in Behçet's disease (75,76). There were increased thrombin generation, fibrinolysis, and thrombomodulin in Behçet's disease, but these abnormalities were not related to thrombosis (76). These results therefore
suggest that thrombophilia in Behçet's disease might be related more to inflammation than to clotting disorder.

- Arterial involvement, although rare, does occur in Behçet's disease. The arterial manifestations in Behçet's disease resemble those of Takayasu's arteritis, including arterial occlusion and aneurysm formation. Histopathological studies revealed that the number of vasa vasorum with infiltration of neutrophils and lymphocytes was significantly increased in vascular-Behçet's disease compared with in Takayasu's arteritis and other inflammatory aneurysms (70). It was therefore suggested that arterial involvement in vascular-Behçet's (vasculo-Behçet) disease might be caused by a neutrophilic vasculitis targeting the vasa vasorum, leading to degeneration of the arterial wall. (70,73,74)

- The extra-axial-meningitic type

  - Aseptic meningitis is one of the uncommon manifestations of Behçet disease, with a frequency ranging from 0.05% from 8%. Meningeal thickening with enhancement associated with dural sinus thrombosis could also be present. See figure 6A

<table>
<thead>
<tr>
<th>Table 1. Lesion characteristics in the primary parenchymal neuro-Behçet type</th>
</tr>
</thead>
</table>

- The lesion in the primary parenchymal neuro-Behçet type is a focal brain stem meningoencephalitis affecting the midbrain primarily with selective involvement of the corticospinal tract bilaterally.

- The most common clinical findings are pyramidal signs. Sensory symptoms or signs are much less frequent in neuro-Behçet disease.

- The corticospinal tract lesions extend cephalocaudally in a linear fashion from the mesencephalon down to the pons and less frequently to the medulla and up to the posterior limb of the internal capsule. The cephalocaudal extension of the midbrain corticospinal tract lesions could be either due to wallerian degeneration or extension of vasogenic edema along the myelinated fibers of the corticospinal tract.

- The corticospinal tract pathology is manifested by MR imaging as bilateral and asymmetrical longitudinal linear lesions extending from the posterior limb of the internal capsule down to the midbrain, pons and less frequently the medulla. The midbrain is more severely affected. The corticospinal tract linear lesions are hyperintense on the MRI T2 images and hypointense on the MRI T1 images and show contrast enhancement in the acute stage. Contrast enhancement is due to break down of the blood brain barrier and this in favour of the corticospinal tract MRI signal changes being due vasogenic edema. (70,73,74)

- The corticospinal tract linear lesions are sometimes surrounded by a hypointense edema area with positive mild mass effect.
Table 2. The differences between the primary parenchymal neuro-Behçet type and the vascular-Behçet's type

<table>
<thead>
<tr>
<th>Parameter</th>
<th>The primary parenchymal neuro-Behçet type</th>
<th>Vascular-Behçet's type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical picture</td>
<td>The clinical picture of neuro-Behçet is dominated by a mainly motor clinical picture with bilateral pyramidal tract signs, pseudo-bulbar palsy, subcortical dementia etc. Sensory symptoms are uncommon</td>
<td>The clinical picture of vascular Behçet is that of acute and chronic cerebral sinusovenous thrombosis and its parenchymal complications (headache, seizures, focal sensory and motor deficits, bilateral papilledema, pseudotumor cerebri, etc.).</td>
</tr>
<tr>
<td>Incidence</td>
<td>More common (70-93%)</td>
<td>Less common (7-33%)</td>
</tr>
<tr>
<td>Pathology &amp; pathogenesis</td>
<td>It is primary parenchymal neural disease, a focal brain stem meningoencephalitis affecting the midbrain primarily with upward and downward extension (along the pyramidal tract fibers to the posterior limb of the internal capsule, the basis pontis and the medulla) and with selective involvement of the corticospinal tract bilaterally.</td>
<td>Venous thrombosis is a reflection of thrombophilia in Behçet's disease. Thrombophilia in Behçet's disease might be related more to inflammation than to clotting disorder.</td>
</tr>
<tr>
<td>Radiological findings</td>
<td>The corticospinal tract pathology is manifested by MR imaging as bilateral and asymmetrical longitudinal linear lesions extending from the posterior limb of the internal capsule down to the midbrain, pons and less frequently the medulla. The midbrain is more severely affected. The corticospinal tract linear lesions are hyperintense on the MRI T2 images and hypointense on the MRI T1 images and show contrast enhancement in the acute stage. Contrast enhancement is due to break down of the blood brain barrier and this is in favour of the corticospinal tract MRI signal changes being due vasogenic edema. (70,73,74)</td>
<td>The MRI picture is that of sinusovenous thrombosis and its parenchymal complications (70)</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Bad, higher incidence of being transformed into the progressive type with subcortical dementia, etc.</td>
<td>Better</td>
</tr>
<tr>
<td>Management</td>
<td>Steroid responsive</td>
<td>Anticoagulants, steroid may play a role</td>
</tr>
</tbody>
</table>
Currently, the most widely used diagnostic criteria of Behcet's disease is the International Study Group's classification, which requires recurrent oral ulcerations plus two of the following in order to establish a definite diagnosis: recurrent genital ulcerations, skin or eye lesions, or a positive pathergy test (13). The epidemiology of disease shows geographic variation, encountered more commonly along the Silk Road, which extends from the Mediterranean region to Japan (15). This is coupled with a similar variation in HLA B51 (human leukocyte antigen), which has been reported to be strongly associated with the disease in the high prevalence areas (16–19). Despite broadened clinical understanding of this disease, the etiologic factors remain obscured and speculative: viral agents, immunologic factors, genetic causes, bacterial factors, and fibrinolytic defects have all been implicated (3, 20–25). Vessel wall and perivascular mononuclear cell infiltration, which is consistent with vasculitis involving both arterial and venous systems, has been shown in histopathologic studies (20, 21). It has been postulated that genetic susceptibility together with a possible trigger by an extrinsic factor, such as an infectious agent, is responsible for the observed vasculitis (24, 26).

Table 3. The International Study Group criteria for the diagnosis of Behcet disease

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 3 episodes of oral ulceration must occur in a 12-month period. They must be observed by a physician or the patient and may be herpetiform or aphthous in nature.</td>
</tr>
<tr>
<td>At least 2 of the following must occur:</td>
</tr>
<tr>
<td>• Recurrent, painful genital ulcers that heal with scarring.</td>
</tr>
<tr>
<td>• Ophthalmic lesions, including anterior or posterior uveitis, hypopyon, or retinal vasculitis.</td>
</tr>
<tr>
<td>• Skin lesions, including erythema nodosum, pseudofolliculitis, or papulopustular lesions (may also include atypical acne).</td>
</tr>
<tr>
<td>• Pathergy: defined as a sterile erythematous papule larger than 2 mm in size appearing 48 hours after skin pricks with a sharp, sterile needle (a dull needle may be used as a control).</td>
</tr>
</tbody>
</table>

Neurologic involvement in Behcet's disease, was first reported in 1941 by Knapp (27), and the term neuro-Behçet syndrome was introduced by Cavara and D'Ermo in 1954 (28). The reported rate of development of neurologic involvement among Behcet's disease patients...
ranges from 4% to 49% (9, 29). This rate was found to be 6.7% in a large nonselective series of patients (30).

**Figure 2.** A case with Neuro-Behçet showing anteriorly located midbrain hyperintense lesions in the presumed anatomical position of the corticospinal tract.

Neuro-Behçet syndrome may present as an acute focal or multifocal CNS dysfunction, and the clinical picture of neuro-Behçet syndrome may resemble multiple sclerosis (MS) (7, 31–35). It has been observed that a substantial number of patients with neuro-Behçet syndrome will have a relapsing-remitting course while others may develop a secondary-progressive course; some neuro-Behçet syndrome patients have an insidious onset, with primary-progressive CNS dysfunction, and others may display symptoms attributable to intracranial hypertension associated with dural venous sinus thrombosis (12, 36, 37). Although non-neurologic involvement generally precedes neurologic findings, the non-neurologic involvement may go unrecognized in some cases or it may appear late in the patient’s course, thus posing diagnostic difficulties (38–40). Peripheral nerve involvement, although reported in neuro-Behçet syndrome, is relatively uncommon (41).

The most common imaging lesion seen in the acute or subacute stage of neuro-Behçet syndrome is an asymmetric mesodiencephalic junction lesions (7–9, 33). These lesions extend along long fiber tracts and spare the red nucleus, suggesting that this downward extension is due to edema. The reversibility of the extension, leaving small residual lesions at the center, as observed on follow-up MR studies, further supports their edematous
nature. This feature was also noted in earlier publications (9, 11, 42). Accordingly, pontobulbar involvement is an extension of lesions located at other sites, particularly the mesodiencephalic junction. The distribution and intensity of changes of the residual lesions closely corresponded to pathologic descriptions of secondary demyelination (20, 21, 43, 44). In the chronic cases, Changes may extend to the cervical cord, along the corticospinal tract, and this might be explained by wallerian degeneration. This was noted in some pathologic studies as well (20, 43, 44).

Figure 3. A case with Neuro-Behcet showing anteriorly located midbrain hyperintense lesions in the presumed anatomical position of the cortico-spinal tract.

The following clinico-radiological signs must be emphasized and highlighted in neuro-Behçet syndrome:

1. In general the observed pathology in these cases represents demyelination and edema along the cortico-spinal tract fibers (in fact the pyramidal tract is actually anatomically mapped by the MRI signal changes of vasogenic edema and contrast enhancement) and is found to be located mainly in the midbrain/thalamus (which probably constitutes the primary site of involvement) with upward extension to the posterior limb of the internal capsule and downward extension to the basis pontis. The upward and downward extension of the primary midbrain/thalamic lesions might be explained by wallerian degeneration or vasogenic edema (which characteristically spreads along the myelinated fibers of long tracts) and this was noted in some pathologic studies as well (20, 43, 44).

2. The selective involvement of the corticospinal tract would explain the clinical picture of these patients which is dominated by pyramidal tract involvement and pseudo-bulbar palsy with absence of sensory changes. In fact the clinical picture and the MRI findings in neuro-Behçet syndrome closely resemble those of motor neuron disease with pseudo-bulbar palsy (they both shared common topographic distribution and spatial extension of the corticospinal tract lesions), however the corticospinal tract lesion in motor neuron disease does not show contrast
enhancement. (70). The corticospinal tract linear lesion appeared larger in size in acute neuro-Behçet syndrome compared with that of motor neuron disease probably due to the contribution of edema in neuro-Behçet syndrome. The corticospinal tract lesion is reversible in the acute neuro-Behçet syndrome, however it is irreversible in motor neuron disease. In general the lesion in acute neuro-Behçet syndrome has an acute onset and a regressive course, while that of motor neuron disease has a chronic progressive course. The MRI signal changes along the course of the corticospinal tract are mainly due to reversible vasogenic edema in acute neuro-Behçet syndrome, while the MRI signal changes along the course of the corticospinal tract in motor neuron disease are mainly due to wallerian degeneration. See table 4

3. Neuro-Behçet cases share common clinical (purely motor clinical presentation) and common MRI findings (selective pyramidal tract involvement). However sinus thrombosis (vascular Behçet) is much less common and is rarely associated with neuro-Behçet. Which simply means that the parenchymal lesion demonstrated in neuro-Behçet syndrome is a primary neuronal lesion and not secondary to sinus thrombosis (Behçet's disease is a relapsing and remitting, but often progressive, focal meningoencephalitis that most often affects the brain stem). Sinus thrombosis is probably a product of the primary pathology. In general the midbrain lesions characteristic of the primary neural type of Behçet disease can associated with cerebral sinus thrombosis and both the primary parenchymal neural type and the vascular type of Behçet disease can coexist in a single patient, but this uncommon. Vascular Behçet is rarely associated with neuro-Behçet. See fig. 5,6,7,8,9 The predominant histopathological features in the inflamed tissues in Behçet's disease are infiltration of lymphocytes and monocytes, and sometimes polymorph nuclear leukocytes, through small veins without microscopic changes in the vessel walls. Thrombophilia or thrombophlebitis involving small and large veins is also common, whereas arteritis is rare. In these regards, Behçet's disease is unique compared with other vasculitides.

4. The existence of meningeal enhancement in Neuro-Behçet is simply a reflection of a meningitic process that is occasionally present in Behçet disease. The meninges are typically thickened and adherent to the brain surface in neuro-Behçet syndrome, and acutely there may be considerable meningeal inflammation; hence the common reference to neuro-Behçet's disease as a meningoencephalitis. (70).
Table 4. Differences between motor neuron disease and acute neuro-Behçet syndrome, with regard to the corticospinal tract affection

<table>
<thead>
<tr>
<th>The corticospinal tract lesion in neuro-Behçet syndrome</th>
<th>The corticospinal tract lesion in motor neuron disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>The corticospinal tract linear lesion appeared larger in size probably due to the contribution of edema</td>
<td>Smaller in size</td>
</tr>
<tr>
<td>Reversible</td>
<td>Irreversible</td>
</tr>
<tr>
<td>Show contrast enhancement</td>
<td>Does not show contrast enhancement</td>
</tr>
<tr>
<td>Has an acute onset and a regressive course</td>
<td>Has a chronic progressive course</td>
</tr>
<tr>
<td>MRI signal changes are mainly due to reversible vasogenic edema</td>
<td>MRI signal changes are mainly due to Wallerian degeneration</td>
</tr>
</tbody>
</table>

Figure 4. A case with vascular Behcet showing multi-sinus thrombosis

Sometimes an asymmetric subcortical and deep periventricular white matter involvement (involving mainly the posterior limb of the internal capsule) without cortical involvement is observed in neuro-Behcet. In the majority of reported cases with hemispheric involvement, the lesions were located subcortically, particularly within temporal and occipital regions (7–11, 34, 39, 45, 46). In the acute stage the periventricular white matter changes are due to edema, while in the chronic stage these white matter changes are due to wallerian degeneration, gliosis, and demyelination (4, 20, 21, 43, 44, 47, 48).

Vasculitis is regarded as the key feature in neuro-Behçet syndrome (3, 26), as biopsy specimens from mucous and cutaneous lesions show those changes (54, 55). Arterial and venous large vessel involvement, such as narrowing, occlusion, and aneurysmal formation, has been reported in up to 27% to 35% of cases, with 12% arterial and 88% venous (52). An even greater proportion of patients with neuro-Behçet syndrome may have small vessel vasculitis, and recently this has been validated as the pathologic basis of various histologic changes observed in different organ systems (26).
Lesions of arterial origin may be observed in some patients, in whom these lesions, for example, may lie within the pons without crossing the midline, consistent with involvement of the penetrating arteries. Although such lesions, resulting from small or medium-sized intracranial arteries, have been reported either microscopically or radiologically in neuro-Behçet syndrome, they are not as common as the arterial lesions observed with the involvement of other systems (20, 21, 40, 43, 47, 48, 50–52). There are also a few publications concerning the involvement of large intracranial arteries (40, 51–53). Hemorrhagic lesions seen in some patients most likely resulted from "diapedesis of red cells around veins," as already reported, and are not of arterial origin (21).

Autopsy studies and biopsy specimens of the CNS lesions are consistent with vasculitis as well, and they show a clear venous predominance (20, 21, 49). Radiologic studies support this finding that lesions seen in neuro-Behçet syndrome are not compatible with arterial territories. Furthermore, significant perilesional edema with a tendency to disappear or to leave proportionally small residua on follow-up studies has been reported. This feature is consistent with venous infarction, since not all signal intensity changes seen in venous occlusive disease necessarily represent infarction, but rather an accumulation of water within interstitial spaces (56, 57). This information, together with our observations, supports the probable inflammatory-venous pathogenesis for the CNS lesions seen in Behcet’s disease.

| Table 5. Factors that support the probable inflammatory-venous pathogenesis for the CNS lesions seen in neuro-Behçet syndrome |
| Arterial lesions are unilateral and do not cross the middle line, while lesions observed in neuro-Behçet syndrome are frequently bilateral with frequent midline crossing. |
| Autopsy studies and biopsy specimens of the CNS lesions are consistent with vasculitis with a clear venous predominance (20, 21, 49). |
| Significant perilesional edema with a tendency to disappear or to leave proportionally small residua on follow-up studies has been reported. This feature is consistent with venous infarction, since not all signal intensity changes seen in venous occlusive disease necessarily represent infarction, but rather an accumulation of water within interstitial spaces (56, 57). |

If one considers the possible venous territories in which brain stem lesions have occurred in neuro-Behçet syndrome, it is clear that the affected venous structures are indeed small intraaxial veins of the brain stem (58). That particular predilection of occurrence raises the question of why these veins are affected or why occlusion of them causes symptoms. The literature on autopsy studies states no apparent tendency toward these venous channels, and brain stem veins and cerebral hemispherical veins are equally affected, although there is a clear-cut predominance of lesions in the brain stem. The question can also be addressed according to regional hemodynamic properties. It is well known that cerebral hemispherical structures are drained by superficial and deep venous systems, both of which anastomose via medullary veins. They interconnect superficial pial veins to the internal cerebral vein and the basal vein of Rosenthal, the former being more common than the latter (59), whereas in the brain stem, intraparenchymal radial and longitudinal anastomotic channels are nearly absent (58). In the spinal cord, intraaxial anastomoses are
claimed to be prominent at the thoracic level (60). The particular arrangement of veins in
the cerebral hemisphere permits them to flow in both directions via medullary veins, as
seen with certain disorders, such as deep arteriovenous malformations, Sturge-Weber
disease, and the developmental venous anomalies (60), possibly explaining the small
diameter and unimportance of parenchymal lesions when such a vein is thrombosed. At the
mesencephalic, diencephalic, and pontine levels, thrombosis of small veins might be
accompanied by a very large, sometimes hemorrhagic lesion, since there is nearly no
collateral venous pathway. The same anatomic arrangement might also explain the
vulnerability of the cervical spinal cord (7, 44). It appears, therefore, that the variability of
venous anatomic arrangements at different levels of the CNS might explain the predilection
of lesions for different regions.

Vasculitis, like inflammation in other tissues, is caused by many different agents and
pathogenic mechanisms; however, these different causes produce only a limited number of
histologic expressions of injury. The major type of injury to nervous tissue in vasculitis is
ischemia. Therefore, the same clinical manifestations can result from etiologically and
pathogenetically different vasculitic diseases. In vasculitic processes, location, extension,
and distribution of vascular involvement might point to a specific diagnosis, such as
Takayasu or temporal arteritis (26, 61–65). In neuro-Behçet syndrome, lesions therefore
appear secondary to the small vessel venous vasculitis, and the anatomy of those intraaxial
venous structures explains the dominant involvement of the upper brain stem and
diencephalic structures.

Pathologically proved small vessel arteritis, either alone or with venous inflammation, has
also been reported in conjunction with neuro-Behçet syndrome, and it is probable that
some of the cerebral hemisphere and midbrain lesions might result from small vessel
arteritis (62, 63). In this case, there appeared to be at least one lesion that occurred within a
probable pontine arterial territory, and the hemispheric lesions seen in neuro-Behçet
syndrome were not significantly different from the CNS lesions of other vasculopathies of
accepted arteritic origin.

It is possible to explain the selective involvement of the corticospinal fibers observed in this
patient. If the primary pathology in Behçet disease is inflammatory vascular process with
secondary demyelination, then the myelinated fibers in the long tracts will suffer more. The
posterior part of the brain stem is mainly reticular while the anterior part is compact and
is occupied mainly by the pyramid in the cerebral peduncle, crus cerebral and basis pontis.
It is quite illogical to see inflammatory demyelination in the reticular posterior parts of the
brain stem. The inflammatory demyelinating process will affect the anteriorly located long
myelinated fibers in the corticospinal tract.

Vasogenic edema is the most common type of edema associated with brain tumors, venous
congestion and other causes and results from local disruption of the blood brain barrier.
This leads to extravasation of protein-rich filtrate of plasma into the interstitial space, with
subsequent accumulation of vascular fluid. This disruption results from loosening of the
tight junctions between endothelial cells, and the neoformation of pinocytic vesicles. Once
the barrier is breached, hydrostatic and osmotic forces work together to extravasate
intravascular fluid. Once extravasated, fluid is retained outside the vasculature, mostly in the white matter of the brain, and within the bundles of myelinated axons of long tracts and commissural fibers. This is because axons run in parallel bundles of fibres with loose extracellular space (that offer low resistance and facilitates the extension of vasogenic edema along myelinated axons which are spread apart by the edema) as opposed to gray matter, which has high cell density and is enmeshed in an interwoven network of connecting fibres that offer high resistance to the formation and spread of edema. By definition, this type of edema is confined to the extracellular space. (70) In neuro-Behcet case reports of diffusion weighted imaging (DWI) of the T2 hyperintense lesions revealed elevated ADC values compared to normal subjects, indicating restricted diffusion and the presence of vasogenic edema (71,72). Contrast enhancement of the corticospinal tract in this case is due to break down of the blood brain barrier along the course of the corticospinal tract and it is a good sign of vasogenic edema which is mainly due to break down of the blood brain barrier. (70)

Another explanation for the selective involvement of the corticospinal tract in neuro-Behcet is that the signal changes observed in the MRI study is due to vasogenic edema secondary to venous congestion, vasogenic interstitial edema spreads in the white matter along myelinated fibers of long tracts and commissural fibers (This is because axons of long tracts run in parallel bundles of fibres with loose extracellular space that offer low resistance to the formation and spread of edema as opposed to grey matter). The long tracts are anteriorly located within the brain stem in the crus cerebra, cerebral peduncle, and basis pontis. Subsequently brain stem interstitial or vasogenic edema is much more likely to be concentrated anteriorly within the corticospinal tract as vasogenic edema spreads the myelinated fibers apart and extends along them. In the presented case the MRI signal changes were maximum in the upper midbrain and internal capsule, present to a lesser extent in the pons and to a much less extent in the medulla. Anatomically the corticospinal tract remains abundant, compact and in a single bundle as it transverses in the posterior limb of the internal capsule down to the cerebral peduncle (crus cerebri) in the midbrain. The corticospinal and corticobulbar fibers gradually decreases in number as they descend down to the pons, and through the medulla to the spinal cord. Also starting from the level of pons and downward the corticospinal tract starts to fragment into scattered, irregular and isolated bundles. The corticospinal fibers, being more abundant and more compact at the internal capsule and midbrain levels, compared with corticospinal fibers at the level of pons and medulla, would explain why MRI signal changes were maximum in the internal capsule and upper midbrain. However selective involvement of the corticospinal tract in Behcet disease still needs further explanation.

Concerning the differential diagnosis, hemispheric white matter lesions are not common in neuro-Behçet syndrome, and when they are present, they are more likely to be subcortical than periventricular. Furthermore, these are generally associated with brain stem–diencephalic lesions. That combination is unlikely in systemic lupus erythematosus (SLE) and non-Behçet vasculitides. CNS involvement due to SLE and other systemic vasculitis tends to involve arterial territories, and as a result, cortical involvement is frequently observed (34, 66, 67). We have not observed cortical involvement in neuro-Behçet syndrome, despite pathologic studies in which such involvement has been reported (21).
These changes, however, are minor in neuro-Behçet syndrome, which may explain the radiologic-pathologic discrepancy. Periventricular and ovoid lesions suggestive of MS are not expected to be seen in neuro-Behçet syndrome.

Figure 5. Precontrast MRI T1 images showing focal signal hypointensity in the left basis pontis, left crus cerebri (cerebral peduncle) and the posterior limb of the internal capsule. The focal hypointense lesions has no or very mild mass effect and they are apparently continuos cephalocaudally. Contralaterally, the pontine basis is showing a very small hypointense lesion in the right side. The lesions are located in the presumed anatomical area of the corticospinal (pyramidal) tract.
Figure 6. Postcontrast MRI T1 images showing enhancement of the hypointense lesions shown in figure 5 (same patient). The lesion in the right anterior pontine zone is more definite now and is better delineated by contrast enhancement. All enhanced areas are surrounded by a hypointense edema area with mild mass effect. Also notice contrast enhancement of the meningeal covering of the pons and midbrain which indicates the existence of a meningitic element.
Figure 7. Postcontrast coronal MRI T1 images showing that the pontine, midbrain and capsular lesions described in figure 5,6 (same patient) are continuous cephalocaudally as a linear long lesion, the lesion is surrounded by a hypointense edema area and is located in the presumed anatomical area of the corticospinal (pyramidal) tract. The corticospinal tract was actually mapped by contrast enhancement. The contralateral side is involved to a lesser degree. Notice meningeal enhancement which reflects a meningitic element. Contrast enhancement of the corticospinal tract in this case is due to break down of the blood brain barrier along the course of the corticospinal tract and it is a good sign of vasogenic edema which is mainly due to break down of the blood brain barrier (70). Notice middle line crossing of the lesions suggesting its venous rather that arterial origin. Also notice the mild mass effect induced by the pyramidal tract lesion in the left side which could be due to edema.
Figure 8. Postcontrast sagittal MRI T1 images showing that the pontine, midbrain and capsular lesions described in figure 5,6,7 (same patient) are continuous cephalocaudally as a linear long lesion in the anterior parts of the pons and midbrain, the lesion is located in the presumed anatomical area of the corticospinal (pyramidal) tract and is seen surrounded by a hypointense edema area. The corticospinal tract was actually mapped by contrast enhancement. Also notice meningeal enhancement. Thrombosis of the superficial and deep venous systems is also seen.

Figure 9. MRI T2 image showing the capsular lesion (in the posterior limb of the internal capsule), The lesion is mainly hyperintense with some hypointense zones probably representing a hemorrhagic element. (same patient as in figure 5,6,7,8)
Extensive confluent periventricular changes that are seen in MS and occasionally in sarcoidosis are not observed in patients with neuro-Behçet syndrome. Posterior fossa lesions, particularly those located around the fourth ventricle with or without the associated supratentorial lesions seen in MS, are not similar to the neuro-Behçet syndrome lesions described above. Brain stem lesions in MS are usually small, even in the acute stage, and prominent brain stem and/or cerebellar atrophy without cerebral volume loss, which is observed in the chronic phase of neuro-Behçet syndrome, is unusual in MS (7, 34). When one considers cervical involvement, this rarely extends more than a few vertebral segments in MS (68), unlike the more extensive lesions we observed in neuro-Behçet syndrome. Leptomeningeal contrast enhancement is a typical finding of sarcoidosis (69). We did not encounter this finding in patients with neuro-Behçet syndrome. Devlin et al (38) reported abnormal leptomeningeal enhancement in two of their patients with neuro-Behçet syndrome. Abnormal meningeal enhancement secondary to dural venous occlusion or to lumbar puncture should be excluded before attributing it to the disease itself (70).

Table 6. Differences between neuro-Behçet syndrome and other similar diseases

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS lupus versus neuro-Behçet</td>
<td>CNS involvement due to SLE and other systemic vasculitis tends to involve arterial territories, and as a result, cortical involvement is frequently observed (34, 66, 67).</td>
</tr>
<tr>
<td>MS versus neuro-Behçet</td>
<td>Periventricular and ovoid lesions suggestive of MS are not expected to be seen in neuro-Behçet syndrome.</td>
</tr>
<tr>
<td></td>
<td>Extensive confluent periventricular changes that are seen in MS and occasionally in sarcoidosis are not observed in neuro-Behçet syndrome.</td>
</tr>
<tr>
<td></td>
<td>Posterior fossa lesions, particularly those located around the fourth ventricle with or without the associated supratentorial lesions seen in MS, are not similar to the neuro-Behçet syndrome lesions.</td>
</tr>
<tr>
<td></td>
<td>When one considers cervical involvement, this rarely extends more than a few vertebral segments in MS (68), unlike the more extensive lesions observed in neuro-Behçet syndrome.</td>
</tr>
<tr>
<td></td>
<td>Brain stem lesions in MS are usually small, even in the acute stage, and prominent brain stem and/or cerebellar atrophy without cerebral volume loss, which is observed in the chronic phase of neuro-Behçet syndrome, is unusual in MS (7, 34)</td>
</tr>
<tr>
<td></td>
<td>Abnormal meningeal enhancement is unusual in MS and reported in neuro-Behçet syndrome. (38)</td>
</tr>
</tbody>
</table>

Inflammatory demyelinating diseases, such as MS, and inflammatory vascular disorders (vasculitides), such as neuro-Behçet syndrome and SLE, can affect the CNS primarily or secondarily, and onset tends to occur in young adulthood. Although the clinical presentation of these diseases may be similar, the radiologic findings of neuro-Behçet
syndrome are quite distinct, which may help differentiate it from other disorders, even in the absence of overt systemic involvement.

The diagnosis of Behcet's disease is clinical. Patients with Behcet's disease and venous thrombosis are often heterozygotes or homozygotes for the factor V Leiden allele. The CSF in patients with neurologic involvement is typically characterized by a pleocytosis (usually less than 100/mm³) that is equally likely to be neutrophil or lymphocyte predominant. CSF protein is only slightly elevated. There have been reports of intrathecal synthesis of oligoclonal IgA and IgM. An immunofixation electrophoretic pattern of oligoclonal bands has been reported in 16% of patients. Magnetic resonance imaging in patients with CNS disease typically reveals multiple 3-10 mm in diameter sharply marginated, irregular, and often confluent lesions in the spinal cord, brain stem, thalamus, basal ganglia, and deep cerebral white matter. The lesions may be quite extensive. In some cases, they may be difficult to distinguish from those of multiple sclerosis, but Dawson's fingers are not seen. (70)

High-dose corticosteroids (prednisone 60 mg/day) are effective in suppressing skin, mucosal, and arthritic manifestations of Behcet's disease. Pulse corticosteroids (methylprednisolone 1 gm/day for 3 days) are often employed effectively for acute flares of neurologic disease, but the effect of corticosteroid treatment on chronic or recurrent neurologic disease is less satisfactory. Corticosteroids are clearly ineffective in halting the progression of uveitis and chlorambucil; 0.1-0.2 mg/kg/day has been used with considerable success in treating this disabling manifestation. (70) O'Duffy, (3) also induced remission in eight of nine patients with meningoencephalitis using chlorambucil. Azathioprine (Imuran), cyclosporine A, and colchicine have been shown in prospective, randomized studies to be highly effective in halting or preventing the ocular manifestations of Behcet's disease; however, cyclosporine A is relatively contraindicated in the presence of neurologic disease. Acute neurologic symptoms are remarkably reversible and justify aggressive treatment during flares. Patients with cerebral venous thrombosis respond well to chronic anticoagulation without significant risk of intracranial hemorrhage. (70)

Thalidomide (Thalomid) is highly effective in suppressing oral and genital manifestations of Behcet's disease; however, between 6% and 50% of patients develop an axonal sensorimotor polyneuropathy that may be dose related. (70)
Figure 10. Atypical neuro-Behçet lesion in a 30-year-old woman. (a) T1-weighted MR image (500/10) shows a large area of low signal intensity (arrow) in the left parietotemporal lobe. (b) Gadolinium-enhanced T1-weighted MR image (500/10) shows strong enhancement of the masslike lesion, mimicking an abscess. (c) Follow-up MR image obtained after steroid treatment shows a marked decrease in the extent of the lesion (arrow).

SUMMARY

The parenchymal distribution of lesions in neuro-Behçet syndrome seems to support the hypothesis of small vessel vasculitis, mainly venular involvement. The known anatomic arrangement of CNS intraaxial veins explains the predominant involvement of the brain stem structures observed in these patients. This pattern of lesion distribution might help to differentiate neuro-Behçet syndrome from other vasculitides as well as from the inflammatory-demyelinating diseases of the CNS, such as MS. Our experience with neuro-Behçet syndrome has caused us to consider neuro-Behçet syndrome in the differential diagnosis of patients who have brain stem and/or diencephalic lesions that extend along the long tracts and have a tendency to resolve on subsequent imaging studies, whether or not they are associated with periventricular and subcortical lesions. CNS involvement generally manifests several years after the onset of systemic Behcet's disease, but occasionally it may be an initial feature and even precede other disease manifestations. According to the diagnostic criteria of Behcet's disease of the International Study Group's classification (13), it is very difficult to diagnose Behçet disease without oro-genital ulcerations. However and in the author experience, primary parenchymal neuro-Behçet
disease with selective involvement of the corticospinal tract (and with a purely motor clinical presentation) taken together with the characteristic MR imaging findings of selective pyramidal tract involvement are highly suggestive of Behçet disease even if CNS involvement precedes other disease manifestations.

References

diagnosis of Behçet's disease: an analysis of clinicopathologic data from multiple
58. Bracard S, Braun M, Meder JF, Velut S. Anatomie et radioanatomie du systeme
veineux intracranien. Neurochirurgie 1996;42(Suppl 1):11-44
59. Lasjaunias P, Berenstein A. Surgical Neuroangiography. Berlin: Springer;
1990;3:68-80, 240-245
60. Jennette JC, Falk RJ, Milling DM. Pathogenesis of vasculitis. Semin Neurol
1994;14:291-299
61. Harris KC, Tran DD, Sickels WJ, Cornell SH, Yuh WTC. Diagnosing intracranial
vasculitis: the roles of MRI and angiography. AJNR Am J Neuroradiol 1994;15:317-
330
62. Greenan TJ, Grossman RI, Goldberg HI. Cerebral vasculitis: MRI imaging and
64. Cohen BA, Biller J. Hemorrhagic stroke due to cerebral vasculitis and the role of
65. Vermess M, Bernstein RM, Bydder GM, et al. Nuclear magnetic resonance (NMR)
imaging of the brain in systemic lupus erythematosus. J Comput Assist Tomogr
1983;7:461-467
66. Aisen AM, Gabrielsen TO, McCune WJ. MR imaging of systemic lupus
erythematosus involving the brain. AJR Am J Roentgenol 1985;144:1027-1031
sclerosis: relation to clinical subtype and disability. AJNR Am J Neuroradiol
1997;18:1041-1048
Neuroradiol 1997;18:1182-118
69. River Y, Schwartz A, Gomori JM, Soffer D, Siegal T. Clinical significance of diffuse
dural enhancement detected by magnetic resonance imaging. J Neurosurg
1996;85:777-783
70. Metwally, MYM. Textbook of neuroimaging, CD-ROM based publication, in
Metwally (ed), WEB-CD agency for electronic publication, version 8.4a ; 2007
71. Suner NR. Neuro-Behçet's disease: diffusion MR imaging and proton MR
72. Baysal T, Dogan M, Karlidag R, Ozisik HI, Baysal O, Bulut T, Sarac K. Diffusion-
weighted imaging in chronic Behçet patients with and without neurological findings.
74. Kidd D, Steuer A, Denman AM, Rudge P. Neurological complications in Behçet's


The author

Professor Yasser Metwally

www.yassermetwally.com
INTRODUCTION

CNS sarcoidosis is a disease that can involve any part of the CNS, producing varied clinical and MR expressions. It can mimic other neurologic diseases, such as multiple sclerosis, tuberculosis, isolated angiitis of the CNS, and meningioma, and is often indistinguishable from them. Patients with symptoms usually have corresponding CNS lesions on MR images. However, patients with cranial nerve deficits and pituitary dysfunction often have no abnormal findings at routine contrast-enhanced MR imaging. On the other hand, MR findings may be clinically silent. Patients with dura-based lesions, cranial nerve lesions, and, to a lesser degree, nonenhancing brain lesions fared better than did patients with leptomeningeal, brain parenchymal, and spinal lesions. In general, resolution of lesions on MR imaging lags behind resolution of clinical symptoms. The role of MR imaging in
neurosarcoidosis is to confirm clinical suspicion, establish subclinical disease, and document the response of pathologic lesions to treatment.

The pathophysiological mechanism behind sarcoidosis remains elusive. In theory, it is thought to represent an immune-mediated response to an as yet unidentified antigen. Both an acute self-limited course with spontaneous resolution and an insidious, relentless course ultimately resulting in fibrosis have been identified. The disease most commonly afflicts African Americans (female > male) in the third to fourth decade of life but can occur in every race and has a wide age range. (11, 12).

**NEUROLOGIC MANIFESTATIONS & GENERAL ASPECTS OF SARCOIDOSIS**

Sarcoidosis is a multisystem granulomatous disease of unknown etiology. Though first described as a cutaneous disorder, it commonly affects the lungs and other organs. Neurologic manifestations occur usually as a part of the spectrum of the systemic disease. Though relatively uncommon, neurosarcoidosis is a serious disease associated with poor outcome. Much progress has been made in the understanding of the immunopathogenesis, but there is limited knowledge about appropriate therapy, and very little is known of its etiology. The epidemiologic features, immunopathogenesis, and immunomodulatory therapy of neurosarcoidosis do not differ from the systemic disease. Most of the appreciation of neurosarcoidosis is gained from studies involving patients with systemic sarcoidosis, individual case reports, and case series of patients with nervous system disease. Patients with sarcoidosis do not generally undergo neurologic evaluation unless neurologic manifestations are prominent. Most patients with neurosarcoidosis also have other organ systems involved by the inflammatory process. In light of these reasons, it is important to understand the general features of sarcoidosis to evaluate and manage patients with neurosarcoidosis.

Jonathan Hutchinson initially described the cutaneous aspects of the disease, but mistook them for gout. Caesar Boeck subsequently described several patients with similar skin manifestations and called them "sarkoid," because of the resemblance of the histologic features to sarcoma. He emphasized the systemic nature of the disease. Ansgar Kveim and Louis Siltzbach developed a cutaneous test for diagnosis of the disease. Heerfordt in 1909, in his description of "uveoparotid fever," first reported neurologic manifestations in the form of cranial nerve palsies.

In the last 2 decades the understanding of the disease has been improved by several reports that describe the immunopathologic and epidemiologic aspects. It most commonly affects middle-aged adults. The annual incidence rate is 0.85% for whites and 2.4% for blacks, and the prevalence is 40 per 100,000. The highest rates are observed in Swedes, Danes, and African-Americans. The mortality rate in sarcoidosis is 1 % to 5%, mostly because of respiratory failure. Familial studies in African-Americans, and in human leukocyte antigens (HLA) studies, show a higher prevalence of the disease among first-generation relatives of patients with sarcoidosis. The increased risk in particular racial or ethnic populations, familial clustering of cases, and disease association with certain HLA
phenotypes in some countries, argue for the role of genetic factors in the disease process. Spatial, seasonal, and familial clusterings of cases have been observed, suggesting possible transmission of an infective pathogen, common exposure to environmental agents, and genetic factors. Several organisms have been proposed as the causative agents, including viruses, mycobacteria, Borrelia, and, more recently, propionibacterium acnes, but none have shown strong evidence. Noninfectious enviromental agents like aluminum, beryllium, and zirconium are also believed to trigger the disease because of their ability to induce a granulomatous response.

The inflammatory process is associated initially with an accumulation of activated T cells and macrophages that release interferon-γ, interleukin-2 and other cytokines and proinflammatory factors. The T cell antigen receptor (TCR) repertoire in sarcoidosis suggests an interaction of sarcoid antigen with a combination of specific T cell antigen receptor and HLA antigen presentation molecules, which would trigger the immune-mediated inflammatory response. Contrary to earlier views of suppressed immunity, there is now evidence that suggests sarcoidosis is associated with heightened immunity, mediated primarily by CD4+helper cells and macrophages. The immunology of sarcoidosis is associated with a dichotomy of depressed systemic cellular immunity and heightened T lymphocyte activity locally in the affected organs.

The diagnostic histopathologic lesion of sarcoidosis is a noncaseating epitheloid cell granuloma. There is an accumulation of CD4 cells at sites of active inflammation. The inflammatory process is similar in all organs affected by sarcoidosis, including the nervous system. These granulomas resolve spontaneously or with treatment. Persistence of the inflammatory process induces fibrotic changes, resulting in irreversible tissue damage. Similar granulomatous changes are observed in conditions other than sarcoidosis such as some carcinomas, regional lymph nodes of carcinomas, and lymphomatous disorders. About 20% of granulomatous lesions have an undetermined etiology. These clinical syndromes are grouped under the rubric "GLUS" (Granulomatous Lesions of Unknown Significance). The elevated serum angiotensin converting enzyme (SACE) levels noted in sarcoidosis are results of increased release from epitheloid cells derived from macrophages.
Figure 1. A, Sarcoidosis. Many Langhans giant cells (arrows) are seen surrounded by epithelioid histiocytes and an inflammatory reaction. Note absence of caseation necrosis as seen in tuberculosis. B, Sarcoidosis, high power, illustrating multi-nucleated Langhans giant cell (large arrow) and epithelioid cells (small arrows) and dark lymphocytes.

The clinical presentation of sarcoidosis varies with the specific organ involved. The lungs are involved in 90% of patients with sarcoidosis, and the severity ranges from asymptomatic to severe interstitial lung disease. Other organs commonly involved include the lymph nodes (33%), liver (histopathologic abnormalities seen in 50% to 80% of biopsy specimens), skin (25%), eyes (11%-83%), musculoskeletal system (25%- 39%), and endocrine glands. Sarcoidosis in children occurs more commonly in caucasions. The distribution of organ involvement is similar to adults, but is usually associated with a better prognosis. Sarcoidosis does not usually affect the outcome of pregnancy, but the disease may worsen after delivery.
Sarcoidosis is a disease of exclusion. An effective diagnostic approach to sarcoidosis involves accurate clinical assessment of the extent, severity, and nature of the pathology affecting different organs. This is supported by various diagnostic tools and histologic confirmation of the presence of noncaseating granulomata. Developments in diagnostic tools like fiberoptic bronchoscope, bronchoalveolar lavage (BAL), SACE, and imaging techniques have made the diagnostic process more effective and less dangerous.

The natural history and prognosis of the disease vary depending on specific organ involvement and extent, as well as ethnicity and genetic factors. Spontaneous remissions occur in about two thirds of patients, the majority within the first 2 years. Approximately 10% to 20% of sarcoidosis patients develop a chronic form of the disease. Most of the functional disability is from cardiac, ocular, neurologic, or severe pulmonary disease. Serious extrapulmonary involvement is present in 4% to 7% of patients at presentation. Most patients with systemic sarcoidosis improve or stabilize with or without treatment, but relapse occurs in 16% to 74%. The mortality rate varies from 1% to 5%, mainly related to severe pulmonary, cardiac, and neurologic disease.
Sarcoidosis is a granulomatous (mononuclear) inflammatory disease, systemic in scope, of undetermined etiology. While lymphoid tissue is particularly involved, any organ in the head and neck area can be affected, especially lungs, skin, eyes, and salivary glands. Blacks are affected, at least in North American, ten times more often than whites.

Histopathology demonstrates granulomas composed of nodules of epithelioid histiocytes that are non-caseating (unlike tuberculosis). A mixed inflammatory reaction commonly surrounds the granulomas. Langhans type giant cells are common. Special intracytoplasmic inclusions—stellate shapes called asteroid bodies—and also Schaumann bodies (laminated basophilic calcifications) are found. A similar picture may appear in other diseases so that eventually the diagnosis may become a matter of excluding an infectious agent.

An acute presentation is generally considered to be associated with a good outcome. Poor prognostic signs or factors include age at onset > 40 years, black race, lupus pernio, chronic uveitis, chronic hypercalcemia, progressive pulmonary pathology, nasal mucosal disease, bone cysts, cardiac involvement, and neurosarcoidosis. Specific treatment with immunosuppressants is generally held in asymptomatic or mild disease. Corticosteroids were first used as therapeutic agents to treat sarcoidosis in 1951, and they have become the mainstay of current therapy. Systemic corticosteroid treatment is definitely indicated in progressive lung disease, cardiac, eye, or neurologic involvement.

Despite these advances in the understanding of the disease, specific triggering factors are unknown, and a single factor cannot be identified as a cause of the disease. The current evidence suggests that the interaction of environmental factors a genetically susceptible individual is most likely responsible for induction of the disease. It appears that the chronicity of the sarcoid lesions is caused by persistence of an antigenic stimulus and/or an intrinsic dysregulation of the immune systems. Multinucleated giant cells may provide a cellular reservoir for the antigen. There is an ongoing multicenter case-control study by the NIH to address the etiologic mechanisms of sarcoidosis.

**RADIOLOGICAL MANIFESTATIONS OF NEUROSARCOIDOSIS**

- **Dural Thickening/Mass**

Dural/epidural mass lesions has an imaging appearance similar to that of meningioma/epidural lymphoma and are not associated with intraparenchymal extension. Dural/epidural sarcoidosis probably represents blood borne deposits of the disease in the epidural spaces. The annual incidence of these lesions exceeds the annual incidence of meningiomas (2.3 per 100,000) (13) by 130 times. These lesions tend to be isointense with gray matter on T1-weighted MR images and hypointense on T2-weighted images, and they enhance uniformly. This hypointensity on T2-weighted images has been reported
previously (14, 15) and is thought to be related to fibrocollagenous buildup. Unfortunately, this is not a unique finding. Eighteen percent of meningiomas (typically fibroblastic or transitional types) demonstrate low signal on T2-weighted images (16). In addition to meningioma, differential considerations for sarcoidosis involvement of the dura should include other causes of chronic meningitis, such as lymphoma, adenocarcinoma, Wegener's, idiopathic hypertrophic cranial pachymeningitis (IHCP), granulomatous infection, and leukemia. Cheng et al (17) reviewed the cases of 37 patients who underwent biopsy for chronic meningitis. Of the 16 diagnostic biopsies in this study, 31% revealed sarcoidosis and 25% revealed adenocarcinoma. Although most patients with neurosarcoidosis have systemic involvement (2), isolated dural involvement may be confused pathologically with IHCP because both are granulomatous diseases negative for AFB or fungal staining. Unlike IHCP, which tends to manifest more diffuse involvement, dural sarcoidosis is often focal and has nonnecrotizing epithelioid granulomas (18–20).

Figure 3. 33-year-old white woman with chronic headache. A–D, An extraaxial left parietal mass is hypointense on noncontrast T2-weighted MR image (2517/90/1 [TR/TE/excitations]) (A), enhances on contrast-enhanced T1-weighted (533/11/2) image (arrows, B), and is isointense with gray matter on noncontrast T1-weighted image.
Substantial fibrocollagenous material and noncaseating granulomas were seen at biopsy. The patient's symptoms resolved with steroids; however, a T1-weighted image (400/16/2) 28 months later showed only partial regression of the lesion (D).

- **Leptomeningeal Involvement**

Leptomeningeal involvement is best shown on spin-echo contrast-enhanced T1-weighted images (23). Leptomeningeal infiltration typically involves the suprasellar and frontal basal meninges but may occur anywhere and is more concentrated in the depths of the sulci (5). Granulomatous lesions are accompanied by varying degrees of fibrosis and hyalinization (6). Occasionally, granulomas coalesce to form masslike lesions, particularly in the region of the chiasm, floor of the third ventricle, and pituitary stalk (2). Clinical symptoms correlate with the location of the lesion on MR images. Furthermore, it was found that these lesions recur frequently. Disease entities that can involve the basal leptomeninges and mimic leptomeningeal sarcoidosis on imaging include granulomatous disease (such as tuberculosis), Wegener's granulomatosis and fungal meningitis, pyogenic meningitis, leptomeningeal lymphoma, demyelination, meningoangiomatosis, acute lymphocytic leukemia, and leptomeningeal carcinomatosis (10).

![Figure 4. 33-year-old woman with right-sided visual loss, panhypopituitarism, polydipsia, and polyuria (with normal ADH). A and B, T1-weighted contrast-enhanced MR image (400/15/2) (A) shows basal meningeal enhancement and an enhancing pituitary mass involving both lobes, the infundibulum, and the right optic nerve (not shown). Pituitary and meningeal biopsy revealed noncaseating granulomas with negative AFB and fungal stains.](image-url)
The visual symptoms resolved with steroid treatment; however, 21 months later she returned with a left abducens palsy. A T1-weighted image (400/12/2) shows resolution of the pituitary lesion but new involvement of the left cavernous sinus (arrows, B).

The relatively low rate of occurrence of combined dural and leptomeningeal disease in the same location can be explained by the presence of the arachnoid barrier cells. This portion of the arachnoid mater lacks extracellular spaces, has numerous cell junctions, and has a basement membrane separating it from the subarachnoid space. It can thus act to slow down or prevent the infiltration of lymphocytic cells (10, 21).

- **Enhancing Brain Parenchymal Lesions**

The frequent association of intraparenchymal granulomas with small arteries and veins (veins are more affected than arteries) suggests that lesions infiltrate the brain through perivascular Virchow-Robin spaces (6, 24, 25). This usually occurs along the adventitia, but the infiltration may, on occasion, destroy the elastic lamina and encroach on and occlude the vessel lumen, potentially causing infarction (5). It is often difficult to distinguish sarcoidosis angiitis from primary isolated angiitis of the CNS on a histopathologic basis (6, 26, 27). Although no part of the CNS is immune to sarcoidosis, frequently affected brain parenchymal locations include the hypothalamus, brain stem, cerebral hemispheres, and cerebellar hemispheres (5, 6, 24–26, 28). Granulomatous infiltration into the subependymal layers of the ventricular system is thought to be responsible for hydrocephalus associated with neurosarcoidosis (5, 6, 12, 25). Involvement of the pituitary is less common.

The development of neurosarcoidosis is primarily leptomeningeal and vascular in nature. It may result in the disruption of the leptomeningeal blood-brain barrier, which permits the granulomatous infiltrate to enter the brain parenchyma along the so-called perivascular or Virchow-Robin spaces that accompany the penetrating arteries up to the capillaries. Vasculitic lesions and perivascular involvement may cause stenosis, which results in vasculopathy, and multiple granulomas may coalesce to produce intraaxial masses, often with adjacent edema.
Figure 5. Diagram of the arrangement of the leptomeninges in the periarterial spaces (curved arrows) around the perforating brain vessels (based on data derived from references 17-20). The pia matter (thick black arrow) separates the subarachnoid space (closed arrow) from the subpial space (open arrow); the glial basement membrane (thin black arrow) overlies the cerebral cortex (arrowheads delineate the corticomedullary junction). The larger arterioles (A) in the cortex, which supply the deep white matter, have a periarterial layer of leptomeninges that surround a continuous perivascular channel. The small subpial arterioles (B) have no pial sheath. The basal perforating arteries (C1, C2) have two coats of leptomeninges that delineate the perivascular space (as described in the generally accepted concept of the vascular penetration of vessels with a free communication between the perivascular space and the subarachnoid space [C1]), but the perivascular space is, in fact, continuous around the arteries in the subarachnoid space (C2).

Enhancing brain parenchymal lesions commonly start in the subependymal or the pial (leptomeningeal) microvascular systems then invade the brain in a centrifugal or centripetal ways forming multiple enhancing masses in the periventricular or corticomedullary regions. Long standing lesions are commonly associated with tissue destruction, encephalomalacia, reactive astrogliosis and extensive connective tissue formation. These reactive lesions are responsible for the MRI picture of confluent or nonconfluent nonenhancing white matter pathology in the periventricular regions.
Figure 6. 52-year-old man with seizure disorder. Imaging revealed hydrocephalus and a brain parenchymal lesion. His seizures gradually became more difficult to control. A and B, Contrast-enhanced T1-weighted MR images obtained 9 (483/13/2) (A) and 11 (500/16/2) (B) years after seizure onset show interim progression of meningeal thickening (arrows, B) and enlargement and multiplication of enhancing foci (arrowheads, B).

The most common symptom occurring with enhancing brain parenchymal lesions is seizures, although headache, encephalopathy, diabetes insipidus, and hypopituitarism also occur. Seizures have previously been associated with poorer prognosis in neurosarcoidosis (29). Histopathologically, this disease infiltrates via the perivascular spaces to reach the brain parenchyma. It would thus be reasonable to hypothesize that if the disease is revealed by imaging to predominantly involve leptomeninges with little parenchymal involvement, it is at an earlier stage. The clinical course in patients with either leptomeningeal or parenchymal disease is hampered by recurrences or deterioration. Although diabetes insipidus is often identified in neurosarcoidosis, it is frequently associated with a normal vasopressin level, thus implying hypothalamic dysfunction (30).
Figure 7. Midsagittal T1-weighted contrast-enhanced spoiled gradient-echo images (50/12, 45° flip angle) in a 29-year-old man with a 2-year history of sexual impotency and sinusitis that led to the diagnosis of sinonasal sarcoidosis with thoracic involvement. (A) Image obtained before starting the high doses of corticosteroids shows an enlarged enhanced hypothalamus (thick solid arrow), tuber cinereum (thin solid arrow), lamina terminalis of cerebrum (curved arrow), and lateral walls of the third ventricle (arrowheads). There is a thickening of the mucosa (open arrow) of the septum and sphenoidal sinus (*). (B) Image obtained after 4 months of attack treatment shows that the hypothalamic lesions have regressed, but the punctate infundibular thickening (arrow) persists. The lesions described above progressed when the dose of corticosteroids was decreased. These later regressed when high doses were reintroduced. (Follow-up MR images obtained later are not shown.)
Granulomatous angiitis is a frequent finding in sarcoidosis.
- Venous involvement is seen far more frequently than arterial involvement. Granulomas may also be seen in lymphatics.
- Elastic tissue stains are very helpful in identifying these lesions, particularly in small vessels where the lumen is completely obliterated.
- Granulomatous angiitis, although highly characteristic, is not specific for sarcoidosis and may also be seen in infectious granulomatous diseases, Wegener's granulomatosis, foreign body embolization, schistosomiasis, necrotizing sarcoid granulomatosis, and beryllium disease.
Figure 9. 34-year-old man with seizures, dysphagia, and lower extremity weakness. A, T2-weighted MR image (2416/90/1) shows multiple hyperintense lesions in the brain stem and cerebellum as well as the cerebral hemispheres and basal ganglia (not shown), which demonstrated contrast enhancement. B, Biopsy specimen shows atypical lymphoid tissue with noncaseating granulomatous plaques (arrow) and granulomatous perivasculitis (arrowheads) (hematoxylin-eosin). The symptoms and MR abnormalities disappeared 15 months after treatment with steroids and hydroxychloroquine sulfate.

- **Nonenhancing Brain Parenchymal Lesions (Periventricular white matter disease)**

These lesions tend to occur in the periventricular white matter but may also occur in the brain stem and basal ganglia and the corticomedullary junction. Periventricular lesions are nonspecific and can occur in association with multiple sclerosis, hypertension, and vasculitis. Theoretically, they can result from periventricular granulomas or from small areas of infarction caused by granulomatous angiopathy. The exact nature of these lesions has not been identified in the literature. They are not as often associated with leptomeningeal or enhancing brain parenchymal lesions, and we suggest that they could differ pathologically from enhancing lesions that infiltrate basal meninges and associated blood vessels, thus disturbing the blood-brain barrier. Of interest is that elevated oligoclonal bands in the CSF, typically associated with multiple sclerosis, are often seen with neurosarcoidosis as well (31). Symptomatic improvement usually did not correspond to improvement on MR imaging studies. This behavior differed from that of enhancing brain lesions for which symptoms often correlated with imaging findings and symptomatic improvement correlated with regression on MR images. These facts also imply that the nonenhancing brain parenchymal lesions and the enhancing lesions have different pathophysiological mechanisms.

These findings suggest that they are ancient, irreversible lesions. This pattern of evolution has been reported in the literature. These lesions are the chronic glial sequelae of previous inflammatory or ischemic lesions or may be directly due to granulomatous masses. The development of irreversible chronic reactions after inflammation has been previously reported on the basis of the clinical data (2). The large medullary arterioles that supply the whole depth of the white matter are surrounded by a continuous pial channel (23) that correlates well with the deep periarterial draining of the inflammatory cells, which is
presumed to have occurred in the nonenhancing brain parenchymal lesions. These lesions may also be caused by ischemia that ranges from ischemic gliosis to infarction due to invasion of the perivascular space of the perforating vessels by a granuloma (16). These white matter lesions are closely associated with local perivascular enhancement (15).

White matter disease is probably the end stage of a pathological spectrum which starts with leptomenigitis, that is followed by brain parenchymal invasion of the sarcoid granuloma through the virchow robin spaces resulting in inflammatory or ischemic brain lesions (enhancing brain parenchymal lesions). The end result is white matter disease in the periventricular and the corticomedullary regions (nonenhancing brain parenchymal lesions). These white matter lesions are the chronic glial sequelae of previous inflammatory or ischemic lesions or may be directly due to granulomatous masses (White matter disease in neurosarcoidosis most probably represent tissue destruction, encephalomalacia, reactive astrogliosis and extensive connective tissue formation secondary to the long standing previous inflammatory or ischemic lesions). White matter disease is best seen on the MRI T2 and FLAIR studies and is seen as confluent or nonconfluent hyperintense patches in the periventricular and corticomedullary regions. These patches do not show contrast enhancement and have no mass effect.

Table 1. Pathological stages in sarcoidosis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Leptomeningitis</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Enhancing brain parenchymal lesions</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Nonenhancing brain parenchymal lesions</td>
</tr>
</tbody>
</table>
Figure 10. A 30-year-old woman with a 10-year history of thoracic sarcoidosis and weakness who was treated with corticosteroids. (A) Transverse conventional dual-echo intermediate-weighted spin-echo image (2,400/40) obtained at the level of the lateral ventricles shows confluent hyperintense signal abnormalities (arrows) within the periventricular white matter, mainly in the paraatrial areas. (B) Midsagittal T2-weighted fast spin-echo image (2,500/100, four signals acquired) of the cervical spine obtained at the same time as in A shows areas of nonspecific increased signal intensity (arrowheads) within the cord. All lesions showed no contrast enhancement on the corresponding T1-weighted contrast-enhanced spin-echo images (not shown), and on follow-up MR images (not shown) there was no evidence of regression after 4 years of steroid therapy.
A 54-year-old woman with a 30-year history of systemic sarcoidosis with no neurologic symptoms in whom steroid therapy was started because of thoracic and ophthalmologic involvement. Transverse T2-weighted spin-echo image (2,400/100) obtained at the level of the lateral ventricles shows bilateral foci with high signal intensity (arrows) in the white matter near the cortex in the frontal and parietal lobes. All lesions showed no contrast enhancement on the corresponding T1-weighted contrast-enhanced spin-echo images (not shown), and on follow-up MR images (not shown) there was no evidence of regression after 18 months of steroid therapy.

Note

- These MR imaging features and the ability of neurosarcoidosis to cause multivisceral vasculitis suggest that these parenchymal lesions are microarteriolar ischemic complications consistent with true neurosarcoid vasculitis. These foci are predominantly present in the corticomedullary junction and the periventricular gray matter (thalamus and basal ganglia). They could be linked to the infiltration of the entire wall of small leptomeningeal vessels, which led to thrombotic occlusion and to the surrounding patchy areas of ischemic tissue. The small subpial blood vessels entering the cortex have no layer of pial cells, and the perivascular spaces around the capillaries are obliterated by the fusion of the endothelial and glial basement membranes. This prevents the perivascular draining of the inflammatory cells into the subcortical white matter that is supplied by the terminal twigs of the longest cortical arterioles.

- These abnormal hyperintense foci at the corticomedullary junction or the periventricular gray matter on T2-weighted images are nonspecific. They can be seen in a variety of noninflammatory and inflammatory disorders, including granulomatous vasculitis of the nervous system, also known as primary vasculitis of the central nervous system. Histopathologically, primary vasculitis of the CNS is very similar to neurosarcoid vasculitis. Primary vasculitis of the CNS has a special predilection for the small leptomeningeal vessels and may appear with prominent leptomeningeal enhancement and minimal parenchymal findings on MR images.

- Similarly, these vasculitic lesions in sarcoidosis are initially those of leptomeningeal vasculopathy in which there had been no perivascular propagation of the granulomatous
process into the brain. There could also be an association between the enhanced hyperintense white matter foci and another systemic nonspecific thrombus-inducing pathophysiologic mechanism, such as circulating antiphospholipid antibodies. The presence of antiphospholipid antibodies in disseminated sarcoidosis and similar white matter abnormalities in patients with nonsystemic lupus erythematosus and with antiphospholipid antibodies support this hypothesis. An increased frequency of focal white matter lesions has also been described in patients with inflammatory bowel disease.

Figure 12. A. Sequential MR images in a 32-year-old woman with a 4-year history of systemic sarcoidosis with uveitis who was treated with corticosteroids. (A) Transverse T2-weighted spin-echo image (2,400/100) obtained at the level of the lateral ventricles shows confluent areas of hyperintensity (arrowheads) within the periventricular white matter and multifocal areas of hyperintensity (arrows) within the subcortical white matter. No enhanced lesion was observed on the corresponding T1-weighted contrast-enhanced spin-echo images (not shown). (B) Coronal T1-weighted contrast-enhanced spin-echo image (550/18) obtained after 2 years of treatment with minimal doses of corticosteroids shows nonenhanced demyelinated lesions (arrowheads) just above the bodies of the lateral ventricles and micronodular enhanced lesions (arrows) in the subcortical and deep white matter. This patient later showed complete regression of the enhanced lesions on T1-weighted contrast-enhanced spin-echo images obtained when high doses of corticosteroids were reintroduced (not shown).
Figure 13. MR images in a 36-year-old woman with a 7-year history of systemic sarcoidosis who had undergone steroid therapy and who had facial nerve palsy and aseptic lymphocytic meningitis. (A) Transverse T2-weighted spin-echo image (2,400/100) at the level of the lateral ventricles shows multifocal hyperintense areas (arrows) within the peripheral white matter. A new frontal lesion appeared when this image was compared with initial MR images (not shown). All lesions showed no contrast enhancement on corresponding T1-weighted contrast-enhanced spin-echo images (not shown). (B) Transverse T1-weighted contrast-enhanced spine-echo image (550/18) of the brainstem obtained at the same time as the image in A demonstrates the development of pial involvement, which is recognized by a thin linear area of enhancement (arrowheads) that surrounds the pons.

- Cranial Nerve Involvement

Involvement of every cranial nerve has been described in association with sarcoidosis (2). Most frequently, the facial nerve is involved clinically. The annual incidence of Bell's palsy in the general population is 25 per 100,000 (32). In patients with sarcoidosis, it is 14 times that. Imaging, however, revealed that the optic nerve and/or chiasm are the most frequently affected cranial nerves.
Clinical and imaging cranial nerve involvement frequently do not concur, and, furthermore, clinical resolution often does not imply imaging resolution. Although most patients showed response to steroids, patients with optic nerve involvement often had residual symptoms or no response to treatment. We conjecture that this may be related to the fact that other cranial nerves are surrounded by Schwann cells, which can regenerate more readily than can oligodendroglial myelin, thus allowing for more effective regeneration of function (9).

Cranial nerve involvement is not well understood. Pathologic examination has revealed perivascular and intraneural lymphocytic infiltration (33). Nerve root and cranial nerve involvement are caused by compressive effects from adjacent granulomas (4).

Figure 14. Sequential MR images in a 48-year-old man with a 5-year history of parenchymal neurosarcoidosis who had been and was treated with corticosteroids. (A) Transverse T1-weighted contrast-enhanced spin-echo image (550/18) obtained before starting the follow-up MR imaging to adapt the corticosteroid regimen shows micronodular enhanced lesions (straight arrows) in the right basal ganglia and along the margin of the lateral ventricle (arrowheads) in the regions supplied by the lateral striate arteries. There is an ischemic lacuna (curved arrow). (B) Transverse T1-weighted contrast-enhanced spin-echo image (550/18) obtained at the same level as in a 6 years after the start
of long-term maintenance corticosteroid therapy shows a decrease in the marked contrast enhancement (arrows) depicted in A.

- Spinal Cord and Nerve Root Involvement

Spinal cord and nerve root involvement has been reported as an unusual manifestation of sarcoidosis. Furthermore, the majority of the patients are male. This is especially interesting because sarcoidosis more frequently affects females. Most patients improve with steroid or cyclophosphamide (Cytoxan) administration; however, long-term steroid dependence with episodes of recurrence associated with tapering the administration can occur in patients with cord lesions. Improvement on MR images might lag behind steroid treatment. A review of the literature by Nagai et al (34) found that early treatment with steroids can result in remarkable recovery; however, with a delayed diagnosis and treatment, the disease typically only partially resolves and may recur. Nagai et al additionally commented that decompressive laminectomy as well as lysis of adhesions may also benefit the patient.

Figure 15. 36-year-old man with gradual onset of weakness, numbness, spasticity, and bowel and bladder dysfunction. A–C, T1-weighted MR image (450/15/2) (A) shows intramedullary enhancement and enhancement along the surface of the cord, associated with cord signal abnormality and disk herniation on T2-weighted fast spin-echo image (B). The patient underwent surgical diskectomy and initially did worse. His symptoms and the findings on a T2-weighted fast spin-echo image (3000/102/2) (C) improved with steroids, but recurred 5 months later.
Histopathologic specimens have shown granuloma formation with lymphocytic infiltrates. Lesions usually have an extramedullary component; however, pure intramedullary tumors have been described (35). The lesions have been found to represent granulomatous meningitis with nodular studding infiltrating the perivascular space and forming intramedullary granulomas (34). Lesions have been reported to occur throughout the spinal cord but more frequently in the cervical spine (34, 36). At imaging, they manifest cord swelling, with increased signal intensity on long TR images and a pattern of enhancement that predominates in the periphery of the cord but includes patchy multifocal enhancement of the cord. Imaging findings are thus nonspecific and can mimic multiple sclerosis, cord tumor, vacuolar myelopathy, tuberculosis, or fungal infection (36–39). Junger et al (38) hypothesized that patients with spinal cord sarcoidosis progress in four phases, which begin with a linear leptomeningeal pattern of enhancement and progress to a phase in which there is cord enlargement with faint enhancement or no enhancement. Enhancement then progresses but the cord begins to reduce in size until it reaches a final stage of atrophy without any enhancement. Although it is fairly evident that patients who present with cord atrophy will most likely not respond to steroid treatment, it is unclear whether the degree of enhancement plays a role in treatment response.
<table>
<thead>
<tr>
<th>Type of lesions</th>
<th>Comment</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dural Thickening/Mass</td>
<td>Dural/epidural mass lesions has an imaging appearance similar to that of meningioma/epidural lymphoma and are not associated with intraparenchymal extension. These lesions tend to be isointense with gray matter on T1-weighted MR images and hypointense on T2-weighted images, and they enhance uniformly. This hypointensity on T2-weighted images has been reported previously (14, 15) and is thought to be related to fibrocollagenous buildup.</td>
<td></td>
</tr>
<tr>
<td>Leptomeningeal Involvement</td>
<td>Leptomeningeal involvement is best shown on spin-echo contrast-enhanced T1-weighted images (23). Leptomeningeal infiltration typically involves the suprasellar and frontal basal meninges but may occur anywhere and is more concentrated in the depths of the sulci (5). Granulomatous lesions are accompanied by varying degrees of fibrosis and hyalinization (6). Occasionally, granulomas coalesce to form masslike lesions, particularly in the region of the chiasm, floor of the third ventricle, and pituitary stalk (2). Clinical symptoms correlate with the location of the lesion on MR images. Furthermore, it was found that these lesions recur frequently. Disease entities that can involve the basal leptomeninges and mimic leptomeningeal sarcoidosis on imaging include granulomatous disease (such as tuberculosis), Wegener's granulomatosis and fungal meningitis, pyogenic meningitis, leptomeningeal lymphoma, demyelination, meningoangiomatosis, acute lymphocytic leukemia, and leptomeningeal carcinomatosis (10).</td>
<td></td>
</tr>
<tr>
<td>Enhancing Brain Parenchymal Lesions</td>
<td>The frequent association of intraparenchymal granulomas with small arteries and veins (veins are more affected that arteries) suggests that lesions infiltrate the brain through perivascular Virchow-Robin spaces (6, 24, 25). This usually occurs along the adventitia, but the infiltration may, on occasion, destroy the elastic lamina and encroach on and occlude the vessel lumen, potentially causing infarction (5). It is often difficult to distinguish sarcoidosis angiitis from primary isolated angiitis of the CNS on a histopathologic basis (6, 26, 27). Although no part of the CNS is immune to sarcoidosis, frequently affected brain parenchymal locations include the hypothalamus, brain stem, cerebral hemispheres, and cerebellar hemispheres (5, 6, 24–26, 28). Granulomatous infiltration into the subependymal layers of the ventricular system is thought to be responsible for hydrocephalus associated with neurosarcoidosis (5, 6, 12, 25). Involvement of the pituitary is less common.</td>
<td></td>
</tr>
<tr>
<td>Nonenhancing Brain Parenchymal Lesions (Periventricular)</td>
<td>These lesions tend to occur in the periventricular white matter but may also occur in the brain stem and basal ganglia and the corticomedullary junction. Periventricular lesions are nonspecific and can occur in association with multiple sclerosis, hypertension, and vasculitis. Theoretically, they can result from periventricular granulomas or from</td>
<td></td>
</tr>
</tbody>
</table>
### Stage 3

White matter disease) small areas of infarction caused by granulomatous angiopathy. The exact nature of these lesions has not been identified in the literature. They are not as often associated with leptomeningeal or enhancing brain parenchymal lesions, and we suggest that they could differ pathologically from enhancing lesions that infiltrate basal meninges and associated blood vessels, thus disturbing the blood-brain barrier. Of interest is that elevated oligoclonal bands in the CSF, typically associated with multiple sclerosis, are often seen with neurosarcoidosis as well (31). Symptomatic improvement usually did not correspond to improvement on MR imaging studies. This behavior differed from that of enhancing brain lesions for which symptoms often correlated with imaging findings and symptomatic improvement correlated with regression on MR images. These facts also imply that the nonenhancing brain parenchymal lesions and the enhancing lesions have different pathophysiologic mechanisms.

### Cranial Nerve Involvement

Involvement of every cranial nerve has been described in association with sarcoidosis (2). Most frequently, the facial nerve is involved clinically. The annual incidence of Bell's palsy in the general population is 25 per 100,000 (32). In patients with sarcoidosis, it is 14 times that. Imaging, however, revealed that the optic nerve and/or chiasm are the most frequently affected cranial nerves.

### Spinal Cord and Nerve Root Involvement

Spinal cord and nerve root involvement has been reported as an unusual manifestation of sarcoidosis. Furthermore, the majority of the patients are male. This is especially interesting because sarcoidosis more frequently affects females. Most patients improve with steroid or cyclophosphamide (Cytoxan) administration; however, long-term steroid dependence with episodes of recurrence associated with tapering the administration can occur in patients with cord lesions.

### References


The Author

Professor Yasser Metwally

www.yassermetwally.com
TUBEROUS SCLEROSIS

Tuberous sclerosis is a heritable disorder characterized by the development of early in childhood of hamartomas, malformations and congenital tumours of the CNS, skin and viscera. The pathological changes of tuberous sclerosis are widespread and include lesions in the brain, skin, bone, retina, skin and others. Clinically it is characterized by the occurrence of epilepsy, mental retardation and adenoma sebaceous in various combination.

Tuberous sclerosis (TS) is one of the most common phakomatoses. Its occurrence is around 1-20:500,000 births, and Donegani et al., based on autopsy records, estimate its
prevalence at 1:10,000. Ahlsen et al. in a study carried out in Sweden on a population up to 20 years old, observed a prevalence of 1: 12,900 with a peak of 1:6,800 in the 11-15-year age group. TS is inherited as an autosomal dominant disorder with high penetrance and variable expressivity, with no racial or sexual predilection. As many as 60% of cases have been described as sporadic, resulting from spontaneous genetic mutations in the offspring of healthy parents. The number of true sporadic cases is now decreasing as the parents of affected children undergo ocular fundoscopy and renal and cardiac echography. TS, like every phakomatosis, can be defined as a primary cytologic dysgenesis. The genetic disorder has been identified, with the TSCI and TSC2 genes localized respectively on chromosome 9 band q 34.3 and chromosome 16 band p 13.3. Nevertheless, a specific molecular marker that would allow recognition of the asymptomatic and quasi-asymptomatic cases has not yet been found. The genetic disorder is inherited, with the TSCI and TSC2 genes localized respectively on chromosome 9 band q 34.3 and chromosome 16 band p 13.3. Nevertheless, a specific molecular marker that would allow recognition of the asymptomatic and quasi-asymptomatic cases has not yet been found. The genetic disorder has been identified, with the TSCI and TSC2 genes localized respectively on chromosome 9 band q 34.3 and chromosome 16 band p 13.3. Nevertheless, a specific molecular marker that would allow recognition of the asymptomatic and quasi-asymptomatic cases has not yet been found. 

TS is a multiorgan disease (skin, retina, lungs, heart, skeleton, and kidneys) involving the embryonic ectoderm, mesoderm, and endoderm. The central nervous system (CNS) is always affected, and CNS disease is often the first indicator of the disorder. The primary anomaly of TS is an abnormal differentiation and growth of the neuronal and glial cells, associated with migration anomalies and disorganization of the cortical architecture, formation of tumor-like cell clusters [hamartias or hamartomas according to Gomez], and rarely neoplasia. The presence of cell dysplasia, however, differentiates phakomatoses from CNS malformations.

- Genetic causes

TSC is inherited in an autosomal dominant pattern. An affected parent has a 50% chance of transmitting the disease to offspring. There are a significant number of sporadic mutations, estimated to occur in approximately two thirds of cases.

Two genes, TSCI and TSC2, have been identified. TSCI is located on chromosome 9 and was identified in 1997. This gene encodes for the protein hamartin. The protein tuberin is encoded by the gene TSC2. TSC2, located on chromosome 16, was the first TSC gene discovered in 1993. Approximately 50% of cases are due to TSCI, and the remaining 50% are due to TSC2. Of sporadic cases, 75% are due to a mutation in the TSC2 gene.

**Table 1. Genetics of tuberous sclerosis**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene Location</th>
<th>Gene Product</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSCI</td>
<td>Chromosome 9</td>
<td>Hamartin</td>
<td>Recent findings support the hypothesis that the TSC2 gene and perhaps the TSCI gene act as tumor suppressors. When the TSC mutation occurs, the defective gene product of the TSC mutation is unable to suppress the tumor growth caused by a random somatic cell mutation that produces an oncogene stimulating the formation and growth of hamartomas.</td>
</tr>
<tr>
<td>TSC2</td>
<td>Chromosome 16</td>
<td>Tuberin</td>
<td></td>
</tr>
</tbody>
</table>
At the present time, TSC is a clinical diagnosis, because genetic testing currently is not routinely available. Genetic mutation analysis is available on a research basis. Family members may also be tested on a clinical basis if a mutation is detected. Information regarding this topic is available at the following website: www.geneclinics.org

Criteria for germline mosaicism have recently been outlined. Parents who have no evidence of either major or minor criteria of TSC and also have 2 or more children affected with TSC are said to meet the criteria for germline mosaicism. For this reason, parents who have none of the manifestations of TSC but do have 1 child affected with TSC should be counseled about a 1-2% chance of having another child affected with TSC. The incidence of germline mosaicism is estimated to be approximately 10-25%.

**RADIOLOGICAL PATHOLOGY OF TUBEROUS SCLEROSIS**

Pathologically tuberous sclerosis is characterized by the presence of Cortical tubers, Subependymal nodule, Giant cell astrocytoma, White matter lesions and Deep white matter lesions.

**Table 2. Pathology of tuberous sclerosis**

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cortical tubers</strong></td>
<td>They involve gray matter and contiguous white matter. Sometimes two or more adjacent gyri are affected. They may cause gyral broadening and thickening. At histlogic examination the laminar architecture of affected cortex is completely disorganized. Normal neurons and normal glial cells are scanty and abundant undifferentiated neuroepithelial cells and atypical neuron-like cells are observed, with rare clusters of abnormal bizarre glial cells. The subcortical white matter adjacent to a cortical tubers is abnormal, and is usually with defective myelination of neural fibers and gliosis. The cortical tubers surface is smooth but becomes depressed due to degenerative phenomena with cellular loss in the affected cortex. Dystrophic calcifications are infrequently present in cortical tubers.</td>
</tr>
<tr>
<td><strong>Subependymal nodule</strong></td>
<td>Typically located in the subependymal walls of the lateral ventricles, usually bilateral and mainly at the foramina of Monro. subependymal nodules have never been observed in the third ventricle. Their number and size are quite variable. Subependymal nodules contain the same kind of cell abnormalities as cortical tubers, but with very many large, bizarre glial cells, fusiform cells, and undifferentiated neuroectodermal cells. However, neuron-like cells are scant. Much vascular and fibroglial stroma with accumulations of calcium deposits is often found. Focal hemorrhages and necrosis have also been reported.</td>
</tr>
<tr>
<td><strong>Giant cell astrocytoma</strong></td>
<td>Subependymal Giant-Cell Astrocytomas are clinically and histopathologically benign. They grow slowly, have no surrounding edema, are noninvasive, and rarely show malignant degeneration. There are no qualitative histopathologic differences between subependymal</td>
</tr>
</tbody>
</table>
nodules and Subependymal Giant-Cell Astrocytomas. Like subependymal nodules, Subependymal Giant-Cell Astrocytomas contain large amounts of undifferentiated giant cells or abnormally differentiated cells resembling astrocytes or spongioblasts, together with a few abnormal neurons. The fibrovascular stroma contains dystrophic calcifications and cystic or necrotic areas of degeneration. Subependymal Giant-Cell Astrocytomas may originate from subependymal nodules located near the foramen of Monro. Recent findings support the hypothesis that the TSC2 gene and perhaps the TSC1 gene act as tumor suppressors. When the TSC mutation occurs, the defective gene product of the TSC mutation is unable to suppress the tumor growth caused by a random somatic cell mutation that produces an oncogene stimulating the formation and growth of hamartomas.

**White matter lesions**

Radial curvilinear bands, straight or wedge-shaped bands, and nodular foci were found. Radial white matter lesions run from the ventricle through the cerebral mantle to the normal cortex or cortical tuber, wedge-shaped white matter lesions have their apex near the ventricle and their base at the cortex or at the cortical tuber, and nodular foci are located in the deep white matter. White matter lesions are composed of clusters of dysplastic giant and heterotopic cells, with gliosis and abnormal nerve fiber myelination. These anomalies are almost identical to those of the inner core of the cortical tubers. The site, shape, and histopathologic findings of white matter lesions confirm that TSC is a disorder of both histogenesis and cell migration.

**Deep white matter lesions**

These are focal, single or multiple lesions, always in the deep or periventricular white matter.

- **Cortical tubers**

Tuberous sclerosis histopathological features are not dissimilar to those of cortical dysplasia. In tuberous sclerosis, however, severe gliosis may be noted in the subpial area.

In tuberous sclerosis, the most common clinical presentation is seizure, occurring in more than 80% of cases. The brain characteristically reveals multiple nodules ("tuber") in the crest of cerebral gyri. The nodules are generally most abundant in the frontal lobe. The involved cortex is firm in consistency and shows some blurring of the junction between the cortex and white matter. Histologically, the subpial area is thickened by proliferating astrocytes that may be large and bizarre with abundant processes. Laminar organization of the cortex is obscured by numerous large, irregularly oriented neurons with coarsely granular Nissl substance. In addition, there are, large cells with abundant, pale cytoplasm and large, round nuclei with prominent nucleoli. These cells are free of Nissl substance and some seem to be of astrocytic lineage because of their GFAP immunopositivity. They are more frequently found in the white matter, occasionally arranged in clusters. Overall, these features are not dissimilar to those of cortical dysplasia of Taylor. In tuberous sclerosis, however, severe gliosis may be noted in the subpial area.
Figure 1. Postmortem specimens showing cortical tubers, the affected gyri are abnormally broad and flat.
Figure 2. A,B CT scan precontrast and C, CT scan postcontrast study, D,E,F precontrast MRI T1 images, G,H,I MRI T2 images. Notice the calcified cortical tuber in the left frontal region. The tuber is hyperdense in CT scan studies and hypointense on the MRI T2 studies (due to calcification). The precontrast T1 hyperintensity observed in the subcortical white matter in (E,F,G) could be due to defective myelination. The cerebral cortex appears lissencephalic and pachygyric especially over the frontal lobes. The cortical tubers surface is smooth but depressed due to degenerative phenomena with cellular loss in the affected cortex. The subcortical white matter adjacent to the cortical tubers shows the characteristic radial white matter lesions, they are wedge-shaped white matter lesions with their apex near the ventricle and their base at the cortex or at the cortical tuber. These white matter lesions are hyperintense on the T2 MRI images and hypointense on the MRI T1 images. They can also be seen as hypodense regions in CT scan studies. Radial white
matter lesions are dysplastic heterotopic neurons seen as migration lines running though the cerebral mantle to a normal cortex or a cortical tuber. Subependymal nodules are also seen in (F) forming what is called candle guttering.

Cortical tubers involve gray matter and contiguous white matter. Sometimes two or more adjacent gyri are affected. They may cause gyral broadening and thickening. On MRI, the affected cortex is frequently pseudopachygyric, but the gray matter does not show signal abnormalities on both short and long TR SE images. At histologic examination the laminar architecture of affected cortex is completely disorganized. Normal neurons and normal glial cells are scanty and abundant undifferentiated neuroepithelial cells and atypical neuron-like cells are observed, with rare clusters of abnormal bizarre glial cells. The high cortical cellularity implies a free water loss in gray matter, and this explains the normality of the MR signal.

Figure 3. MRI T1 images (A,B,C,D) and MRI T2 images (E,F). A case of tuberous sclerosis, notice that cortical tubers have broad, irregular, and slightly depressed surface and most marked in the frontoparietal regions. The brain is lissencephalic and pachygyric. Also notice the characteristic radial white matter lesions, they are wedge-shaped white matter lesions with their apex near the ventricle and their base at the cortex or at the cortical tuber. These white matter lesion are hyperintense on the T2 MRI images and hypointense on the MRI T1 images. Radial white matter lesions are dysplastic heterotopic neurons seen as migration lines running though the cerebral mantle to a normal cortex or a cortical tuber. Some of these lesions are seen in (F) forming what is called candle guttering.
The precontrast T1 hyperintensity observed in the subcortical white matter in (E) could be due to defective myelination or hypercellularity (Normal neurons and normal glial cells are scanty and abundant undifferentiated neuroepithelial cells and atypical neuron-like cells are seen as migration lines running through the cerebral mantle to a normal cortex or a cortical tuber, these neurons might have a high nuclear to cytoplasmic ratio, with little extracellular water resulting in precontrast T1 hyperintensity and T2 hypointensity).

However, the subcortical white matter MR signal is abnormal adjacent to a cortical tuber, and is usually hyperintense on long TR SE images. This is due to defective myelination of neural fibers and gliosis. The subcortical white matter in newborns and very young infants appears hyperintense on TIWI and hypointense on T2WI. This can be explained by a greater amount of free water in the unmyelinated white matter compared to the inner core of the cortical tubers. The cortical tubers surface is smooth but becomes depressed due to degenerative phenomena with cellular loss in the affected cortex. Dystrophic calcifications cause marked focal hypointensity on T2WI. This is not common in cortical tubers. Signal enhancement on TIWI after GD-DTPA administration is reported in less than 5% of cases. Follow-up MRI might show an increase in the number and/or size, or increase of signal enhancement after GD-DTPA of cortical tubers.

Figure 4. Postmortem specimens showing cortical tubers with flat surface

- Subependymal nodule

Typically located in the subependymal walls of the lateral ventricles, usually bilateral and mainly at the foramina of Monro. Subependymal nodules have never been observed in the third ventricle. Their number is quite variable in each patient, and their size from a few millimeters to over 1 cm. Subependymal nodules contain the same kind of cell abnormalities as cortical tubers, but with very many large, bizarre glial cells, fusiform cells, and undifferentiated neuroectodermal cells. However, neuron-like cells are scant. Much vascular and fibroglial stroma with accumulations of calcium deposits is often found. Focal hemorrhages and necrosis have also been reported.
Figure 5. Postmortem specimens showing cortical tubers in A and subependymal tubers in B.

Figure 6. CT scan precontrast showing subependymal calcified nodules projecting into the ventricular cavity (candle guttering).
The brain is usually normal in size, but several or many hard nodules occur on the surface of the cortex or along the subependymal covering of the ventricular system. These nodules are smooth, rounded or polygonal and project slightly above the surface of the neighboring cortex. They are whitish in colour and firm.

Histopathologically, the nodules are characterized by the presence of a cluster of atypical glial cells in the center and giant cells in the periphery. The nodules are frequently, but not necessarily, calcified. These nodules occasionally give rise to giant cell astrocytoma when they are large in size.

On MRI, the subependymal nodules appear to impinge on the ventricular cavity from the subependymal walls. Their signal depends mainly on the presence and amount of mineral deposits. If calcifications are widespread, subependymal nodules are very hypointense in all pulse sequences, occasionally surrounded by a hyperintense rim on long TR; otherwise, they are usually isointense to white matter on short TR and slightly hyperintense on long TR.\textsuperscript{3,12} Calcifications are rare in newborns and infants, making diagnosis difficult both by CT and MRI.\textsuperscript{14} However, in children over I year and in
adults, calcification of the stroma is usual, and CT, owing to its greater ability to detect
calcium, has been considered best for assessment of subependymal nodules. Nevertheless,
MR gradient echo pulse sequences with short flip angle are equally useful because of the
magnetic susceptibility of calcified lesions, which appear profoundly hypointense. After
contrast medium, subependymal nodules do not enhance on CT, whereas on MRI they
show nodular or annular hyperintensity. This may be due to higher MRI sensitivity and
also to enhancement of uncalcified gliovascular stroma after GD-DTPA administration,
while the calcified component remains markedly hypointense.

The tuberous sclerosis nodules are variable in size and might attain a huge size. On sectioning
the brain, sclerotic nodules may be found in the subcortical gray matter, the white matter and the
basal ganglia. The lining of the lateral ventricles is frequently the site of numerous small nodules
that project into the ventricular cavity (candle gutterings). Sclerotic nodules are characteristically
found in or near the foramen of monro and commonly induce hydrocephalus. The cerebellum,
brain stem, and spinal cord are less frequently involved.

Figure 9. (A,B) In tuberous sclerosis the lining of the lateral ventricles is frequently the site
of numerous small nodules that project into the ventricular cavity (candle gutterings) (blue
arrows in A). Also notice cortical tubers (black arrow in A)

- Giant cell astrocytoma

The subependymal giant cell astrocytoma (SGCA) is another low-grade (WHO grade 1)
astrocytic neoplasm. This neoplasm is most commonly seen (>90%) in association with
clinical or radiologic evidence for tuberous sclerosis. Tuberous sclerosis is an autosomal
dominant phakomatosis, characterized by disseminated hamartomas of the CNS, kidneys,
skin, and bone. True neoplasms also occur, with approximately 15% of patients developing
SGCA. The tumor is sometimes called the intraventricular tumor of tuberous sclerosis. The lesion usually presents in the teens or 20s.

Subependymal Giant-Cell Astrocytomas are clinically and histopathologically benign. They grow slowly, have no surrounding edema, are noninvasive, and rarely show malignant degeneration. There are no qualitative histopathologic differences between subependymal nodules and Subependymal Giant-Cell Astrocytomas. Like subependymal nodules, Subependymal Giant-Cell Astrocytomas contain large amounts of undifferentiated giant cells or abnormally differentiated cells resembling astrocytes or spongioblasts, together with a few abnormal neurons. The fibrovascular stroma contains dystrophic calcifications and cystic or necrotic areas of degeneration. Subependymal Giant-Cell Astrocytomas may originate from subependymal nodules located near the foramen of Monro.

Figure 10. Close-up view of the frontal horn of the left lateral ventricle, showing a giant cell astrocytoma filling the anterior horn in a 15-year-old boy with tuberous sclerosis.

On MRI, uncalcified Subependymal giant-cell astrocytomas are isointense to white matter on short TR images: calcified components are hypointense. On long TR images the signal increases in the parenchymal component of the lesion, whereas calcifications become profoundly hypointense on T2WI. Serpentine, linear, or punctate signal voids believed to be due to dilated tumor vessels. Subependymal Giant-Cell Astrocytomas enhance on CT after iodinated contrast medium administration, whereas subependymal nodules do not increase in density. This was believed to be due to a breakdown of the blood-brain barrier in the Subependymal Giant-Cell Astrocytomas, and therefore CT was considered best for differential diagnosis. Both Subependymal Giant-Cell Astrocytomas and subependymal nodules located at the foramen of Monro show nodular enhancement on MRI after GD-DTPA. Recent findings support the hypothesis that the TSC2 gene and perhaps the TSC I gene act as tumor suppressors. When the TSC mutation occurs, the defective gene product of the TSC mutation is unable to suppress the tumor growth caused by a random somatic cell mutation that produces an oncogene stimulating the formation and growth of hamartomas.
Figure 11. Giant cell astrocytoma.

Figure 12. Subependymal giant cell astrocytoma. Axial T1-weighted gadolinium-enhanced MR image (A) and postcontrast CT scan (B) show a well-demarcated intraventricular mass in the left frontal horn at the foramen of Monro. The lesion is growing into the ventricle as a polypoid lesion, attached to the head of the caudate nucleus.

Grossly the lesion is a well-demarcated mass. It is almost always in the lateral ventricle, near the foramen of Monro. The lesion is fixed to the head of the caudate nucleus but does not spread through it. As the name implies, an intact layer of ependyma covers the tumor. Thus cerebrospinal fluid dissemination and spread through the brain are not typical. Histologically the lesion contains giant cells that have been variously described as astrocytes, neuronal derivatives, or something in between. The histology is distinctive and may suggest not only this particular tumor, but also the association with tuberous sclerosis that is so common. Calcification is frequent.
The appearance of SGCA on imaging studies is usually typical, characteristic, and almost pathognomonic. First, most patients show other features of tuberous sclerosis, including cortical tubers and subependymal modules. Second, the tumor location is almost unique-intraventricular, near the foramen of Monro, and attached to the head of the caudate nucleus. Enhancement is often present on both CT and MR. Calcification is common and may be in the form of irregular chunks and nodules. The lesion has a polypoid shape as it protrudes into the lumen of the lateral ventricle. Secondary changes of hydrocephalus, from obstruction of the foramen of Monro, are frequent. Ventricular enlargement may be unilateral (on the side of the tumor) or bilateral.

- **White matter lesions**

White matter lesions are dysplastic heterotopic neurons seen as migration lines running from though the cerebral mantle to a normal cortex or a cortical tuber. They are wedge-shaped with their apex near the ventricle and their base at the cortex or at the cortical tuber. Gliosis is commonly present in white matter lesion of tuberous sclerosis.  

Radial curvilinear bands, straight or wedge-shaped bands, and nodular foci are found. Radial white matter lesions run from the ventricle through the cerebral mantle to the normal cortex or cortical tuber, wedge-shaped white matter lesions have their apex near the ventricle and their base at the cortex or at the cortical tuber, and nodular foci are located in the deep white matter.

White matter lesions are composed of clusters of dysplastic giant and heterotopic cells, with gliosis and abnormal nerve fiber myelination.  These anomalies are almost identical to those of the inner core of the cortical tubers. Therefore, on MRI, the white matter lesions are similarly hyperintense on long TR and isointense or hypointense on short TR images. No signal enhancement with GD-DTPA contrast WAS found. The site, shape, and histopathologic findings of white matter lesions confirm that TSC is a disorder of both histogenesis and cell migration. Heterogeneous gray structures in the white matter without calcification may also be present.
- **Deep white matter lesions**

These are focal, single or multiple lesions, always in the deep or periventricular white matter. On MRI they are isointense to the cerebrospinal fluid in all pulse sequences, sometimes surrounded by a hyperintense rim on T2WI, without mass effect.

### Table 3. Summary of radiological signs in tuberous sclerosis

#### MRI or CT scan of the brain

- An MRI of the brain is recommended for the detection and follow-up of cortical tubers, Subependymal nodule, and giant cell astrocytoma. Perform MRI during the initial diagnostic work-up and also every 1-3 years in children with TSC. The MRI may be performed less frequently in adults without lesions and as clinically indicated in adults with lesions. Also, perform an MRI in family members if their physical examinations are negative or not definitive for a diagnosis. MRI is preferred over CT scan due to improved visualization and no risk of radiation with repeat examinations.

- Cortical tubers, best detected on T2-weighted images, often occur in the gray-white junction. On T2-weighted images, they have increased signal and often are in wedged (tuber) or linear shapes (radial migration lines). Conversely, they have decreased signal uptake on T1-weighted imaging. Previously thought to be pathognomonic, they no longer are considered specific for TSC since isolated cortical dysplasia may have a similar radiographic appearance. There appears to be a correlation between the number of tubers on MRI and severity of mental retardation or seizures.

- Subependymal nodules (SEN) are located in the ventricles and often become calcified. The lesions are detected best by CT scan, although they sometimes are noted on MRI or plain film if calcified. They give a candle-dripping appearance.

- Subependymal nodule may grow and give rise to a giant cell astrocytoma. A giant cell astrocytoma may cause obstruction with evidence of hydrocephalus or mass effect in some patients. These lesions usually appear in the region of the foramen of Monro, are partially calcified, and often are larger than 2 cm. Detection of a giant cell astrocytoma is slightly more sensitive with MRI than CT scan.

- **Tuberous sclerosis as a disorder of neuronal cell proliferation, differentiation and migration**

Tuberous sclerosis is a primary cell dysplasia resulting from embryonic ectoderm, mesoderm, and endoderm anomalies. In the CNS they involve neuroepithelial cells, which also show disordered cell migration and organization. All the lesions are hamartias or hamartomas, and histologic differences among them are slight and quantitative; therefore, all of these lesions may change with time. The arrest of cell migration at different stages explains the different sites of the various anomalies. Subependymal nodules and
periventricular white matter anomalies reflect a failure of migration, white matter lesions an interruption, and cortical tubers an abnormal completion of migration with disordered cortical architecture. Subependymal giant-cell astrocytomas are the only neoplastic growth, and they derive from subependymal nodules that have some proliferative potential.

Disorders such as tuberous sclerosis, in which both tumor development and areas of cortical dysplasia are seen, might be a differentiation disorder. The brain manifestations of this disorder include hamartomas of the subependymal layer, areas of cortical migration abnormalities (tubers, cortical dysgenesis), and the development of giant-cell astrocytomas in upwards of 5% of affected patients. Two genes for tuberous sclerosis have been identified: TSC1 (encodes for Hamartin) has been localized to 9q34, and TSC2 (encodes for Tuberin) has been localized to 16p13.3.

Table 4. Tuberous sclerosis as a disorder of neuronal cell proliferation, differentiation and migration

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subependymal nodules and periventricular white matter anomalies.</td>
<td>Failure of migration.</td>
</tr>
<tr>
<td>White matter lesion</td>
<td>An interruption of migration.</td>
</tr>
<tr>
<td>Cortical tubers.</td>
<td>An abnormal completion of migration with disordered cortical architecture.</td>
</tr>
<tr>
<td>Subependymal giant-cell astrocytomas (the only neoplastic growth)</td>
<td>They derive from subependymal nodules that have some proliferative potential.</td>
</tr>
</tbody>
</table>

- Overview of normal neuronal migration

At the most rostral end of the neural tube in the 40- to 41-day-old fetus, the first mature neurons, Cajal-Retzius cells, begin the complex trip to the cortical surface. Cajal-Retzius cells, subplate neurons, and corticopetal nerve fibers form a preplate. The neurons generated in the proliferative phase of neurodevelopment represent billions of cells poised to begin the trip to the cortical surface and to form the cortical plate. These neurons accomplish this task by attaching to and migrating along radial glial in a process known as radial migration or by somal translocation in a neuronal process. The radial glia extend from the ventricle to the cortical surface. In the process of migration, the deepest layer of the cortical plate migrates and deposits before the other layers. Therefore, the first neurons to arrive at the future cortex are layer VI neurons. More superficial layers of cortex then are formed—the neurons of layer V migrate and pass the neurons of layer VI; the same process occurs for layers IV, III, and II. The cortex therefore is formed in an inside-out fashion.
A possible mode of movement in neuronal migration on glia would be the attachment of the neuroblast to a matrix secreted by either the glia or the neurons. The attachment of the neuron would be through integrin receptors, cytoskeletal-linking membrane-bound recognition sites for adhesion molecules. That attachment serves as a stronghold for the leading process and soma of the migrating neuron. Neuron movement on radial glia involves an extension of a leading process, neural outgrowth having an orderly arrangement of microtubules. Shortening of the leading process owing to depolymerization or shifts of microtubules may result in movement of the soma relative to the attachment points. This theory of movement of neurons also must include a phase of detachment from the matrix at certain sites, so that the neuron can navigate successfully along as much as 6 cm of developing cortex (the maximum estimated distance of radial migration of a neuron in the human). Finally, the movement of cells must stop at the appropriate location, the boundary between layer I and the forming cortical plate. Therefore, some stop signal must be given for the migrating neuron to detach from the radial glia and begin to differentiate into a cortical neuron. Perhaps that signal is reelin, a protein that is disrupted in the mouse mutant Reeler and is expressed solely in the Cajal Retzius cells at this phase of development.

REFERENCES


60. Kotagal P, Rothner AD: Epilepsy in the setting of neurocutaneous syndromes. Epilepsia 34 (suppl 3):S71- S78, 1993


Professor Yasser Metwally

www.yassermetwally.com
INTRODUCTION

WG is a systemic disease characterized by the triad of granulomatous lesions of the upper and lower respiratory tract, focal segmental glomerulonephritis, and disseminated necrotizing vasculitis. Clinical features are detailed in Table 1. Most patients present with symptoms and signs referable to the upper respiratory tract, and most will have concurrent evidence of lower respiratory tract involvement, sometimes subclinical. This is now referred to as initial phase or limited disease. After a median delay of 5 months, the systemic phase of the disease appears, marked by systemic necrotizing vasculitis, preferentially involving small arterioles, capillaries and post-capillary venules, and crescentic glomerulonephritis, with rapid progression to renal failure.
# Table 1. CLINICAL FEATURES OF WEGENER'S GRANULOMATOSIS

<table>
<thead>
<tr>
<th>Feature</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male: female ratio</td>
<td>1.2:1</td>
</tr>
<tr>
<td>Age range (mean)(years)</td>
<td>9-83(41-50)</td>
</tr>
<tr>
<td><strong>Signs and Symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>• Fever (%)</td>
<td>50</td>
</tr>
<tr>
<td>• Anorexia and weight loss (%)</td>
<td>35</td>
</tr>
<tr>
<td>• Sinusitis (%)</td>
<td>61-85</td>
</tr>
<tr>
<td>• Otitis media</td>
<td>32-42</td>
</tr>
<tr>
<td>• Eye manifestations (orbital pseudotumor, 41-52 episcleritis, scleritis, uveitis, retinitis [%])</td>
<td></td>
</tr>
<tr>
<td>• Cough (%)</td>
<td>20-28</td>
</tr>
<tr>
<td>• Pleuritis (%)</td>
<td>67</td>
</tr>
<tr>
<td>• Nodules/infiltrates on chest radiograph</td>
<td>11-30</td>
</tr>
<tr>
<td>• Hemoptysis (%)</td>
<td>45</td>
</tr>
<tr>
<td>• Skin lesions (palpable purpura, papules, 67 vesicles, ulcers, nodules</td>
<td></td>
</tr>
<tr>
<td>• Arthralgias/arthritis (%)</td>
<td>29</td>
</tr>
<tr>
<td>• Neurologic manifestations</td>
<td>15</td>
</tr>
<tr>
<td>• Peripheral nervous system</td>
<td>8</td>
</tr>
<tr>
<td>• Central nervous system (%)</td>
<td>39-45</td>
</tr>
<tr>
<td><strong>System Involvement</strong></td>
<td></td>
</tr>
<tr>
<td>• Respiratory tract</td>
<td></td>
</tr>
<tr>
<td>• Upper (%)</td>
<td>90</td>
</tr>
</tbody>
</table>
Neurologic involvement (Table 2) may occur in any phase of the disease, and particular neurologic features reflect the particular pathologic process involved: direct invasion of paranasal and para-aural tissues by the granulomatous process, "metastasis" of the granulomatous process to sites within the CNS that are not contiguous with the upper airways, and necrotizing vasculitis. Direct invasion of the orbit and temporal bone appears to account for orbital pseudotumor with associated involvement of extraocular muscles, the optic and oculomotor nerves, and deafness caused by labyrinthine involvement-as well as destruction of the seventh and eighth cranial nerves; however, most cranial nerve palsies, as well as pituitary damage, appear to reflect granulomatous basilar meningitis, reflecting "metastatic disease" that is not contiguous with disease of the upper airways. This pachymeningitis can extend well up over the cerebral convexity or along the falx or tentorium and can account for "cerebritis" associated with seizures and focal neurologic deficits. (1) It may also involve the spinal canal, producing myelopathy. Vasculitis offers the best explanation for peripheral neuropathy, which, like the neuropathy of PAN, is characteristically a mononeuritis multiplex. Vasculitis also offers a plausible explanation of ischemic stroke and intracerebral and subarachnoid hemorrhage (rare), and has been pathologically demonstrated in a number of cases.

Table 2. NEUROLOGIC MANIFESTATIONS OF WEGENER'S GRANULOMATOSIS.
Drachman, † Nishino et al, ‡

- Exophthalmos 12%
- Any cranial neuropathy 6%
- Ophthalmoplegia 3-5%
- Optic nerve or chiasm involvement 7%
- Pituitary involvement, diabetes insipidus 4%
- Cranial nerve VII palsy 4%
- Vestibular involvement or deafness 3%
- Involvement of base of brain, meninges 7%
- Cerebrovascular events 4%
- Ischemic stroke 3%
- Venous thrombosis 1%
- Intracerebral hemorrhage 3%
- Subarachnoid hemorrhage 2%
- Cerebritis 1.5%
- Seizures 3%
- Neuropathy 16%
  - Mononeuritis multiplex 13%
  - Polyneuropathy 8%
- Myopathy 4%

---

- **Etiology and Pathogenesis**

The etiology of WG remains uncertain; however, a number of observations implicate ANCA, in conjunction with intercurrent infection, in the pathogenesis. The proposed mechanism is as follows: infection leads to the production of cytokines such as interleukins 1 and 8 and tumor necrosis factor alpha, which cause neutrophils to express adhesion molecules (leading them to stick to vascular endothelium), and to express proteins that provide the targets for ANCA (proteinase 3 and myeloperoxidase, among others). Circulating ANCA then binds to these proteins and induces neutrophil degranulation, generation of oxygen-free radicals, and endothelial cell injury. The presence of ANCA, regardless of the specific underlying disease, is strongly associated with the human leukocyte antigens (HLA) allele DQB*0301. By this mechanism, infection might potentiate disease activity in WG, and there is compelling empirical evidence that this occurs.

- **Diagnosis**

Despite the peculiar and seemingly pathognomonic nature of the WG clinical triad, the often prolonged initial phase of the disease and its somewhat protean nature provide the basis for a broad differential diagnosis, which includes many other vasculitides; relapsing polychondritis; lethal midline granuloma (nasopharyngeal disease, which may be caused by a limited and locally aggressive form of WG, B-cell lymphoma, and a limited form of lymphomatoid granulomatosis, also termed polymorphic reticulosis, actually a T-cell lymphoma); systemic lymphomatoid granulomatosis; sarcoidosis; eosinophilic pneumonia; and a host of infectious diseases such as tuberculosis, fungal diseases, syphilis, rhinoscleroma, and leprosy. Routine laboratory abnormalities (anemia, leukocytosis, thrombocytosis, low titer rheumatoid factor) are nonspecific. The most helpful serologic test is an assay for cytoplasm or C-ANCA (related to antibodies to the serine proteinase, proteinase-3), which is 98% specific, and in active, generalized WG, has a sensitivity of 96%. Sensitivity drops to 65% in initial phase or inactive disease. In contrast, antiperinuclear or P-ANCA (related primarily to antibodies to myeloperoxidase) is associated primarily with MPA and AG. Tissue diagnosis (lung, renal, or sural nerve biopsy) is often necessary.

The diagnosis of WG is strongly supported by the histologic features of granulomatous inflammation and vasculitis in the resected tissue mass, coupled with the finding of positive cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA).
Figure 1. Wegener granulomatosis. Histologic sections of the dura in a patient with Wegener’s granulomatosis showed permeation by a dense, diffuse and focally nodular granulomatous infiltrate composed of histiocytes, lymphocytes, plasma cells, scattered multinucleate giant cells (arrows), eosinophils and neutrophils. The polymorphous infiltrate showed no cytologic features of malignancy. In several areas the granulomatous infiltration is clearly vasocentric and focally small blood vessels showed fibrinoid necrosis with intramural neutrophils and karyorrhectic debris, and petechial hemorrhage. An elastic tissue stain (Verhoeff-van Gieson) showed fragmentation of the elastica, confirming the impression of a vasculitic granulomatous process. Special stains for bacteria, mycobacteria, and fungi were negative.

NEUROIMAGING FINDINGS IN WEGENER'S GRANULOMATOSIS

- **Pachymeningeal Enhancement**

In Wegener granulomatosis, the meninges are considered to be abnormal (involved by the disease) if they showed either diffuse or focal thickening on contrast-enhanced MR images. Involvement of both the tentorium cerebelli and the dura overlying the convexity of the cerebrum might occur in combination, however the tentorium cerebelli might be the sole site of involvement. In Wegener granulomatosis the condition is primarily pachymeningitis and leptomeningeal involvement by the disease is only very rarely demonstrated. Two distinct MRI patterns of distribution of meningeal involvement are noted in Wegener granulomatosis (See table 3)
Table 3. *Wegener granulomatosis types*

<table>
<thead>
<tr>
<th>Type</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease contiguous with disease of the upper airways.</td>
<td>• Focal dural thickening and enhancement adjacent and/or contiguous with orbital, nasal, or paranasal disease. This represent direct invasion of paranasal and para-aural tissues by the granulomatous process. Direct invasion of the orbit and temporal bone appears to account for orbital pseudotumor with associated involvement of extraocular muscles, the optic and oculomotor nerves, and deafness caused by labyrinthine involvement. Focal dural thickening might be nodular or linear. Nodular dural thickening might produce a mass that might require surgical decompression.</td>
</tr>
<tr>
<td>Disease not contiguous with disease of the upper airways.</td>
<td>• Diffusely abnormal meninges unrelated to sinus or orbital disease reflecting &quot;metastatic disease&quot; that is not contiguous with disease of the upper airways. This pachymeningitis (primarily dural involvement) can extend well up over the cerebral convexity or along the falx or tentorium and can account for &quot;cerebritis&quot; associated with seizures and focal neurologic deficits. It may also involve the spinal canal, producing myelopathy. Dural involvement might be asymmetric or symmetric The dura overlying the spinal cord might be involved in a similar fashion. Dural biopsy is diagnostic of Wegener granulomatosis. Severe headache is the reason for referral for MR imaging in meningeal involvement.</td>
</tr>
</tbody>
</table>
Figure 2. (a) Transverse and (b) coronal T1-weighted contrast-enhanced spin-echo MR images (500/9) demonstrate diffuse symmetric linear dural thickening and enhancement (arrowheads).
Two distinct patterns of abnormal meningeal enhancement may be observed on intravenous gadolinium-enhanced MR imaging. Dural (i.e., pachymeningeal) enhancement follows the inner contour of the calvaria, whereas pial-subarachnoid (i.e., leptomeningeal) enhancement extends into the depths of the cerebral and cerebellar sulci and fissures. Enhancement surrounding the brain stem is always of the pial-subarachnoid space type because the arachnoid mater is clearly separated from the pia by the intervening basal subarachnoid cisterns in this region. Although leptomeningeal enhancement has been shown to occur more commonly in the setting of meningitis than with neoplastic involvement, inflammatory and neoplastic processes may appear similar or identical on imaging studies. A diffuse, thin, regular sheetlike enhancing appearance over the surface of the brain favors an inflammatory cause, whereas irregular, nodular meningeal enhancement occurs more commonly, although not exclusively, with neoplastic subarachnoid dissemination.

Figure 3. (a) Sagittal and (b) transverse T1-weighted contrast-enhanced spin-echo MR images (500/9) show extensive thickening and enhancement of the dura (arrows) overlying the thoracic spinal cord.
Figure 4. A, Coronal fat-suppressed T1-weighted contrast-enhanced spin-echo MR image (500/9) demonstrates focal thickening and enhancement of the dura (arrows) overlying the inferior aspect of both frontal lobes and contiguous with extensive nasal and paranasal disease. B, Transverse fat-suppressed T1-weighted contrast-enhanced spin-echo MR image (500/9) shows thickening and enhancement of the dura overlying the anterior left temporal lobe (arrows) contiguous with extensive paranasal disease.
Figure 5. A-C, MR images in a case of Wegener's granulomatosis with intracranial involvement and meningeal involvement.

Figure 6. Wegener granulomatosis. MRI T1 postcontrast images showing chronic inflammatory reaction involving the orbital fat, extraocular muscles, and lacrimal gland (A). Notice leptomeningitis demonstrated as meningeal contrast enhancement with brain edema (probably due to cerebritis). Biopsy confirmed the diagnosis in this case.
Nonhemorrhagic infarcts that affected the cortex, white matter, or both, in a typical vascular distribution might be seen in Wegener granulomatosis. Multiple infarctions can occur. Ischemic brain lesions might be related to cerebral vasculitis.

- Nonspecific White Matter Lesions

Nonspecific white matter lesions with high signal intensity on intermediate-weighted and T2-weighted images are occasionally seen in Wegener granulomatosis. These lesions can be multiple and are commonly seen in the periventricular, subcortical regions, the basal ganglia, the mesencephalon and pons. White matter disease - in Wegener granulomatosis- is probably ischemic in nature.
- **Discrete Parenchymal granulomas**

Discrete parenchymal lesions with high signal intensity on intermediate-weighted and T2-weighted images, low signal intensity on T1-weighted images, and some peripheral enhancement on gadolinium-enhanced images are occasionally demonstrated in Wegener granulomatosis.
Figure 9. Transverse T2-weighted fast spin-echo MR image (3,000/105 [effective]) in a patient with gradual onset of ataxia shows a discrete right cerebellar lesion (arrow) with high signal intensity. An intracerebral granulomatous lesion was thought to be the most likely cause because of the location, gradual onset of symptoms, peripheral enhancement, and improvement in ataxia and reduction in the size of the lesion after treatment.

- **Pituitary Abnormalities**

Enhancement and/or enlargement of the pituitary gland are occasionally demonstrated in Wegener granulomatosis. The enhancement is commonly homogeneous with thickening and/or enhancement of the infundibulum, especially superiorly. The pituitary involvement can occur by direct invasion of the granulomatous disease from the sphenoidal sinus or secondary to basal pachymeningitis. Diabetes insipidus can occur when the pituitary gland is involved.
Figure 10. Coronal T1-weighted contrast-enhanced spin-echo MR image (500/9) in a patient with diabetes insipidus shows diffuse enlargement of the pituitary gland (straight arrows) with thickening and enhancement of the infundibulum (curved arrows). There also is filling and rim enhancement (arrowheads) in the sphenoid sinuses, consistent with inflammatory disease.

- Cerebral and cerebellar Atrophy

Cerebral atrophy that is more marked than expected given the patients age can be demonstrated in Wegener granulomatosis. Cerebral atrophy usually ranges from mild to moderate. Atrophy can also involve the cerebellum. Patients with cerebral atrophy commonly have symptoms suggestive of cerebral vasculitis, including peculiar intellectual affect, headaches, confusion, and transient neurologic events such as paraesthesia, blackouts, and visual loss.
Table 4. Types of CNS involvement in Wegener granulomatosi

<table>
<thead>
<tr>
<th>Type</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pachymeningeal Enhancement</strong></td>
<td>In Wegener granulomatosis, the meninges are considered to be abnormal (involved by the disease) if they showed either diffuse or focal thickening on contrast-enhanced MR images. Involvement of both the tentorium cerebelli and the dura overlying the convexity of the cerebrum might occur in combination, however the tentorium cerebelli might be the sole site of involvement.</td>
</tr>
<tr>
<td><strong>Infarcts</strong></td>
<td>Nonhemorrhagic infarcts that affected the cortex, white matter, or both, in a typical vascular distribution might be seen in Wegener granulomatosis. Multiple infarctions can occur. Ischemic brain lesions might be related to cerebral vasculitis.</td>
</tr>
<tr>
<td><strong>Nonspecific White Matter Lesions</strong></td>
<td>Nonspecific white matter lesions with high signal intensity on intermediate-weighted and T2-weighted images are occasionally seen in Wegener granulomatosis. These lesions can be multiple and are commonly seen in the periventricular, subcortical regions, the basal ganglia, the mesencephalon and pons. White matter disease in Wegener granulomatosis is probably ischemic in nature.</td>
</tr>
<tr>
<td><strong>Pituitary Abnormalities</strong></td>
<td>Enhancement and/or enlargement of the pituitary gland are occasionally demonstrated in Wegener granulomatosis. The enhancement is commonly homogeneous with thickening and/or enhancement of the infundibulum, especially superiorly.</td>
</tr>
<tr>
<td><strong>Cerebral and cerebellar Atrophy</strong></td>
<td>Cerebral atrophy that is more marked than expected given the patients age can be demonstrated in Wegener granulomatosis. Cerebral atrophy usually ranges from mild to moderate. Atrophy can involve the cerebellum.</td>
</tr>
</tbody>
</table>

**DISCUSSION**

In a 1963 literature review of 104 patients with Wegener granulomatosis, Drachman (5) identified three processes of nervous system involvement. First, vasculitis occurred in 29 (28%) patients and produced mononeuritis multiplex, polyneuritis, myopathy, intracerebral hemorrhage, subarachnoid hemorrhage, and cerebral arterial or venous thrombosis. Second, granulomatous lesions resulting from contiguous invasion from nasal, paranasal, or orbital disease and involving the optic nerve, optic chiasm, pituitary, nasal vestibule, base of the brain, and meninges were present in 27 (26%) patients. Third, granulomatous lesions remote from nasal granulomas and involving the meninges, cranial nerves, brain, and parietal bone were described in four (4%) patients.

Because cerebral and meningeal involvement by Wegener granulomatosis is rare, with a reported prevalence of 2%–8% (1,4,6), there are few reports of small series (7,8) in which the MR imaging appearances were described. Asmus et al (7) reported the MR imaging
findings in seven patients: Six patients had small, sometimes multiple, focal areas of increased signal intensity in the white matter on T2-weighted images, and one had an infarct. Provenzale and Allen (8) reported the computed tomographic (two patients) and MR imaging (five patients) findings in seven patients, which included dural thickening and contrast enhancement in three patients, infarcts in two, areas of high signal intensity in the white matter on T2-weighted MR images in two, and abnormal high signal intensity in the brainstem on T2-weighted MR images in two. Direct intracranial spread from nasal, paranasal, or orbital disease or remote, discrete granulomatous lesions in brain parenchyma were not reported in either series.

Remote granulomatous involvement of the meninges in Wegener granulomatosis is rare (4–6,10). At postmortem examination in one of 104 patients in Drachman's review (5), meningeal involvement by a necrotic and granulomatous process was observed. Nishino et al (6,10) reported that only one of 324 patients with Wegener granulomatosis had thickening and enhancement of the right tentorium cerebelli, which caused multiple cranial neuropathies and severe headaches. None of 85 patients described by Fauci et al (4) had meningeal involvement with Wegener granulomatosis. The typical MR imaging appearance is that of bilateral diffuse symmetric linear dural thickening and enhancement. Such findings were described by Provenzale and Allen (8) in three patients, although focal and nodular thickening have also been previously reported (11). Large areas of high signal intensity in the white matter underlying thickened meninges on T2-weighted images have been previously noted (11,12). Diffuse dural thickening and enhancement might occur both intracranially and overlying the thoracic cord. Spinal dural thickening might produce myelopathy. There is one previous report (10) of dural thickening overlying the thoracic cord in a case of Wegener granulomatosis, and this resulted in a subacute myelopathy.

Leptomeningeal thickening and enhancement overlying the sulci in addition to dural enhancement is quite rare and to our knowledge, this radiologic finding has rarely been reported, although thickening, fibrosis, and numerous granulomas that often surround the involved blood vessels, as seen at histologic examination of the pia-arachnoid, have been reported (11).

The differential diagnosis for diffuse symmetric linear meningeal thickening is broad and includes neurosarcoid, primary dural tumors such as lymphoma and meningioma, metastases, infectious meningitis, neurosyphilis, and hypertrophic cranial pachymeningitis. In neurosarcoid, the pia is involved more frequently than the dura (13). Clinical evaluation and laboratory and radiologic investigations help the radiologist determine the most likely diagnosis, although biopsy may be necessary for confirmation.

Direct intracranial invasion from adjacent extracranial disease has been reported (5,14) to be the most common means by which the central nervous system is involved with Wegener granulomatosis. This commonly occurs as extensive nasal, paranasal, or orbital disease spreading intracranially to adjacent dura.

The ability to acquire multiplanar images without irradiating the eyes makes MR imaging an excellent modality for demonstration of subtle intracranial spread from nasal,
paranasal, or orbital disease. Because thickened dura can be difficult to differentiate from cerebrospinal fluid on T2-weighted images, we advocate the use of fat-suppressed T1-weighted MR imaging with gadolinium enhancement when direct spread is suspected.

Vasculitis most frequently affects the peripheral nervous system, causing mononeuritis multiplex or polyneuritis; it involves the brain or meninges in 0%–6% of patients, causing intracerebral hemorrhage, subarachnoid hemorrhage, and cerebral arterial or venous thrombosis (4–6). These hemorrhagic complications are thought to be secondary to weakening of blood vessel walls by means of an inflammatory vasculitis, resulting in vessel rupture and bleeding. Patients with WG might have symptoms suggestive of vasculitis, such as altered consciousness or altered affect, or symptoms suggestive of ischemic episodes, such as paraesthesia, blackouts, or internuclear ophthalmoplegia.

Patients with WG might have nonspecific areas of high signal intensity were seen in the white matter on intermediate-weighted and T2-weighted MR images and most probably these white matter lesions are ischemic in nature and this is consistent with vasculitic granulomatous nature of WG. There are several other possible causes of infarct in cases of Wegener granulomatosis: arterial occlusion secondary to a granulomatous mass that extends from nasal or paranasal sites into the skull base (15), emboli from marantic endocarditis (8), infarct secondary to renal failure–induced hypertension, and other causes unrelated to Wegener granulomatosis.

Remote granulomatous lesions in brain parenchyma are the least common form of central nervous system involvement with Wegener granulomatosis (5), although there have been a few reported cases (16–18). Patients may present with seizures, and the lesions may be single or multiple (17,18). Homogeneous and ring enhancement have been demonstrated, and the lesions have high signal intensity on T2-weighted MR images and have been shown to either decrease in size or disappear with treatment (17). Cerebral granulomas have been found to be dark brown, scarred, indurated, and poorly demarcated at surgery and to contain plasma cells, lymphocytes, histiocytes, and giant cells at histologic examination (18).

Multiple nonspecific lesions with increased signal intensity on intermediate-weighted and T2-weighted MR images are seen in the white matter in many conditions, including postinfectious encephalitis, viral infections, sarcoidosis, multiple sclerosis, Behçet syndrome, and the leukodystrophies, and are commonly seen in the elderly. This white matter pathology might have ischemic aetiology and this is supported by the pathological impression that granulomatous infiltration in WG is clearly vasocentric (Fig. 1c) and focally - in white matter lesions- small blood vessels commonly show fibrinoid necrosis with intramural neutrophils and karyorrhectic debris.

However the exact etiology of white matter lesions in relation to Wegener granulomatosis is unclear. Similar white matter lesions in cases of Wegener granulomatosis have also been reported by Provenzale and Allen (8) and Asmus et al (7). Asmus et al reported that these areas represented areas of microinfarct, and Drachman (5) reported the postmortem examination finding of small (<4 x 6-mm) areas of infarct in the thalamus, cortex,
mesencephalon, pons, and subcortical white matter in a patient with cerebral vasculitis secondary to Wegener granulomatosis.

The pituitary and infundibulum may be involved in Wegener granulomatosis by means of distant granulomas or direct spread. Four patients in Drachman's series (5) had involvement of the pituitary gland due to direct extension from nasal, paranasal, or orbital disease that caused diabetes insipidus. Czarnecki and Spickler (19) reported a case of diabetes insipidus and hyperprolactinemia; this was probably secondary to remote granulomatous involvement with Wegener granulomatosis because there was no evidence of direct extension from extracranial disease. MR imaging demonstrated a sellar mass, absence of the posterior pituitary high-signal-intensity spot, and thickening and enhancement of the infundibulum, with almost complete resolution of findings at repeat imaging performed 2 months after treatment with high-dose steroid therapy (19). In general in patients with diffuse enlargement of the pituitary gland and infundibular thickening, it is impossible to be certain whether this represented distal granulomatous involvement with Wegener granulomatosis or direct spread from extensive inflammatory changes in the sphenoid sinus, even when floor of the pituitary fossa appears to be intact in both patients.

Finally, the exact etiology of brain atrophy in cases of Wegener granulomatosis is unclear, but possible explanations include cerebral vasculitis, drugs used in treatment (eg, steroids), and other unrelated causes such as senile atrophy. Yamashita et al (20) reported the development of cerebral atrophy over 6 months in a patient with cerebral vasculitis secondary to Wegener granulomatosis.

In summary, in patients with cerebral and meningeal involvement with Wegener granulomatosis, there is a wide spectrum of MR imaging findings, which reflect the three means by which the central nervous system can be affected in this disease: vasculitis; direct spread from adjacent disease in the nasal, paranasal, or orbital region; and remote granulomatous lesions. MR imaging, with which it is possible to acquire multiplanar images without radiation, is an excellent modality for demonstration of these abnormalities, especially for evaluation for direct spread to the meninges from orbital, nasal, or paranasal disease.

- **Treatment of Wegener granulomatosis**

The 2-year case fatality rate in untreated WG is 93%. Optimal treatment consists of daily intravenous or oral cyclophosphamide, 2 mg/kg/day. Monthly pulse intravenous cyclophosphamide, preferred because of its better side-effect profile, is insufficient to reliably induce remission but may be employed to sustain remission. Cyclophosphamide treatment is generally maintained through 1 year of stable remission. Daily prednisone, 1 mg/kg/day is routinely employed during the first 6-12 months. With this approach, Hoffman et al (1) achieved marked improvement or partial remission in 91% of patients and complete remission in 75%. The high morbidity rate associated with this treatment (infections, hemorrhagic cystitis, secondary neoplasia) has led to an avid search for alternative approaches. Methotrexate is successfully employed to induce remission in
patients who present with relatively more indolent disease and may be effective in sustaining remission. Cotreatment of patients on cyclophosphamide regimens with trimethoprim-sulfamethoxazole (Bactrim, Septra) significantly reduces the rate of relapse.

Initially, WG was uniformly fatal within a few months of diagnosis; the prognosis was minimally improved after institution of steroid therapy.

Cyclophosphamide has since been used very effectively and is the usual drug of choice for induction of remission. The well-recognized toxicity of oral cyclophosphamide has lead to institution of pulse therapy as the present standard of care.

Azathioprine may be used as maintenance therapy or as initial therapy in patients unable to tolerate cyclophosphamide.

Less frequently employed therapies include methotrexate. Excellent remission is achieved in about 70% of patients but unfortunately relapses are common. Aggressive treatment of pulmonary and renal involvement at the time of disease onset seems to lessen the probability of later neurologic involvement.

References

17. Miller KS, Miller JM. Wegener's granulomatosis presenting as a primary seizure disorder with brain lesions demonstrated by magnetic resonance imaging. Chest 1993; 103:316-318.

The author
Professor Yasser Metwally
www.yassermetwally.com
Discogenic spine disease is the most common surgically treatable form of pain due to nerve root compression. Patients who present with reproducible radicular back and extremity pain that is unresponsive to conservative management can obtain excellent results with surgical excision of the offending herniated intervertebral disc. Careful consideration of a patient's clinical symptoms and signs and close correlation with the appropriate radiologic examination are mandatory. The spine surgeon and the radiologist must collaborate to determine the optimal imaging modality for an individual patient and his or her pathologic process.
Radiographic imaging is a vital adjunct to the neurosurgical evaluation of the patient with potential discogenic disease of the spine. Magnetic resonance (MR) imaging has emerged as the imaging modality of choice for evaluation of lumbar disc disease. Technical advantages of MR imaging include superior soft-tissue contrast, direct multiplanar capability, and the lack of ionizing radiation. Computed tomography (CT) (enhanced, nonenhanced, and postmyelographic) is still widely used and also provides excellent images. The optimal combination of studies and individual study protocols for discogenic disease is quite variable and is under continuous investigation.

Disc degeneration can often be attributable to the combined effects of biomechanical stress and age related changes. The cervical and lumbar discs are subject to more mechanical stress than thoracic discs. Structural support provided by the thoracic rib cage and adjacent musculature as well as the coronal orientation of the facet joints are factors that attenuate biomechanical stresses on the thoracic discs. Disc herniation most commonly occurs at the C5-6, C6-7, L4-5, and L5-S1 levels. Symptoms referable to a specific spinal root level help define the optimal radiographic examination. Correlation of imaging results with the clinical characteristic of neurologic dysfunction from disc disease is of paramount importance in formulating an appropriate treatment plan.

Figure 1. Normal lumbar disc anatomy. Notice that it is difficult to differentiate between the nucleus pulposus and annulus fibrosus

ID = Intervertebral disc, S= Superior articular facet, I = Inferior articular facet, L = Ligamentum flavum, G = Gray matter, W= white matter, F= Facet joint
Pathophysiology of disc degeneration

Posterior elements of the lumbar spinal functional unit typically bear less weight than anterior elements in all positions. Anterior elements bear over 90% of forces transmitted through the lumbar spine in sitting; during standing, this portion decreases to approximately 80%. As the degenerative process progresses, relative anterior-to-posterior force transmission approaches parity. The spine functions best within a realm of static and dynamic stability. Bony architecture and associated specialized soft tissue structures, especially the intervertebral disc, provide static stability. Dynamic stability, however, is accomplished through a system of muscular and ligamentous supports acting in concert during various functional, occupational, and avocational activities.
The overall mechanical effect of these structures maintains the histologic integrity of the tri-joint complex. Net shear and compressive forces must be maintained below respective critical minima to maintain tri-joint articulation integrity. Persistent, recurrent, nonmechanical, and/or excessive forces to the motion segment beyond minimal thresholds lead to microtrauma of the disc and facet joints, triggering and continuing the degenerative process. Degenerative cascade is the widely accepted pathophysiologic model describing the degenerative process as it affects the lumbar spine and individual motion segments. This process occurs in 3 phases that comprise a continuum with gradual transition, rather than 3 distinct clearly definable stages.

- **Phase I**

The dysfunctional phase, or Phase I, is characterized histologically by circumferential tears or fissures in the outer annulus. Tears can be accompanied by endplate separation or failure, interrupting blood supply to the disc and impairing nutritional supply and waste removal. Such changes may be the result of repetitive microtrauma. Since the outer one third of the annular wall is innervated, tears or fissures in this area may be painful. Strong experimental evidence suggests that most episodes of LBP are a consequence of disc injury, rather than musculotendinous or ligamentous strain. Circumferential tears may coalesce to form radial tears. The nucleus pulposus may lose its normal water-imbibing abilities as a result of biochemical changes in aggregating proteoglycans.

Studies suggest proteoglycan destruction may result from an imbalance between the matrix metalloproteinase-3 (MMP-3) and tissue inhibitor of metalloproteinase-1 (TIMP-1). This imbalance results in diminished capacity for imbibing water, causing loss of nuclear hydrostatic pressure and leading to buckling of the annular lamellae. This phenomenon leads to increased focal segmental mobility and shear stress to the annular wall. Delamination and fissuring within the annulus can result. Annular delamination has been shown to occur as a separate and distinct event from annular fissures.

Microfractures of collagen fibrils within the annulus have been demonstrated with electron microscopy. MRI at this stage may reveal desiccation, disc bulging without herniation, or a high-intensity zone (HIZ) within the annulus. Structural alteration of the facet joints following disc degeneration is acknowledged widely, but this expected pathologic alteration does not necessarily follow. Changes associated with zygapophyseal joints during the dysfunctional phase may include synovitis and hypomobility. The facet joints may serve as a pain generator.
Figure 3. Dessication of the nucleus pulposus associated with multiple annular tears (eg, radial, circumferential). Notice that the disc is bulging without actual herniation. Because of the existing disc degeneration, it is possible to differentiate between the nucleus pulposus and annulus fibrosus. 1. Annulus fibrosis, 2. Circumferential annular tears, 3. Posterior longitudinal ligament, 4. The desiccated nucleus pulposus.

Figure 4. Dessication of the nucleus pulposus associated with multiple annular tears (eg, radial, circumferential). Notice that the disc is bulging without actual herniation. Because of the existing disc degeneration, it is possible to differentiate between the nucleus pulposus and annulus fibrosus. Notice the existence of articular facet pathology and tegmental flavum hypertrophy. 1. Annulus fibrosis, 2. Circumferential annular tears with infiltration by nuclear material, 3-4. The desiccated nucleus pulposus.

*Phase II*

The unstable phase, or phase II, may result from progressive loss of mechanical integrity of the tri-joint complex. Disc-related changes include multiple annular tears (eg, radial, circumferential), internal disc disruption and resorption, or loss of disc-space height. Concurrent changes in the zygapophysial joints include cartilage degeneration, capsular laxity, and subluxation. The biomechanical result of these alterations leads to segmental instability. Clinical syndromes of segmental instability, internal disc disruption syndrome, and herniated disc seem to fit within this phase.
Figure 5. Disc degeneration with multiple disc bulging without herniation

G = Gray matter
W = white matter
PLL = Posterior longitudinal ligament
DD = Disc degeneration
B = Disc bulging

○ Phase III

The third and final phase, stabilization, is characterized by further disc resorption, disc-space narrowing, endplate destruction, disc fibrosis, and osteophyte formation. Discogenic pain from such discs may be of much lower incidence than pain from discs in phases I and II; however, great variation of phases can be expected within different discs in any given individual, since much variation exists between individuals of similar ages.
Figure 6. The desiccated nucleus (1) is unable to redistribute much of the vertical load radically, causing the annulus to bulge posteriorly (4), pushing the posterior spinal ligament (3), this can result in annular tear and herniation of the nucleus pulposus (2).

- **Histologic Findings**

The lumbar intervertebral disc is composed of the nucleus pulposus and annulus fibrosus. The disc is related intimately as a functional unit to the cartilaginous endplate. The intervertebral disc contains water, collagen, and proteoglycans. The nucleus pulposus normally is well hydrated, containing approximately 85-90% water in the first decade and 70-80% water in the adult. Elongated fibrocytes are organized loosely, forming a gelatinous matrix. The nucleus has a higher content of proteoglycans than the disc annulus.
Figure 7. The desiccated nucleus (1) is unable to redistribute much of the vertical load radically, this can result in annular tear and herniation of the nucleus pulposus (2,4,7). Notice posterior annulus bulge (6). (3= the annulus, 5= the cauda roots)

The annulus fibrosis contains 75% water in the first decade of life and 70-80% water in the adult. The peripheral annulus is composed primarily of type 1 collagen, lending tensile strength to the intervertebral disc. The inner annulus is composed primarily of type 2 collagen, which, in conjunction with the nucleus pulposus, provides compressive strength. Type 2 collagen may have greater water content than type 1 collagen.

The collagenous lamellae are fewer, thinner, and more tightly packed posteriorly than anteriorly. The central depression of the vertebral endplate is covered by hyaline cartilage.
With age-related degeneration, the volume of the nucleus pulposus diminishes with decreasing hydration and increasing fibrosis. Changes in water content are from alteration in the relative composition of proteoglycan, as well as decrease in the extent of aggregating proteoglycans. By age 30 years, in-growth of fibrous tissue into the nucleus results in an intranuclear cleft. Fibrocartilage, derived from cells in the annulus and endplate, gradually replaces mucoid material within the nucleus. Gradual loss of definition between nucleus and inner annular fibers occurs.

Figure 8. A normal nucleus has a sharply demarcated oval contour, and due to increased water content, the nucleus is hyperintense on the MRI T1 images surrounded by the hypointense annulus fibrosis. A firm fibrous band traverses the disc equator and blends imperceptibly with the anulus fibers, this band is seen as a hypointense band traversing the disc equator (L4,L5 disc in A). A degenerated disc is hypointense on the MRI T2 images due to reduced water contents. Degenerated discs are seen bulging in both A,B.

In the final stages of degeneration, the nucleus is replaced completely by fibrocartilage, indistinguishable from the fibrotic disc annulus. Specifically, the type 1 collagen content of the disc annulus increases, especially posteriorly, and type 2 collagen content diminishes. Cartilaginous metaplasia begins in the inner annular fibers with changes in the overall fiber direction from vertical to horizontal. Infolding of fibers of the outer annulus occurs early with myxoid degeneration of the outer annular fibers.
Concentric and/or transverse tears in the annulus fibrosis are frequent findings. Peripheral tears are more frequent posterior or posterolateral where the annular lamellae are fewer. Development of a radial tear, particularly a tear extending to the disc nucleus, is one of the major hallmarks of disc degeneration. The degenerated intervertebral disc loses height and overall volume. Herniation of both nuclear material and annulus fibrosis may occur through the tear. With aging, the cartilage endplate may become thinner and eventually may calcify. In advanced disc degeneration, the cartilage endplate is calcified with fissuring and microfractures. At autopsy, 97% of adults aged 49 years or older demonstrate degenerative changes.

For a structure to be considered a pain generator, it must meet the following 3 criteria: (1) it must have a nerve supply, (2) it must be susceptible to disease or injuries known to be painful, and (3) it must be capable of causing pain similar to that observed clinically. The superficial layers of the annulus fibrosis contain nerve fibers located in the posterior portion of the annulus, which are branches from the sinuvertebral nerves. The sinuvertebral nerves are branches of the ventral rami. They also contain fibers derived from the grey ramus. Small branches from the grey ramus communicans or sympathetic fibers innervate the anterior longitudinal ligament and lateral and anterior annulus. The grey ramus communicans joins the sinuvertebral nerve that reenters the intervertebral foramen and spinal canal to innervate the posterior annulus and the posterior longitudinal ligament.

A dense nerve network on the posterior portion of the lumbar intervertebral disc has been demonstrated in rats, disappearing almost completely after total resection of bilateral sympathetic trunks at L2-L6. The authors concluded that, in rats, the posterior portion of the lumbar intervertebral disc and posterior longitudinal ligament are innervated by sympathetic nerves bilaterally and multisegmentally. A variety of free and complex nerve endings have been demonstrated in the outer one third to one half of the annulus. In addition to annular fissures or tears, Coppes et al observed more extensive disc innervation in the severely degenerated lumbar disc compared with the normal disc.

The nociceptive properties of at least some of these nerves have been suggested by substance P immunoreactivity, which provides further evidence for the existence of a morphologic substrate of discogenic pain. Nerve fibers were restricted to the outer or middle third of the annulus in control samples.

In the patient population undergoing spinal fusion for chronic LBP, nerves extended into the inner third of the annulus fibrosis in 46% and into nucleus pulposus in 22% of patients. Their findings that isolated nerve fibers expressed substance P deep within diseased intervertebral discs and their association with pain suggests an important role for nerve ingrowth into the intervertebral disc in the pathogenesis of chronic LBP.

Weinstein et al identified substance P, calcitonin gene-related peptide (CGRP), and vasoactive intestinal polypeptides (VIP) in the outer annular fibers of the disc in rats. These chemicals all are related to pain perception. Substance P, dopamine, and choline acetyltransferase immunoreactive nerve fibers are found in human longitudinal ligaments
that have been removed surgically. These findings not only provide evidence to support the first criterion but also reveal changes associated with painful discs.

**LUMBAR DISC DISEASE**

- **Introduction**

Lumbar disc disease, a leading cause of correctable lower back pain, often manifests as posterior herniation with radicular symptoms from neural compression. The classical syndrome of lumbar disc herniation features stiffness in the back and pain radiating down to the thighs and feet associated with paresthesia, weakness, and reflex changes. Patients typically flex their backs to reduce the normal lumbar lordosis. Flexion of the low back may alleviate neural compression by widening the neuroforamina caused by posterior rotation of the superior facets. Nerve stretching by the straight leg test and other maneuvers can reproduce or exacerbate radicular pain. Nerve roots L4, L5, and S1 are most commonly affected. Physical impingement from disc herniation most often occurs in the "lateral gutter" of the spinal canal, adjacent to the posterior lateral border of a herniated disc fragment. For instance, at the L5-S1 disc level, the S1 nerve roots are poised in the antero-lateral margin of the thecal sac. They are "tethered" at that location as they acquire an investment of dura and assume an oblique (and eventually transverse) orientation prior to exiting through the neural foramen more inferiorly. Nerve root impingement at each intervertebral disc level typically produces a distinctive and predictable pattern of radiating pain, sensory loss, weakness, and decreased reflexes.

Intervertebral discs are composed of highly specialized connective tissues (glycosaminoglycans and collagen). The central portion of the nucleus pulposus is comprised of a gelatinous mucoid material and is surrounded by the fibrocartilaginous anulus fibrosus. The nucleus pulposus and anulus fibrosus can be differentiated on MR images because of differing water content. With age, the water content of the disc decreases. This degenerative-senescent change is reflected by loss of signal on T2-weighted MR images and is often identified at levels that show disc bulging or frank herniation.

The intervertebral disc can be classified as immature, transitional, adult, early degenerated, or severely degenerated. Up to age 2, the nucleus has a sharply demarcated oval contour. The immature disc is also grossly translucent. By the second decade of life, "transitional discs" exhibit a fibrous structure oriented horizontally in the equator of the disc. The mature adult disc is characterized by a more homogeneous architecture and gross appearance with less distinction between the nucleus pulposus and anulus fibrosus. A firm fibrous band traverses the disc equator and blends imperceptibly with the anulus fibers. An early degenerated disc has a slightly narrowed disc height and reduced fibrocartilage in the nucleus. The severely degenerated disc has amorphous fibers and cystic spaces replacing normal fibrocartilage. The normal adult type of nucleus commonly has an anulus with small concentric or transverse tears but never a radial tear. The early degenerated disc may be associated with a peripheral radial tear of the anulus in up to 92% of cases. The severely degenerated disc is typically associated with a complete disruption of the anulus.
The normal anatomical/radiological picture of the intervertebral discs

Functionally and pathologically, the intervertebral joints are an important aspect of the anatomy of the spine. These joints are amphiarthrodial, with only slightly movable articulations connected by fibrocartilage. Although only a slight amount of motion is possible at each joint, the spine has a considerable amount of mobility because of the number of joints present. The cervical disks are thicker anteriorly than posteriorly, and this shape contributes to the lordosis of the cervical spine.

The major components of the intervertebral disk are the nucleus pulposus, the annulus fibrosus, and the cartilaginous endplates. These components are composed of proteoglycans, fibrocartilage, dense collagenous fibrous tissue, and hyaline cartilage. The cells present in the intervertebral disk include fibroblasts and chondrocytes. The ground substance, a gel-like material, is most plentiful in the nucleus pulposus. After infancy the disk loses its vascularity.

The nucleus pulposus, located centrally in the intervertebral disk, is composed of fibrocartilage that is predominantly type II collagen and proteoglycans that include hyaluronic acid and sulfated glycosaminoglycans. The disk absorbs and retains water because of the negative charge of the proteoglycans. In adults, the nucleus pulposus is hyperintense on T2-weighted imaging and has an indistinct boundary with the annulus fibrosus.

The annulus fibrosus, which is a highly ordered laminated structure, is subdivided into an outer ring and an inner ring. The outer ring inserts onto the ring apophyses of adjacent vertebrae and the adjacent cartilaginous end-plates. The type of collagen present changes across the annulus. At the outer ring of the annulus the collagen is predominantly type I, and at the inner ring the collagen is predominantly type II. More collagen is present in the outer ring than in the inner ring. The proteoglycan content of the intervertebral disk varies inversely with the collagen content; the least amount of proteoglycan is present at the outer aspect of the annulus, and the greatest amount is in the nucleus pulposus.

On T2-weighted images, the outer ring of the annulus fibrosus has a hypointense signal. On T1-weighted images, the outer ring can appear isointense or slightly hypointense but has been described as hyperintense in cadaver specimens. The outer fibrous ring contains little ground substance that would produce hyperintense signal on T2-weighted images. The composition of the inner ring results in a hyperintense signal on T2-weighted images that is similar to that of the nucleus pulposus, and the two cannot be distinguished on MR imaging.

Hyaline cartilage makes up the cranial and caudal aspects of the disk and covers the vertebral endplates. This cartilaginous endplate is attached to the osseous endplate by numerous collagenous fibers. The endplates appear hypointense on MR imaging and this appearance can be accentuated by chemical-shift artifact. In the vertebral endplates are numerous pores through which vascular channels extend. Diffusion of gadolinium-
containing chelates into the intervertebral disk has been shown to occur, presumably through these channels.

The appearance of the intervertebral disk changes from infancy to adulthood, and the described MR imaging appearances of the intervertebral disks are for adults. The biochemical changes that occur with aging are related to the MR imaging characteristics within the intervertebral disks. These changes differ with the location of the disk in the spine and are also different in the annulus fibrosus and nucleus pulposus.

In children and young adults, the nucleus pulposus is a semifluid gel with a water content of 80% or more, but the water content decreases markedly with aging. This decrease is slightly more marked in the cervical intervertebral disks than in thoracic or lumbar intervertebral disks. The collagen content increases and the glycosaminoglycan content of the intervertebral disks decreases with aging. The changes in collagen content and glycosaminoglycan content are less marked in the cervical nucleus pulposus where both remain roughly constant throughout.

On MR imaging, a transverse band of low signal intensity may be seen in the center of intervertebral disks. If the line is narrow and regular in appearance, it is probably caused by truncation artifact. An irregular thick line described in lumbar intervertebral disks has been found to correlate with a higher collagen concentration at the equator of the disks. The irregular thick line has been termed an intranuclear cleft. The intranuclear cleft is broader than the line caused by truncation.

**Table 1. The normal anatomical/radiological picture of the intervertebral discs**

<table>
<thead>
<tr>
<th>Structure</th>
<th>Comment</th>
<th>Radiological picture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleus pulposus</td>
<td>Located centrally in the intervertebral disk, is composed of fibrocartilage that is predominantly type II collagen and proteoglycans that include hyaluronic acid and sulfated glycosaminoglycans. The disk absorbs and retains water because of the negative charge of the proteoglycans. In adults, the nucleus pulposus is hyperintense on T2-weighted imaging and has an indistinct boundary with the annulus fibrosus.</td>
<td>-In adults, the nucleus pulposus is hyperintense on T2-weighted imaging and has an indistinct boundary with the annulus fibrosus. The high T2 contrast of the nucleus pulposus is due to its low specific gravity that results from increased water content. -A transverse band of low signal intensity, on T2-weighted imaging, may be seen in the center of intervertebral disks. This irregular thick line has been termed an</td>
</tr>
</tbody>
</table>
### Annulus fibrosus

Is a highly ordered laminated structure, is subdivided into an outer ring and an inner ring. The outer ring inserts onto the ring apophyses of adjacent vertebrae and the adjacent cartilaginous end-plates. The type of collagen present changes across the annulus. At the outer ring of the annulus the collagen is predominantly type I, and at the inner ring the collagen is predominantly type II. More collagen is present in the outer ring than in the inner ring. The proteoglycan content of the intervertebral disk varies inversely with the collagen content; the least amount of proteoglycan is present at the outer aspect of the annulus, and the greatest amount is in the nucleus pulposus.

On T2-weighted images, the outer ring of the annulus fibrosus has a hypointense signal. On T1-weighted images, the outer ring can appear isointense or slightly hypointense but has been described as hyperintense in cadaver specimens. The outer fibrous ring contains little ground substance that would produce hyperintense signal on T2-weighted images. The composition of the inner ring results in a hyperintense signal on T2-weighted images that is similar to that of the nucleus pulposus, and the two cannot be distinguished on MR imaging.
Figure 9. The internal disc structures with MRI correlation.

1. Body of thoracic vertebra
2. Intervertebral disc
3. Spinal cord
4. Vertebral canal with spinal meninges
5. Spinous process of vertebra
6. Hyaline cartilage over articular surfaces of vertebral bodies
7. Anterior longitudinal ligament
8. Posterior longitudinal ligament
Figure 10. A normal nucleus has a sharply demarcated oval contour, and due to increased water content, the nucleus is hyperintense on the MRI T2 images surrounded by the hypointense annulus fibrosus. A firm fibrous band traverses the disc equator and blends imperceptibly with the annulus fibers, this band is seen as a hypointense band traversing the disc equator.

Figure 11. Degenerated discs have reduced height, are hypointense on the MRI T2 images- due to reduced water contents- and might appear cystic (A)
Figure 12. Dessication of the nucleus pulposus associated with multiple annular tears (e.g., radial, circumferential). Notice that the disc is bulging without actual herniation. Because of the existing disc degeneration, it is possible to differentiate between the nucleus pulposus and annulus fibrosus. Notice the existence of articular facet pathology and tegmental flavum hypertrophy.

1.2. Circumferential annular tears with infiltration by nuclear material
3. Annulus fibrosus
4. The desiccated nucleus pulposus

- Magnetic Resonance Imaging Protocol

Magnetic resonance (MR) imaging, with its excellent ability to provide soft-tissue contrast, can demonstrate signal changes indicative of both disc degeneration and disc herniation. In particular, the anatomic boundaries and interfaces that permit reliable identification of neural impingement caused by disc disease are often best delineated on MR images, provided that the appropriate sequence choices have been made. The set of instrument parameters that are "optimal" depend on several factors, including the field strength and software capabilities of the MR unit, variations in patient anatomy, and to a large extent, user preference. In general, sagittal images are acquired using both T1-weighted and T2-weighted techniques. A field of view and matrix size are chosen to provide ample coverage of the spine (from approximately T2 superiorly through S1 inferiorly) with good spatial resolution. The thickness of individual slices should not exceed 3 to 4 mm. We obtain T1-weighted spin echo images in the sagittal plane using a TR of 500 to 600 msec and a TE of 16 msec. The image slab, or set of individual slices, spans the vertebral column from the lateral aspect of the left neural foramen to the lateral aspect of the opposite neural foramen on the right side. The low signal intensity of cerebrospinal fluid (CSF), high signal intensity of epidural fat, and intermediate signal intensity of disc material are characteristic features of these T1-weighted images.

Sagittal T2-weighted images can be acquired using either spin echo (SE) or gradient refocused echo (GRE) techniques. Using the SE method, a TR value of 1800 to 2500 msec is desirable with a single or dual echo image pair at each slice location (e.g., a single 80 msec echo, or a dual 30/80 msec echo pair). A multiplanar GRE sequence using a lowered flip angle is a suitable short acquisition time substitute for the SE method. Application of a presaturation zone to anatomy anterior to the vertebral column is a valuable adjunct that
may help suppress artifacts from vascular pulsations and respiratory motion. Transaxial or oblique axial T1-weighted SE images of the lumbar spine are also obtained. Our protocol calls for 4-mm thick axial T1-weighted images from the pedicles of L3 through the L5-S1 disc space. Supplemental sections can be added more superiorly if needed for further evaluation of more cephalad abnormalities detected on the sagittal images. Presaturation zones are also applied anterior to the vertebral column to suppress signal from extraneous anatomy and eliminate artifacts from both vascular and respiratory pulsations.

Three sets of images (two in the sagittal plane and one in the axial plane) are sufficient for basic screening purposes in most patients. Additional or modified sequences may occasionally be of value. For instance, patients who have had prior lumbar disc surgery or those with "atypical" appearing disc herniations may benefit from gadolinium-enhanced T1-weighted images. A "fat-saturation" technique that eliminates the signal of epidural fat may help clarify various tissue constituents or improve the visibility of important anatomic boundaries such as scar tissue versus recurrent or residual disc herniation adjacent to the thecal sac. Development of even more advanced pulse sequence modifications as well as newer acquisition methods (such as "fast spin echo") are under way. Availability of these newer technical adjuncts periodically redefine the optimal MR pulse sequences suitable for the evaluation of lumbar disc disease.

- Classification and Terminology

A plethora of sometimes confusing terminology has been used for description of different degrees and types of disc herniation. The classification scheme defined by Macnab correlates well with MR images and clinical relevance and includes disc bulge, prolapse, extrusion, and sequestration. Actual disc herniation implies prolapse, extrusion, or sequestration (free fragment).

Bulging discs demonstrate normal native disc signal intensity, with a slight convexity extending beyond the adjacent vertebral disc margins. The classic teaching is that the anulus fibrosus and Sharpey's fibers remain intact. Yu et al, examined cryotome sections of 149 bulging lumbar discs in 31 cadavers to investigate the association of radial tears of the anulus and intervertebral disc bulging, however. In all but one case of a maximum disc bulge more than 2.5 mm (adults), a radial tear or complete disruption of the anulus fibrosus was demonstrated. Their findings were also correlated with MR and CT images. Results indicated that small tears of the anulus that commonly accompany bulging disc margins may remain occult on CT or MR images, which refuted the concept that the anulus fibrosus is completely intact in bulging discs, although ruptured in only herniated discs.
Figure 13. A bulging disc at L4,L5

Figure 14. Disc herniation classification includes the following:

- **A** - Normal disc anatomy demonstrating nucleus pulposus (NP) and annular margin (AM)
- **B** - Disc protrusion with NP penetrating asymmetrically through annular fibers but confined within the AM
- **C** - Disc extrusion with NP extending beyond the AM
- **D** - Disc sequestration with nuclear fragment separated from extruded disc
### Table 2. Types of degenerative disc disease

<table>
<thead>
<tr>
<th>Lumbar disk disease</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disk bulge</td>
<td>Annular fibers intact</td>
</tr>
<tr>
<td>Disk protrusion</td>
<td>Localized bulging with damage of some annular fibers</td>
</tr>
<tr>
<td>Disk extrusion</td>
<td>Extended bulge with loss of annular fibers, but disk remains intact</td>
</tr>
<tr>
<td>Disk sequestration</td>
<td>Fragment of disk broken off from the nucleus pulposus</td>
</tr>
</tbody>
</table>

**Figure 15.** Extruded disc herniation at L3-4. A, Left parasagittal T1-weighted image shows disruption of the anulus fibrosus of L3-4 (open arrow). Note inferior extrusion of disc material into the left lateral recess beneath the posterior longitudinal ligament and behind the posterior body of L4, where it replaces the normal high-signal intensity of epidural fat (closed arrow). B, Axial T1-weighted image shows the ovoid disc fragment interposed between the left pedicle of L4 with deformation of the thecal sac, which is displaced medially. Note lack of visibility of the descending L4 nerve root. C, Postgadolinium axial T1-weighted image at the same location as that in B shows ring-like enhancement of
granulation tissue around the perimeter of the herniated disc fragment. 

D, Postgadolium axial fat saturation T1-weighted image cancels signal intensity of yellow marrow and epidural fat, providing improved contrast between the disc fragment (large arrow) and laterally displaced L4 nerve root (small arrow). E, Fat saturation axial T2-weighted image shows high signal intensity of the extruded disc fragment, reflecting its high water content. Note high signal intensity of the thecal sac contents (CSF) interrupted by low signal intensity cauda equina. The sharp plane of demarcation between the disc fragment and thecal sac is caused by low signal intensity of the posterior longitudinal ligament and dura.

Prolapsed discs herniate posteriorly through an incomplete defect in the anulus fibrosus. Only the most peripheral (posterior) anulus fibers are intact and appear as low signal fibers on T2-weighted images. Herniated disc material is contiguous with the parent nucleus, connected by a high signal intensity isthmus on T2-weighted images.

![Figure 16. "Squeezed toothpaste sign." A disc herniation at L4-5 with inferior extrusion (arrow) retains contiguity with the parent disc space through a narrow isthmus at the site of anulus disruption.](image)

Extruded discs herniate posteriorly through a complete defect in the anulus fibrosus. The parent nucleus and the extruded portion remain connected by a high signal intensity isthmus. The herniated disc retains high signal intensity on T2- weighted images and may lay anterior or lateral to the posterior longitudinal ligament. Classically, the extruded disc shows the "squeezed toothpaste sign". Lateral disc extrusion affects the adjacent nerve
root, which has already exited the spinal canal (e.g., a lateral disc extrusion at L5-S1 would impinge on the exiting L5 nerve root). Lateral or foraminal disc herniations are usually well demonstrated on both axial and parasagittal images, where disc material can be shown protruding into the neural foramen. 13

Sequestered disc fragments also result from extrusion of nuclear material through a complete anulus fibrosus defect. The herniated disc material has lost continuity with the parent nucleus pulposus, however. This isolated fragment may be anterior or posterior to the posterior longitudinal ligament, superior or inferior to the parent disc, and may be extradural or (rarely) intradural.

Table 3. Types of degenerative disc disease

<table>
<thead>
<tr>
<th>DISC PATHOLOGY</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulging discs</td>
<td>Demonstrate normal native disc signal intensity, with a slight convexity extending beyond the adjacent vertebral disc margins. The classic teaching is that the anulus fibrosus and Sharpey's fibers remain intact.</td>
</tr>
<tr>
<td>Prolapsed discs</td>
<td>Herniate posteriorly through an incomplete defect in the anulus fibrosus.</td>
</tr>
<tr>
<td>Extruded discs (protruded, herniated)</td>
<td>Herniate posteriorly through a complete defect in the anulus fibrosus. The parent nucleus and the extruded portion remain connected by a high signal intensity isthmus. The herniated disc retains high signal intensity on T2-weighted images and may lay anterior or lateral to the posterior longitudinal ligament. Classically, the extruded disc shows the &quot;squeezed toothpaste sign&quot;</td>
</tr>
<tr>
<td>Sequestered disc fragments</td>
<td>Result from extrusion of nuclear material through a complete anulus fibrosus defect. The herniated disc material has lost continuity with the parent nucleus pulposus na might migrates in the epidural spaces</td>
</tr>
</tbody>
</table>

More than 90% of displaced disc components migrate into the right or left half of the anterior epidural space and rarely straddle the midline. Recently, Schellinger et al, 43 described the anatomy of the anterior epidural space. They evaluated lumbar spine MR imaging examinations in 300 patients and correlated their results to cadaver specimens. The anterior epidural space is a well defined space contained by the posterior longitudinal ligament and a thin translucent laterally attached membrane. There is a midline septum (septum posticum) that divides the anterior epidural space into two compartments. Compartmentalization of the anterior epidural space by the dural sac, posterior longitudinal ligament, and fibrous septae causes migrating discs to acquire a smooth and well defined posterior contour. With this model, the anatomy superior and inferior to the disc level is identical, and migration should occur in each direction with approximately equal frequency.
Figure 17. "Squeezed toothpaste sign." A disc herniation at L4-5 with inferior extrusion (arrow) retains contiguity with the parent disc space through a narrow isthmus at the site of anulus disruption.

There is no consensus on the direction of predilection for longitudinal migration of herniated disc fragments. Fries et al, 12 observed higher frequency of superior migration (78%), possibly because of greater space availability superiorly. Dillon et al, 9 looked at 40 patients and found 50% inferior migration, however. Schellinger et al, 43 evaluated 47 patients with disc migration and found 42% with superior migration and 40% with inferior migration.
Figure 18. L5-S1 herniated disc with lateral extrusion into the right L5 foramen. Type 2 vertebral body marrow changes. A. Right parasagittal T1-weighted images show disc material replaces epidural fat and impinges on the undersurface on the right L5 nerve root as it exits (arrows). The normal "keyhole" appearance of high-signal epidural fat interrupted by the exiting nerve root is obliterated at this level. Also note type 2 subchondral vertebral body bone marrow changes as manifested by increased signal intensity. B. Right parasagittal T2-weighted images (same locations as A) reveal that the intraforaminal disc fragment retains high signal (curved arrows) and appears brighter than the exiting L5 nerve root (straight arrow). Note isointensity of type 2 subchondral vertebral body bone marrow changes at L5-S1. C. Axial T1-weighted image confirms the right lateral herniation (arrows).

A bulging disc is less likely to cause sciatica than a herniated disc. Disc extrusions produce signs and symptoms indistinguishable from disc protrusions. On T2-weighted images, an extruded disc fragment usually lacks a boundary of low signal intensity because of complete disruption of anulus fibers at the apex of herniation.
Figure 19. Sequestered disc fragment with migration into right SI foramen. A and B, Right parasagittal TI-weighted image (A) and T2-weighted image (B) show a prominent ovoid focus of CSF-like signal occupying the right St foramen (open arrows), simulating a Tarlov cyst, swollen nerve root, or possibly a schwannoma. C and D, Pre-gadolinium (C) and postgadolinium (D) show lack of intrinsic enhancement within the ovoid TI-weighted disc fragment that occupies the right lateral recess (arrows). E, Coronal TI-weighted image obtained after gadolinium infusion shows the low signal intensity sequestered disc fragment wedged into the right SI foramen (larger arrows). Note linear enhancement of right SI spinal nerve extending cephalad in the thecal sac (small arrows).

- Magnetic Resonance imaging Signal Changes of Degenerative Disc Disease

Although the pathophysiology of degenerative and normal aging changes of intervertebral discs are controversial, disc anatomy and degenerative disease correlate well with signal changes visible on MR imaging. 2,3,27,42,44,47-50 On TI-weighted images, the adult disc (no MR imaging delineation between the anulus and the nucleus) has homogeneous and intermediate signal intensity framed by the low signal intensity of peripheral Sharpey's
fibers. On T2-weighted images, the disc has a high signal intensity with a transverse central low signal from the fibrous plate in the nucleus pulposus. 47

The early degenerated disc demonstrates diminished signal intensity on T2-weighted images. Scheibler et al, 42 described two specific findings of the early degenerated disc: infolding of the intervertebral disc and the appearance of a central low intensity within the disc on T2-weighted images. These signs are visible before disc height reduction and homogeneous signal loss. Concentric anulus fibrosus tears are not seen by standard MR imaging sequences, but transverse and radial tears may be manifested by a higher signal intensity in the periphery of the disc. 48 Gadolinium DTPA-enhanced T1-weighted images may reveal enhancing granulation tissue adjacent to an anular tear. The late degenerated disc shows loss of disc height and a reduction of signal intensity within the disc (on both T1-weighted and T2-weighted images) as fibrous tissue replaces fibrocartilage. Vacuum phenomenon associated with degenerative disc disease appears as signal void on all sequences and may bloom or appear to enlarge in size on T2-weighted images obtained using GRE technique. Dense calcifications can produce a similar appearance. Thus, correlation with a plain film radiograph or CT scan may be needed. 15

In degenerative disease of the spine, the vacuum disc relates to the accumulation of gas (90% nitrogen) created by the deteriorating nucleus and anulus fibrosus. Gas collection may be seen intra-discal, intraosseous, or lying free in the spinal canal in relation to the posterior part of the cartilaginous end plate.
Figure 21. A, plain X ray, B, plain CT scan image of a lumbar vertebra showing the spinal vacuum phenomena demonstrated as a hypodense area. In degenerative disease of the spine, the vacuum disc relates to the accumulation of gas (90% nitrogen) created by the deteriorating nucleus and anulus fibrosus. Gas collection may be seen intra-discal, intraosseous, or lying free in the spinal canal in relation to the posterior part of the cartilaginous end plate.

Early reports stated that herniated discs typically have a low signal on T2-weighted images. 30 This signal decrement was believed to reflect degeneration and lowered water content. Subsequent reports show that a significant percentage of extruded discs and the majority of sequestered discs demonstrate increased signal on T2-weighted images, however. 14, 25 Several mechanisms have been proposed to explain the apparent variability in the hydration status of extruded disc fragments. For instance, the surrounding physical milieu of an extruded fragment may allow imbibition of water and increased hydration compared with the desiccated environment of the parent disc space. In addition, the extruded fragment may be in a different physical environment, exposed to more water than the parent disc. The extruded fragment may represent complete extrusion of the nucleus pulposus (90% water content compared with the anulus, 75%), leaving the disc space devoid of hydrated tissue. 14

Sequestered discs have characteristic MR signals. 14,25 The isolated fragment typically manifests as a distinct and separate isointense or high signal focus in the ventral epidural space of T2-weighted images. The fragment often exhibits a rounded configuration when adjacent to its parent interspace and an oval shape superior or inferior to the interspace. The parent disc space may show low signal intensity on T2-weighted images, whereas the extruded fragment shows comparatively higher signal, reflecting increased hydration.
Modic et al. reported a spectrum of signal changes in the subchondral vertebral body bone marrow of patients with lumbar degenerative disc disease. Initially, two patterns of signal change adjacent to the end plates were described. Type 1 shows a decreased signal on T1-weighted images and increased signal on T2-weighted images. Type 2 shows increased signal intensity on T1-weighted images and isointense or slightly increased signal intensity on T2-weighted images. In either case, the intervening disc space atypically shows a decreased signal on T2-weighted images along with other signs of degenerative disc disease such as decreased disc height and osteophyte formation. These marrow changes can be distinguished from changes seen in vertebral osteomyelitis and discitis. Follow-up studies in most patients with type 1 marrow changes demonstrate a progression to type 2 changes. Some patients with type 1 changes may remain stable and may actually revert to normal, however.

Type 1 endplate changes are characterized by decreased signal intensity in T1-weighted images and increased signal intensity on T2-weighted images. Disruption of the endplate with replacement of the hematopoietic elements within the adjacent marrow by fat result in type 2 changes. Type 2 endplate changes consequently are nearly isointense with fat, show increased signal intensity on T1-weighted images, and demonstrate isointensity or slightly diminished signal intensity on T2-weighted images. Type 1 changes appear to convert to type 2 changes over time. Extensive bony sclerosis with thickening of subchondral trabeculae results in type 2 endplate changes. The type 3 changes demonstrate decreased signal intensity on both T1-weighted and T2-weighted images.

Figure 22. Type 2 bone marrow changes
Type 1 marrow changes are believed to reflect an acute reparative response to injury with marrow edema. Type 2 changes are related to conversion of red to yellow marrow. The amount of endplate sclerosis (woven bone) seen on plain film radiographs does not predict the MR marrow appearance. The marrow changes related to degenerative disc disease often differ from those produced by malignancy or vertebral osteomyelitis. Destructive features of infection include conspicuous involvement of the adjacent marrow spaces with dissolution of the intervening end plates. Enhancement of infected disc material on postgadolinium T1-weighted images, in addition to enhancement of adjoining vertebral bodies and epidural or paravertebral granulation tissue, may help differentiate discitis or osteomyelitis from reactive change. In contrast, destructive changes and multiplicity are hallmark features of neoplasia.

Further study is needed to determine if marrow changes associated with degenerative disc disease themselves are associated with back pain and whether type 2 marrow changes indicate stability of the degenerative disease process. Occasionally, the vertebral marrow has a decreased signal on both T1-weighted and T2-weighted images, a type 3 change, secondary to sclerotic marrow changes. 6,33

### Table 4. MRI SIGNAL CHANGES OF THE BONE MARROW ADJACENT TO THE VERTEBRAL ENDPLATES OF DEGENERATED DISCS

<table>
<thead>
<tr>
<th>TYPE CHANGES</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1</strong></td>
<td><strong>REDUCED SIGNAL ON THE T1 IMAGES AND INCREASED SIGNAL ON THE T2 IMAGES THIS IS DUE TO BONE MARROW OEDEMA</strong></td>
</tr>
<tr>
<td><strong>2</strong></td>
<td><strong>INCREASED SIGNAL INTENSITY ON THE T1 IMAGES AND SIGNAL ISOINTENSITY ON THE T2 IMAGES, THIS IS DUE TO CONVERSION OF RED MARROW TO YELLOW MARROW [INCREASED FAT CONTENT]</strong></td>
</tr>
<tr>
<td><strong>3</strong></td>
<td><strong>T1,T2 HYPOINTENSITY, THIS IS DUE TO BONE MARROW BONY SCLEROSIS</strong></td>
</tr>
</tbody>
</table>

- Schmorl's Nodes (Vertical disc herniation)

Schmorl's nodes are considered to be vertical disc herniations through the cartilaginous vertebral body endplates. They can sometimes be seen radiographically, however they are more often seen on MRI, even when not visible on plain film x-ray. They may or may not be symptomatic, and their etiological significance for back pain is controversial.

In a recent study in Spine by Hamanishi, et al.,53 Schmorl's nodes were observed on MRI in 19% of 400 patients with back pain, and in only 9% of an asymptomatic control group. Plain film x-rays only revealed about 33% of the nodes identified on MRI. They also found a high incidence of nodes in the teenager group who had complaints of lower back pain and
an increased level of participation in contact sports. The authors concluded that Schmorl's nodes are areas of "vertical disc herniation" through areas of weakness in the endplate.

In younger patients, it seems to be more common because the annulus is strong and intact, and thus nuclear material herniates through the weaker endplate. As the annulus degenerates with time and age, transverse or posterolateral herniations are more common.

In a more recent study published in the European Spine Journal by Takahashi, et al.,54 an analysis and correlation was made in symptomatic and asymptomatic patients with MRI evidence of Schmorl's nodes. There were five patients with pain and Schmorl's nodes, and 11 asymptomatic controls. Symptomatic Schmorl's nodes were classified by physical exam, radiographs, MRI, and lab tests. All other possible etiologies were reportedly ruled out. Patients with symptomatic Schmorl's nodes had pain on percussion, and manual compression of the vertebra was involved. Back pain was exacerbated by axial loading and extreme lumbar ROM. They found no differences in the two groups on plain film x-ray evaluation. However, on MRI, in symptomatic cases, the vertebral body bone marrow surrounding the node was seen as low-intensity on T1-weighted images, and high signal intensity on T2-weighted images. These changes were local to the area of the Schmorl's node. The signal changes on MRI are reflective of bone marrow edema and inflammation often seen in cases of fracture. The MRI findings in Takahashi's study were confirmed upon histological section in two cases where surgery was performed. Conservative care was delivered for three patients with symptomatic Schmorl's nodes. All three patients were asymptomatic after 3-4 months of conservative care. Symptomatic Schmorl's nodes represent a fresh fracture of the vertebral endplate, which allows vertical disc herniation and nuclear migration. This may cause diffuse lower back pain without associated radicular findings often seen in transverse type herniations. It must be emphasized that for a Schmorl's node to be considered symptomatic or active subsequent to trauma, an MRI should demonstrate the T1 and T2 signal changes described above.
Figure 23. Schmorl's Nodes demonstrated as a hypodense poorly defined area on plain x Ray

Figure 24. MRI T2 images showing diffuse degeneration of the lumbar discs. A Schmorl's Node is seen between L1, L2 vertebrae as a vertical disc herniations through the cartilaginous vertebral body endplates (Yellow arrows).
Figure 25. MRI T1 images showing diffuse degeneration of the lumbar discs, a Schmorl’s Node is seen between L1, L2 vertebrae as a vertical disc herniations through the cartilaginous vertebral body endplates (Yellow arrows)
Although Schmorl's nodes in the past have been considered clinically insignificant, clearly they may be an active symptomatic process and etiology of pain in some patients. Yochum 55 states that Schmorl's nodes may be caused by numerous factors: trauma; hyperparathyroidism; osteoporosis; Schuermann's disease; osteomalacia; infections; and neoplasm. Yochum, et al., and Walters, et al.,56 state that trauma in adolescent athletes may be responsible for symptomatic Schmorl's nodes. Yochum, et al. also describe a unique large Schmorl's node that can cause a "squared off" vertebral body. They represent vertical disc herniation through a pain-sensitive endplate.

Recent studies have demonstrated that nucleus pulposis activates the release of inflammatory hormones and enzymes, such as leukotrienes, cytokines, PLA2, substance P, etc., and as such may be responsible for C-nociception or diffuse vertebrogenic pain seen in these types of cases.

- **Lumbar Spine: Postoperative Magnetic Resonance Imaging**

Recurrent intractable back pain after spinal surgery (failed back surgery syndrome) may occur in up to 15% to 25% of surgically managed patients. 5,37 Postoperative symptoms are often related to epidural fibrosis or disc reherniation. Other rarer postsurgical causes of back pain include spinal stenosis, arachnoiditis, nerve injury, instability, infection, and wrong level surgery. 37 Postoperative patients who have significant scar tissue formation without disc herniation invariably have a disappointing outcome with reoperation. Therefore, differentiation of scar from a recurrent or residual disc herniation is imperative.
Magnetic resonance imaging has become the imaging modality of choice for evaluation of the postoperative spine. Typically, epidural fibrosis is poorly defined, distributed along the surgical tract, and has no significant mass effect. These features alone usually facilitate reliable differentiation of scar tissue from disc material. Tumefactive or focally prominent scar tissue can mimic a residual or recurrent disc herniation in location and configuration, however. Unenhanced MR images obtained using T1- or T2-weighted technique may show signal differences between fibrosis and disc material. Signal intensity differences are often subtle or unreliable, however, requiring increased reliance on morphology, epidural location and extent, and topographic relationships.

The use of gadolinium-enhanced MR images has evolved as a valuable adjunct for differentiation of scar tissue from disc herniation. This MR contrast agent is injected intravenously after acquisition of "baseline" pregadolinium MR images in the sagittal and axial planes. Gadolinium is most commonly administered in the form of gadopentetate dimeglumine (Gd-DTPA). This intermediate molecular weight compound accumulates in a concentrated manner at sites of blood-brain barrier defects, amidst highly vascular tissue such as the neovasculature of certain tumors, and especially, the reactive inflammatory change associated with subacute scar tissue. Gadolinium is strongly paramagnetic, a property that causes surrounding water protons (in hydrated tissue) to gain signal more efficiently. Thus, T1-weighted images obtained immediately after injection of GD-DTPA can be expected to show high signal intensity of enhancing scar tissue, whereas avascular disc material is shown with low signal intensity, virtually identical to its appearance on the baseline images.

The strategy of obtaining pregadolinium and postgadolinium T1-weighted images for differentiation of epidural fibrosis from disc herniation has emerged as an invaluable diagnostic aid for patients with presumed failed back surgery syndrome.

Immediate imaging (less than 6 weeks) of the postoperative spine often appears identical to the preoperative images. Although significant mass effect on the thecal sac is unusual, edema and anulus disruption do not resolve for 2 to 6 months. Immediate postoperative MR imaging may distinguish disc space infection, pseudomeningocele, or a significant hematoma but not a recurrent herniated disc from scar formation. Unfortunately, MR cannot distinguish between benign postoperative fluid collections and infection.

In the immediate postoperative period, laminectomy defects are manifested by the loss of normal marrow signal, which is replaced by soft-tissue edema or iatrogenically placed fat. Edematous tissue has a heterogeneous intermediate signal on T1-weighted images and a hyperintense signal on T2-weighted images. Within 2 to 6 months after the operation, posterior soft-tissue scarring assumes a more homogeneous appearance. When microsurgical techniques have been used, the laminotomy site may be occult to MR imaging and manifests only indirectly as focal absence of the ligamentum flavum.

Immediate postoperative MR imaging of the discectomy patient typically reveals a persistent anterior epidural "mass" at the level of surgery. This defect is caused by a soft-tissue focus with T2-weighted image hyperintensity that usually persists for several
months. Additionally, soft-tissue edema surrounds the nerve roots and thecal sac, essentially obliterating the normal epidural fat signal on T1-weighted images. Increased signal on T2-weighted images is also apparent. After 2 to 3 months, this soft-tissue edema retracts (scar) but retains T2-weighted image hyperintensity. Thus, MR imaging within 2 months of surgery is seldom useful or definitive for differentiation of scar from disc material.

Boden et al, 5 evaluated 15 patients after operation with clinically improved radicular symptoms. T1-weighted gadolinium-enhanced MR images were obtained at 3 weeks, 3 months, and 6 months after surgery. At the level of surgery, the facet joints and paraspinal muscles enhanced on the initial studies demonstrated gradual resolution over time. The decompressed nerve root enhanced proximally toward the conus medullaris in 62% of the cases at 3 weeks, showing complete resolution at 6 months. Three weeks after the operation at the site of the original disc, lesions with mass effect and peripheral enhancement appeared identical to a herniated disc (38%) despite the asymptomatic clinical presentation. At 3 and even 6 months, 12% of the patients still had a radiographically identifiable lesion creating epidural mass effect with peripheral enhancement.
Figure 27. Pregadolinium axial TI-weighted image shows a large extruded disc fragment (open arrow) in the ventral epidural space exerting mass effect on the right S2 and S3 nerve roots (straight arrows). The right S1 nerve root is unaffected (closed curved arrow).

D, Post-gadolinium axial TI-weighted image (same level as C) shows nonenhancing disc fragment (open arrow) bordered medially by enhancing granulation tissue (closed arrow).

E and F, Pregadolinium (E) and postgadolinium (F) axial TI-weighted images several months after surgery show ill-defined intermediate signal intensity postoperative change (scar tissue) occupying the surgical tract on the right side, extending from the laminotomy site to the posterolateral anulus margin. After gadolinium infusion, reactive fibrous scar tissue enhances homogeneously, delineating in the margins an inflamed right S1 nerve root (curved arrow) as well as a seroma within the laminectomy site posteriorly (straight arrow).

Fusion masses have a variable appearance depending on their fatty marrow content. 37 Autografts tend to show a high signal on TI-weighted images secondary to marrow content. Allografts, however, show a decreased signal on TI- and T2- weighted sequences. Because cortical bone is ill defined by MR imaging, CT, or tomography as well as flexion-extension, plain film views may be needed to help assess the integrity and stability of the fusion mass.

Other postoperative abnormalities demonstrated by MR imaging include pseudomeningocele-fluid collections, fat grafts, arachnoiditis, metal artifacts, and Gelfoam artifact. 37,40 A pseudomeningocele is caused by a dural tear. This fluid collection accumulates posteriorly, where it may be traced through the surgical tract to the thecal sac. Fluid contained within a pseudomeningocele usually displays signal intensity characteristics similar to CSF, although elevated protein content or blood products may increase signal intensity on TI-weighted images. Fat grafts are sometimes placed at the laminectomy site in an attempt to diminish the amount of post-operative fibrosis. This tissue shows TI-weighted image hyperintensity adjacent to the posterior lateral thecal sac within the surgical defect. Arachnoiditis manifests as central or peripheral ("empty sac") clumping of the nerve roots. The affected spinal nerves within the thecal sac may enhance on postgadolinium images. 20 Microscopic metallic fragments, occult to plain film radiographs, can abrade from the surgical instruments at the time of surgery and be deposited in the foramina and recesses where resultant anatomic distortion may be observed on TI- or T2-weighted images. Gel-foam, used for hemostasis, characteristically displays decreased signal on TI- and T2-weighted images.

The affinity of gadolinium for epidural scar tissue in patients evaluated more than several months after spine surgery is associated with conspicuous enhancement that serves to highlight the presence and delineate the extent of scar tissue as well as separate it from nonenhancing disc material. Hueftle et al, 17 evaluated 30 patients with failed back surgery syndrome, including 17 patients with either scar tissue or disc herniation confirmed by pathologic or surgical correlation. Early (less than 10 minutes after injection) postgadolinium enhanced TI-weighted images of these 17 patients correctly distinguished scar from disc in all cases. The typical MR imaging findings of scar issue include absence of mass effect, increased signal intensity on T2-weighted images, location unrelated to the disc space, and uniform enhancement on postgadolinium TI-weighted images. Scar tissue can
occasionally produce mass effect. Enhancement of tumefactive scar tissue on postgadolinium T1-weighted images is a most important discriminator. Distinctive enhancement characteristics can aid differentiation of a mass of scar tissue from postoperative disc herniation.

The morphology and surface contour features (round or ovoid and smooth or polypoid) of a postoperative disc fragment are often characteristic, but it is the lack of contrast enhancement that lends specificity as the single most important MR imaging finding. A herniated disc, which is avascular, shows no intrinsic (internal) enhancement but may be "wrapped" by a shroud of enhancing vascular granulation tissue. The pattern of peripheral enhancement marginating the edges of a herniated disc fragment also may be observed in relation to disc herniations in patients who have not had prior surgery. This feature can be exploited in equivocal cases by generating improved contrast more accurately identifying the precise location and anatomic relationships of an extruded or migrated "free" fragment. This technique also can lend specificity by eliminating the likelihood of lesions that should enhance homogeneously such as schwannomas.

- **Pathology That May Mimic Disc Herniation**

A wide variety of both degenerative and nondegenerative conditions such as postoperative granulation tissue, tumors (meningiomas, schwannoma, epidural metastases), infection (epidural abscess, discitis) as well as miscellaneous "masses" (conjoined nerve roots, synovial cysts, Tarlov cysts, epidural gas) can mimic the appearance of disc disease. Reliable differentiation of these possibilities is predicated on consideration of, clinical findings and detailed analysis of morphologic features and MR signal characteristics detailed in Table 5.

- **Tumors**

Intraspinal tumors derived from nerve sheath elements (schwannoma) as well as arachnoidal tissue (meningioma) can simulate the appearance of a disc herniation. The morphology of a schwannoma typically conforms to the vertical or oblique orientation of the involved nerve root. This geometry can be ascertained on inspection of the set of contiguous axial images or a sagittal view.

The erosion of a neural foramen also may be an indirect clue favoring schwannoma. The presence of uniform enhancement of abnormal tissue in proximity to the posterior lateral disc margin or within the lateral gutter would corroborate the possibility of an enhancing tumor, whereas a disc fragment would not be expected to show homogeneous enhancement in the patient without prior surgery.

- **Synovial (Ganglion) Cyst**

Synovial cysts derive from the facet joints and are most commonplace at the L4-5 level, where 75% of all synovial cysts are encountered. Increased biomechanical stress at this level is believed to account for this peculiar anatomic predilection. Once a synovial
A ganglion cyst has protruded through the joint capsule and lost its connection with the parent joint space, it is referred to as a ganglion cyst. These appear as rounded or ovoid structures based along the dura adjacent to the facet joint, which may be visibly degenerated. Extruded or migrated disc fragments rarely extend posterior to the midcorononal plane of the thecal sac and are unlikely to insinuate posterolateral to the thecal sac within the epidural space, where synovial cysts are encountered.

The signal intensity of a synovial cyst is variable and may reflect proteinaceous fluid (mildly hyperintense relative to CSF on all images) and blood products (which may yield a fluid-fluid level). Air may rarely accumulate within a synovial cyst because of, the vacuum joint phenomenon within the facet joint resulting in sublimation of nitrogen from the surrounding tissues. This gas then migrates into the synovial cyst where it accumulates in the nondependent portion. The peripheral margin or capsule of the synovial cyst may exhibit low signal intensity on T1- and T2-weighted images because of calcification or deposition of blood products. Gadolinium enhancement may improve visibility of the location and contour of the synovial cyst, thus lending specificity to the diagnosis.

Figure 28. Synovial cyst arising from L4, L5 facet joint. A precontrast MRI T1 image, and B, post contrast MRI T1 image shows an ovoid mass with enhancement in the posterolateral epidural spaces. Sequestrated disc fragments rarely migrates to the lateral epidural spaces. C, MRI T2 image showing the synovial cyst as a high signal ovoid lesions with peripheral hypointensity caused by calcium or blood product. D, axial postcontrast MRI T1 image showing degeneration of the parent facet joint (open arrows), low signal intensity fluid within the cyst (starlight arrow) and enhanced medial margin of the cyst.
Conjoined Nerve Roots

Conjoined nerve roots commonly impart asymmetry to the thecal sac contents. This is usually manifested as an asymmetric paucity of epidural fat in the anterolateral recess on a single axial image. An enlarged common proximal sleeve for the anterior and posterior nerve roots of two levels (e.g., L5 and S1 nerve roots) occupies more space in this compartment of the spinal canal, thus explaining the asymmetry. On a single slice adjacent to a posterior disc margin, the appearance of a conjoined nerve root can be very similar to a disc fragment. Careful inspection of the sequence of images in a cephalocaudal direction permits isolation of the individual components of the conjoined nerve root, however, which separate more caudally and exit through their respective foramina. T1-weighted images following gadolinium infusion may help corroborate an impression of conjoined nerve roots by showing absence of abnormal enhancement in relation to the asymmetric "filling defect."

![Conjoined Nerve Roots Image](image_url)
Table 5. SIGNAL CHARACTERISTICS OF INTERVERTEBRAL DISCS AND EXTRADURAL LESIONS

<table>
<thead>
<tr>
<th>Lesion</th>
<th>TIWIs</th>
<th>T2WIs</th>
<th>TIWIs with Gadolinium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Disc</td>
<td>Intermediate</td>
<td>High</td>
<td>Intermediate without enhancement</td>
</tr>
<tr>
<td>Disc Protrusion/Extrusion</td>
<td>Low</td>
<td>Low-High</td>
<td>Low with enhancing granulation tissue</td>
</tr>
<tr>
<td>Disc Sequestration (Free Fragment)</td>
<td>Low</td>
<td>Intermediate-High</td>
<td>Low with enhancing granulation tissue</td>
</tr>
<tr>
<td>Granulation Tissue (Scar)</td>
<td>Low</td>
<td>High</td>
<td>Uniform enhancement</td>
</tr>
<tr>
<td>Meningioma, Nerve Sheath Tumors</td>
<td>Low</td>
<td>High</td>
<td>Uniform enhancement</td>
</tr>
<tr>
<td>Synovial Cysts</td>
<td>Low</td>
<td>High (may have regions of low signal secondary to calcification or blood products)</td>
<td>Low with enhancing granulation tissue</td>
</tr>
<tr>
<td>Tarlov Cyst</td>
<td>Low</td>
<td>High</td>
<td>Low with no enhancement</td>
</tr>
<tr>
<td>Epidural Abscess</td>
<td>Low</td>
<td>High</td>
<td>Uniform enhancement of granulation tissue involving the disc and contiguous endplates</td>
</tr>
<tr>
<td>Vacuum Phenomenon</td>
<td>Signal Void</td>
<td>Signal Void</td>
<td>(Blooming) enhancement No enhancement</td>
</tr>
</tbody>
</table>

Abbreviations: TIWI = T1-weighted image, T2WI = T2-weighted image.

- **Tarlov Cyst**

A perineural or Tarlov cyst refers to asymmetric enlargement of the CSF-filled arachnoid-dural cuff of a proximal nerve root. On the T1-weighted images, a Tarlov cyst approximates signal intensity of a disc fragment. Heavily T1-weighted images using short TR/TE technique show signal intensity closer to that of CSF compared with disc material, however. Isointensity of a Tarlov cyst with CSF is more readily appreciated on T2-weighted images where this normal variant can more easily be distinguished from a disc herniation.

- **Infection**
An epidural abscess may occur in an isolated fashion from hematogenous dissemination, or by direct extension of infected material from discitis or osteomyelitis. Pyogenic material or infected granulation tissue rarely accumulates in the ventral epidural space compared with the frequency of disc herniations. Signs of osteomyelitis or discitis on screening MR images would indicate a need to obtain supplemental gadolinium enhanced images, which may show characteristic features of infection, including homogeneous enhancement of granulation tissue that extends into the epidural space, whereas an avascular disc herniation would not show intrinsic enhancement.

- **Epidural Gas**

Degenerative disc disease accompanied by disc height reduction, desiccation of disc material, and osteophyte formation also may feature the so called vacuum disc phenomenon. The correlative low density shown on plain films is often the result of gas accumulation (nitrogen) subsequent to the vacuum phenomenon. Rarely, this gas can migrate into the ventral epidural space. On MR imaging the appearance of low signal intensity at this location could erroneously suggest the presence of a desiccated or calcified disc fragment. Correlation with plain films or CT may be necessary in order to differentiate epidural gas or vacuum phenomenon from a typical disc herniation.

![Figure 30. Epidural gas simulating calcified disc herniation on MR image. Gas has accumulated from vacuum phenomenon in the parent disc space with subsequent migration into the epidural compartment adjacent to the left St nerve root.](image)

**THORACIC DISC HERNIATION**

Thoracic disc herniation is often overlooked as a potential cause of thoracoabdominal complaints.

Historically, even in patients with suspected thoracic disc herniation, documentation with traditional myelographic technique often remained an elusive goal. Both detection sensitivity and clarity of myelographic images are operator dependent, requiring considerable skill and experience. Postmyelographic CT scanning, however, provides excellent spatial detail and contrast resolution, permitting an accurate diagnosis, provided that the approximate level of involvement can be suspected clinically. More recently, MR imaging has emerged as the imaging modality of choice because of its multiplanar capability, superior image quality, and decreased dependence on operator skill.
The typical patient with thoracic disc herniation presents with midline back pain. Seventy-five percent of herniated thoracic discs occur at T7-8 through T12-L1, with the single most common levels T11 and T12. Seventy-five percent of affected patients exhibit motor or sensory disturbances. Bladder or colon sphincter malfunction is present in up to 30% of patients at presentation. Unfortunately, the typical thoracic disc herniation patient is rare, and atypical "gastrointestinal" or "cardiac" symptoms may predominate.

Because thoracic disc herniation is such a rare entity, evaluation and assimilation of new imaging techniques occur at a slow pace. Ross et al. reported the comparative results of MR imaging to CT myelography of 16 thoracic disc herniations. MR imaging examinations consisted of three sequences: T1-weighted sagittal, T2-weighted sagittal, and T1-weighted axial images. CT myelography demonstrated all disc herniations as did MR imaging, provided all three image sequences were considered. Sagittal T1-weighted images proved the single most useful sequence, identifying the abnormality in 13 of 16 herniations. Sagittal T2-weighted images revealed the pertinent findings with clarity in only 75% of patients. On T1-weighted images, the herniated disc fragment was isointense or slightly hypointense relative to normal disc material and hypointense on T2-weighted images. Herniated fragments were contiguous with the parent disc and exerted mass effect on the thecal sac, often showing displacement or compression of neural elements.

Calcification of a thoracic disc herniation is not uncommon and may result in a signal void on all MR imaging sequences. Calcification can diminish the conspicuousness of a disc herniation. In such cases, correlative CT scanning may be desirable for confirmation.

Magnetic resonance imaging with GD-DTPA also has been evaluated. Postcontrast T1-weighted images can reveal reactive enhancement of the posterior longitudinal ligament or dilated epidural veins adjacent to a herniated disc fragment. An inflamed posterior longitudinal ligament appears as a linear focus of enhancement dorsal to the disc herniation. Deflated epidural veins appear as triangular areas of enhancement above and below the herniation. The use of GD-DTPA may help in differentiating thoracic disc herniations from other categories of disease such as epidural metastases.

Satisfactory MR imaging evaluation of the thoracic spine requires optimization of pulse sequence parameters and utilization of several technical adjuncts. Motion artifact from cardiac, respiratory, or vascular sources may degrade the MR image. Additional artifacts may derive from pulsatile CSF motion. Cardiac gating and the use of presaturation zones also can ameliorate the deleterious effects of physiologic motion. Despite somewhat unique physioanatomic conditions that require a tailored imaging protocol, MR imaging is the examination of choice for initial evaluation of suspected thoracic disc disease.
Figure 31. Calcified disc extrusion in left T10 foramen. A, Left parasagittal T1-weighted image shows an "empty" foramen at the T10 level. The signal void within the normal-sized foramen (arrow) represents a calcified disc fragment, a determination that cannot be made on the basis of this image alone. Note the mild decrease in disc height at the T10-11 level. B, Axial T1-weighted image localizes the calcified disc fragment within the left T10 foramen (arrow). C, Plain film lateral radiograph of the thoracic spine shows diminished disc height with calcification of the parent disc centrum (open curved arrow). Subtle high density is shown within the left T10 foramen (closed curved arrow) compared with normal appearing "lucent" foramina above and below this level. D, Axial CT scan confirms calcification of the disc fragment and parent disc centrum.

CERVICAL SPINE

Cervical spine disc disease is a common cause of neck pain and upper extremity radicular symptoms in the adult population. Not uncommonly, symptoms are vague and do not conform to a classic or specific nerve root distribution. Careful radiographic assessment or evaluation with MR imaging is therefore essential in order to accurately diagnose and localize cervical disc disease.
Cervical disc herniation may occur in an isolated fashion from trauma or in association with spondylosis. Other degenerative changes of spondylosis include desiccation of the nucleus pulposus, disc height reduction, and formation of peripheral osteophytes arising from the vertebral body end plate margins, leading to acquired stenosis of the lateral recesses or canal. Hypertrophic osteophyte formation at the posterior disc margin is usually the most important factor in the central spinal stenosis. Cervical disc herniation peaks in the third and fourth decades. Posterior herniation of a cervical disc fragment typically occurs at a paracentral location or laterally where the anulus fibrosus is weakest and the posterior longitudinal ligament comparatively thin. The most frequent level of herniation is C6-7 (60%), followed by C5-6 (30%). 19, 41, 45

The most commonly used and definitive imaging techniques for evaluation of the cervical spine include myelography with postmyelography CT and MR imaging. In addition, intravenously contrast-enhanced CT is useful in screening patients with radicular symptoms. 19, 41

![Figure 32. Acute nucleus pulposus herniation between C6-C7. This herniation resulted in radiculopathy without evidence of myelopathy in this 29 years old lady](image)

Postmyelographic CT scanning provides excellent cross-sectional evaluation of the bony elements of the spine. In addition, the spinal cord and proximal nerve roots are shown in relief, profiled by the high density of intrathecal contrast material. Compression of the spinal cord or nerve roots by bony structures is easily demonstrated. Even a small laterally placed lesion can be shown with clarity on postmyelographic CT images. Because this
procedure is invasive and involves ionizing radiation, however, MR imaging is often an attractive alternative.

At many centers, MR imaging has gained favor as the most appropriate initial screening examination of degenerative cervical spine disease. Advantages include multiplanar capabilities and excellent soft-tissue contrast without ionizing radiation or need to instill intrathecal contrast material. Disadvantages include relatively poor osseous detail, long acquisition times, variable image quality related to equipment specification or sequence prescriptions, and patient claustrophobia.

A variety of sequences, instrument parameters, and technical adjuncts have been developed for optimization of MR images of the cervical spine. A basic screening study for evaluation of suspected cervical disc disease or spondylosis should include sagittal T1- and T2-weighted images. Three-millimeter thick sagittal T1-weighted images are typically obtained using a SE technique. Sagittal and axial T2-weighted images can be obtained using a GRE technique combined with a low flip angle. As with the lumbar spine, the use of presaturation zones ventral to the spinal column helps reduce artifact from physiologic motion. Thin section images can be obtained using a 3-dimensional Fourier transformation acquisition technique for more detailed evaluation of the neural foramina if sections less than 2 mm in thickness are desired. Gadolinium-enhanced MR imaging seldom contributes additional information in patients who have had prior cervical spine surgery. In patients with myelopathic symptoms, sagittal T2-weighted images may be desired using spin echo technique coupled with peripheral cardiac gating and flow compensation in order to reduce CSF pulsation artifacts and improve visibility of cord tissue.
Satisfactory preoperative evaluation of the cervical spine can be provided with MR imaging and plain film images or, alternatively, CT myelography. In 1986, Modic et al showed a slight deficiency of MR compared with CT myelography for evaluation of extradural degenerative disease. According to Modic et al's data, MR imaging was able to accurately identify the level of disease but was nonspecific. Specifically, difficulty was encountered differentiating soft disc protrusion from spur formation. In 1988, Brown et al confirmed these results but noted that with the addition of plain film radiographs (which easily demonstrate osteophytes), MR imaging can serve as the initial screening examination of patients with suspected degenerative disc disease of the cervical spine. For further evaluation, oblique MR imaging may help delineate neuroforaminal anatomy, but requires increased imaging, time. Contrast-enhanced MR imaging and CT myelography are viable alternatives.
Postoperative Cervical Spine Imaging

Although multilevel cervical spine disease can be surgically treated with a posterior approach, most spine surgeons currently favor an anterior approach for optimal clinical results. Many surgeons perform intervertebral fusion after anterior discectomies. Bone grafts form rectangular areas of altered signal intensity within the disc space. The actual signal intensity varies depending on graft site and marrow constituents. Allografts, comprised of cortical bone and negligible marrow, show decreased signal on all pulse sequences. The signal of autograft marrow constituents usually parallels the normal vertebral body marrow. Unfortunately, there is no systematic correlation of graft signal intensity with stability. The only definitive sign of graft fusion on MR images is a homogeneously high signal intensity from the contiguous vertebral bodies and graft site without the appearance of a discernible intervening disc. Lack of this appearance does not imply nonunion.

Bony stenosis occasionally occurs after cervical spine surgery. Stenosis may be caused by formation of uncovertebral osteophytes or overgrowth of the fusion mass. Most spurs consist of compact cortical bone and thus have low signal intensity, diminishing their visibility compared with spinal canal contents on T1-weighted images. The presence of spurs can be appreciated directly on T2-weighted images owing to the high signal intensity of bordering CSF. T2-weighted images are also of fundamental importance for detection and assessment of cord impingement. Using currently available sequences, distinction between an osteophyte and cervical disc herniation is often imprecise. Specificity can be augmented by performing a noncontrast CT scan if clinically indicated.

SUMMARY

Magnetic resonance imaging has gained favor as the imaging modality of choice for evaluation of disc disease that affects the lumbar and thoracic spinal segments. This new noninvasive modality also competes favorably with myelography and CT for evaluation of cervical spine disc disease. An algorithmic approach to use of various imaging modalities for evaluation of suspected disc disease is provided. Important advantages of MR
imaging relate to its multiplanar capability and unprecedented soft-tissue contrast for simultaneous evaluation of the thecal sac and spinal canal contents. These advantages often translate to more accurate and specific diagnoses related to degenerative disc disease.

References


51. Metwally, MYM: Value of CT scan in the evaluation of spinal cord lesions. MD thesis, Ain Shams University, Cairo, Egypt [Department of Neurology], 1991


The author professor Yasser Metwally

Professor of neurology, An Shams university, Cairo, Egypt.

www.yassermetwally.com