Issues in Radiological pathology

Cerebrovascular disorders

Neuroimaging and neuropathology share common perspectives in medicine. In no field is this more evident than in the diagnosis and study of nervous system pathology: radiology and pathology are anatomically oriented specialties that depend primarily on structural changes to diagnose disease. Both specialties are broadening their perspectives of morphology to demonstrate metabolism, as with functional imaging in radiology and with immunocytochemical markers in anatomical pathology. Pathologists thus regard their radiologic counterparts as colleagues with similar morphologic approaches to diagnosis, despite the different tools used. In no discipline is this companionship more strongly felt than in the respective subspecialties that focus on disorders of the nervous system.
Neuroimaging is nothing but how "neuropathology and neuroanatomy" are approached clinically by neurologists and neurosurgeons through radiological films. Neuroimaging from the neuropathological and neuroanatomical perspectives is how gross pathology and anatomy are demonstrated radiologically. Without having a good knowledge of neuropathology and neuroanatomy it is not possible at all to understand neuroimaging.

Neuroimaging and neuropathology share common perspectives in medicine. In no field is this more evident than in the diagnosis and study of nervous system pathology: radiology and pathology are anatomically oriented specialties that depend primarily on structural changes to diagnose disease. Both specialties are broadening their perspectives of morphology to demonstrate metabolism, as with functional imaging in radiology and with immunocytochemical markers in anatomical pathology. Pathologists thus regard their radiologic counterparts as colleagues with similar morphologic approaches to diagnosis, despite the different tools used. In no discipline is this companionship more strongly felt than in the respective subspecialties that focus on disorders of the nervous system.

Neuropathologists understand, acknowledge, and admire the numerous contributions by neuroimaging in defining many neurological disorders. Neuroimaging enable us to diagnose gross pathology during life. Neuropathologists usually must wait until autopsy to demonstrate tissue changes, but surgical specimens are becoming increasingly more frequent, for example, with the advent of epilepsy surgery.

Neuroradiologists and neuropathologists have a mutual need for collaboration. Radiologists need tissue confirmation to fully understand the significance of images seen, and pathologists' findings need to be relevant to diagnoses that often rest initially with the neurologist/neuroradiologist, and provide insight into pathogenesis through unique tissue examinations.

In my opinion the best neuroradiologist is the neurologist or the neurosurgeons who must be capable of independently interpreting a neuroimaging study. Understanding neuropathology and neuroanatomy, and how they are demonstrated radiologically, are essential for interpreting a neuroimaging study. This EBook is directed primarily to neurologists and neurosurgeons. In this PDF publication, neuroimaging of cerebrovascular disorders is approached from the neuropathological and neuroanatomical perspectives. This publication addresses the question of how neuropathology and neuroanatomy are related to neuroimaging and why they are essential for our basic understanding of a neuroimaging study.

This publication covers cerebrovascular disorders from the radiological pathology point of view. The publication is free of charge and can be freely distributed. I certainly hope that you will find this publication as useful as I truly wish.

Professor Yasser Metwally
www.yassermetwally.com
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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.24 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).12 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 hypoattenuation 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 hypoattenuation 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.12

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 CT45 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. 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. 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. Occlusion of the proximal M1 segment of the MCA correlates with an infarct of 100 mL or greater in the majority of cases. 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 density. Figure 3. A thrombosed middle cerebral artery (arrow) that commonly gives the characteristic hyperdense MCA radiological sign.
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>
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<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 activity 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>
<tr>
<td>After several months</td>
<td>A cystic cavity is organized, the cavity has ragged outlines and is intersected by vascular connective tissues strands and is covered on its outer surface by a thin meningeal membrane.</td>
<td>Stage of cicatrization: The residual cystic cavity becomes surrounded by glial proliferation which is first protoplasmic and then fibrillar (astrogliosis) with frequent vascular connective tissues strand that run across the cavity</td>
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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><strong>Time</strong></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><strong>Pathophysiology</strong></td>
<td>At critical flow rates of 10 to 15 mL/100 g, there is disruption of ion homeostasis in 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><strong>Composition</strong></td>
<td>Increased intracellular water and sodium</td>
<td>Plasma filtrate including plasma proteins</td>
</tr>
<tr>
<td><strong>Location of edema</strong></td>
<td>Gray and white matter</td>
<td>Chiefly white matter</td>
</tr>
<tr>
<td><strong>Pathology</strong></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><strong>Capillary permeability to large molecules</strong></td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td><strong>Neuroimaging</strong></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>
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</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 lentiform 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 40 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>
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<tbody>
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<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>
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<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>
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</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 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 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.
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.
Figure 11. Cortical gyral enhancement. (a) Diagram illustrates gyral enhancement that is localized to the superficial gray matter of the cerebral cortex. There is no enhancement of the arachnoid, and none in the subarachnoid space or sulci. (b) Coronal gadolinium-enhanced T1-weighted MR image in a case of herpes encephalitis shows multifocal, intraaxial, curvilinear, cortical gyri-form enhancement that involves both temporal lobes. The enhancement is most prominent on the right but is also seen in the left insular region (arrows) as well as in the medial frontal lobes and cingulate gyrus (arrowhead).

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.

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.
Figure 17. 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>Vasogenic edema (cytotoxic edema does not contribute to CT hypodensity)</td>
<td></td>
<td>Astrogliosis 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. 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>
<thead>
<tr>
<th>Radiological feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain edema, diffuse low density on the initial CT scan</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>Hyperdense MCA sign</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>Sites of occlusion</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


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)

<table>
<thead>
<tr>
<th>Bland or non-hemorrhagic</th>
<th>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 &quot;predominantly a natural tissue consequence of embolism&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhagic conversion of infarction</td>
<td>Hemorrhagic infarction (HI)</td>
</tr>
<tr>
<td></td>
<td>Parenchymatous hemorrhage associated with a cerebral embolic infarction (PH)</td>
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</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)
<table>
<thead>
<tr>
<th>hemorrhagic infarction <em>(HI)</em></th>
<th>HI appears as a discontinuous heterogeneous mixture of high and low densities occurring within the vascular territory of the infarct</th>
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<tbody>
<tr>
<td>Parenchymatous hemorrhage associated with a cerebral embolic infarction <em>(PH)</em></td>
<td>Parenchymatous hemorrhage associated with a cerebral embolic infarction <em>(PH)</em> 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</td>
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</table>

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 the 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 reirregreation which takes place in the capillary blood vessels that have been damaged by the initial hypoxia. Reirregreation 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>Features</th>
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<tbody>
<tr>
<td></td>
<td>A low frequency of associated bleeding elsewhere in the body.</td>
</tr>
<tr>
<td></td>
<td>Lack of consistent association between ICH and preceding head trauma or cerebral infarction.</td>
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<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

<table>
<thead>
<tr>
<th>Thrombolysis</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Predominantly lobar location, with rare examples of bleeding into the posterior fossa and putamen</td>
</tr>
<tr>
<td></td>
<td>Multiple simultaneous haemorrhages in about one-third of the cases.</td>
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<td></td>
<td>Mortality rate of 44-66%.</td>
</tr>
</tbody>
</table>

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 α 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 trans-formation 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
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.
Table 4. Effect of increased intracranial venous pressure due to sinovenous thrombosis. (50)

<table>
<thead>
<tr>
<th>Comment</th>
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<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>
<tr>
<td>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.</td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td>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>
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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>
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<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>
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</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, paresthesia, weakness, changed mentation, drowsiness, right hemiparesis</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, oedema, 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, obtundation, hemiparesis, astasia</td>
<td>Three patients had measurements taken: 32-38 mm Hg</td>
</tr>
<tr>
<td>IV</td>
<td>Severe edema, with or without hemorrhage</td>
<td>Hemiparesis, oedema, loss of consciousness, coma</td>
<td>Three patients had measurements taken: 42-51 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>
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<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.</td>
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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.
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. (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


INTRODUCTION

Border zone or watershed infarcts are ischemic lesions that occur in characteristic locations at the junction between two main arterial territories. These lesions constitute approximately 10% of all brain infarcts and are well described in the literature. Their pathophysiology has not yet been fully elucidated, but a commonly accepted hypothesis holds that decreased perfusion in the distal regions of the vascular territories leaves them vulnerable to infarction. Two types of border zone infarcts are recognized: external (cortical) and internal (subcortical). To select the most appropriate methods for managing these infarcts, it is important to understand the underlying causal mechanisms. Internal border zone infarcts are caused mainly by hemodynamic compromise, whereas external border zone infarcts are believed to result from embolism but not always with associated hypoperfusion. Various imaging modalities have been used to determine the presence and extent of hemodynamic compromise or misery perfusion in association with border zone infarcts, and some findings (eg, multiple small internal infarcts) have proved to be independent predictors of subsequent ischemic stroke. A combination of several advanced
techniques (eg, diffusion and perfusion magnetic resonance imaging and computed tomography, positron emission tomography, transcranial Doppler ultrasonography) can be useful for identifying the pathophysiologic process, making an early clinical diagnosis, guiding management, and predicting the outcome.

Watersheds or border zones are areas that lie at the junction of two different drainage areas. The vascular supply of the cerebral parenchyma can be envisioned in a similar manner, with defined boundaries between different arterial systems. Cerebral infarcts in border zones were first discussed in 1883 (1) and were defined as ischemic lesions in an area between two neighboring vascular territories (2). These territories can be further classified in two broad categories as (a) external (cortical) or (b) internal (subcortical) border zones. Border zone infarcts constitute approximately 10% of all cerebral infarcts (3). Various theories have been proposed to explain their pathogenesis. It is believed that repeated episodes of severe systemic hypotension are the most frequent cause (3). Susceptibility of border zones to ischemia was proved in an autopsy study of patients with border zone infarcts (4). Various neuropathologic studies have shown neuronal necrosis from hypotension in these regions and have advanced our understanding of the preferential distribution of border zone infarcts (5,6).

The appearances of border zone infarcts depicted by standard imaging modalities are well described. Advanced imaging techniques can help identify areas of misery perfusion associated with these infarcts. Misery perfusion represents a chronic failure of cerebral autoregulation associated with decreased cerebral perfusion pressures in the presence of extracranial and intracranial atheromatous disease. The important information derived from imaging can be useful for patient management and disease prognosis.

The article begins with a discussion of the anatomic locations, classification, and pathophysiology of border zone infarcts. The existing literature about the causal mechanisms of associated hemodynamic compromise is reviewed, and the imaging appearances of the lesions are described in detail.

- **Classification of Border Zone Infarcts**

Border zone infarcts are grouped into two main categories based on their location in either external (cortical) or internal (subcortical) regions at axial computed tomography (CT). Various terms for these lesions have been used in the literature, with the most common summarized in the Table 1.
The external or cortical border zones are located at the junctions of the anterior, middle, and posterior cerebral artery territories. Infarcts in the anterior external border zones and paramedian white matter are found at the junction of the territories supplied by the anterior and middle cerebral arteries, and those in the parieto-occipital areas (posterior external border zones) are found at the junction of the territories supplied by the middle and posterior cerebral arteries.

The internal or subcortical border zones are located at the junctions of the anterior, middle, and posterior cerebral artery territories with the Heubner, lenticulostriate, and anterior choroidal artery territories. Internal border zone infarcts thus may be designated as infarcts of the lenticulostriate–middle cerebral artery, lenticulostriate–anterior cerebral artery, Heubner–anterior cerebral artery, anterior choroidal–middle cerebral artery, and anterior choroidal–posterior cerebral artery territories (7). Infarcts of the lenticulostriate–middle cerebral artery border zone, which is supplied by the end branches of deep perforating lenticulostriate arteries and medullary penetrators from the pial–middle cerebral artery, are the most commonly seen at imaging.

**Table 1. Border Zone Infarcts**

<table>
<thead>
<tr>
<th>External (cortical) infarcts</th>
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<tbody>
<tr>
<td>Frontal cortex (between the anterior and middle cerebral arteries)</td>
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<tr>
<td>Occipital cortex (between the middle and posterior cerebral arteries)</td>
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<tr>
<td>Paramedian white matter (between the anterior and middle cerebral arteries)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Internal (subcortical) infarcts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between the lenticulostriate and middle cerebral arteries*</td>
</tr>
<tr>
<td>Between the lenticulostriate and anterior cerebral arteries</td>
</tr>
<tr>
<td>Between the Heubner and anterior cerebral arteries</td>
</tr>
<tr>
<td>Between the anterior choroidal and middle cerebral arteries</td>
</tr>
<tr>
<td>Between the anterior choroidal and posterior cerebral arteries</td>
</tr>
</tbody>
</table>
Watershed infarcts occur at the border zones between major cerebral arterial territories as a result of hypoperfusion. There are two patterns of border zone infarcts: 1. Cortical border zone infarctions Infarctions of the cortex and adjacent subcortical white matter located at the border zone of ACA/MCA and MCA/PCA. 2. Internal border zone infarctions Infarctions of the deep white matter of the centrum semiovale and corona radiata at the border zone between lenticulostriate perforators and the deep penetrating cortical branches of the MCA or at the border zone of deep white matter branches of the MCA and the ACA.

- **Pathophysiology of Border Zone Infarcts**

Border zone infarcts involve the junction of the distal fields of two nonanastomosing arterial systems (8). The conventional theory implicates hemodynamic compromise produced by repeated episodes of hypotension in the presence of a severe arterial stenosis or occlusion. The lower perfusion pressure found within the border zone areas in this setting confers an increased susceptibility to ischemia, which can lead to infarction. This causal role of severe arterial hypotension has been well described and confirmed by the results of experimental studies in animals (9,10). The typical clinical manifestations of syncope, hypotension, and episodic fluctuating or progressive weakness of the hands are also supportive of this theory of hemodynamic failure (11,12). Radiologic studies also support the hypothesis that border zone infarcts distal to internal carotid artery disease are more likely to occur in the presence of a noncompetent circle of Willis.

In sharp contrast with this widely prevalent interpretation, several pathologic investigations have emphasized an association between border zone infarction and microemboli, and embolic material has been found within areas of border zone infarction in autopsy series (13). Preferential propagation of emboli in the border zone regions also has been found in experimental studies (14).

Border zone infarction may be better explained by invoking a combination of two often interrelated processes: hypoperfusion and embolization (15). Hypoperfusion, or decreased
blood flow, is likely to impede the clearance (washout) of emboli. Because perfusion is most likely to be impaired in border zone regions, clearance of emboli will be most impaired in these regions of least blood flow. Severe occlusive disease of the internal carotid artery causes both embolization and decreased perfusion. Similarly, cardiac disease is often associated with microembolization from the heart and aorta with periods of diminished systemic and brain perfusion. This theory, although it seems reasonable, remains unproved and has been challenged on many accounts.

Color plate 2. This coronal section of the cerebral hemispheres demonstrates the result of a severe global hypoxic-ischemic insult. It is from a person who was resuscitated after experiencing a large pulmonary embolus with severe hypoxia and hypotension. She lived several months following the event, first in coma, then in a vegetative state. This section shows marked thinning of the majority of the cortical ribbon (compare to normal) and atrophy of the deep gray structures. The lateral ventricles are secondarily enlarged; this passive enlargement of the ventricles as a result of loss of brain tissue is known as hydrocephalus ex vacuo.

**EXTERNAL WATERSHED (BORDER ZONE) INFARCTION**

- **Anterior external border zone infarcts**
  - Imaging Appearance

The external, cortical border zones are located between the anterior, middle, and posterior cerebral arteries and are usually wedge-shaped or ovoid. However, their location may vary with differences in the arterial supply. It is sometimes difficult to determine whether a person has sustained a border zone infarct on the basis of the location of the infarct in
relation to the vessels on a CT or MR image (16,17). Because of this extensive anatomic variation, minimum and maximum distribution territories of each vessel have been defined. It is not uncommon to describe a cortical infarct as a “territorial” infarct if it lies completely within the expected or possible maximum area of a vascular territory or as a “potential” infarct if it is outside these maxima (18). Furthermore, the location of cortical border zones may vary because of the development of leptomeningeal collaterals (8). The anatomy of cortical border zones can be complex, with marked variability due to individual differences in the territories supplied by the major arteries of the brain.

Color plate 3. The bilaterally symmetric dark discolored areas seen superiorly and just lateral to the midline represent recent infarction in the watershed zone between anterior and middle cerebral arterial circulations. Such watershed infarctions can occur with relative or absolute hypoperfusion of the brain.
Causal Mechanisms

The mechanism of external border zone infarction has been widely debated. Many studies have documented hemodynamic abnormalities in the anterior watershed or frontal cortical border zone. However, in many studies, no evidence of such hemodynamic impairment was found (19). In other studies, substantially fewer severe stenoses or occlusions of major vessels than border zone infarcts were found (20). The cerebral or carotid vessels may appear entirely normal or show mild or moderate narrowing without hemodynamic compromise. Isolated cortical border zone infarcts may be embolic in nature and are less frequently associated with hemodynamic compromise. Microemboli from the heart or atherosclerotic plaques in major arteries may preferentially propagate to cortical border zones, which have lower perfusion than other areas of the vasculature, and, thus, a limited ability to wash out these emboli. Many patients with cortical border zone infarcts have concomitant smaller cortical infarcts. These findings support the hypothesis that an embolic mechanism plays a crucial role in the pathogenesis of external border zone infarcts.

Figure 1. Coronal fluid-attenuated inversion recovery MR images show the distribution of external (cortical) border zone infarcts at the junctions of the anterior cerebral artery and middle cerebral artery territories (A) and the middle cerebral artery and posterior cerebral artery territories (B). (C) Diffusion-weighted MR images show a cortical border zone infarct at the junction of the anterior cerebral artery and middle cerebral artery territories. Angiography of the right-sided common carotid and internal carotid arteries in the same patient showed normal vessels with no occlusion or stenosis.
Clinical Course

Patients with external border zone infarcts have a more benign clinical course and a better prognosis than those with internal border zone infarcts, although the severity of clinical signs and symptoms and the score on the National Institutes of Health Stroke Scale at the time of admission might not differ substantially between the two patient groups. The external border zone is closer to the cortical surface, where penetrating arteries originate, and thus it has a better chance of developing a collateral supply through leptomeningeal or dural anastomoses. However, when external border zone infarcts occur in association with internal border zone infarcts, there is a higher probability of hemodynamic impairment, and the prognosis may not be good (21).

Figure 2. Bilateral border infarcts. A 60 yo male brought unconscious to casualty with possible cardiac event. On admission MRI Diffusion show bilateral fronto parietal and parieto occipital cortical restricted diffusion. Similar restricted diffusion in caudate nuclei. Area of involvement corresponds to cortical as well as internal border zone infarcts.

- Posterior External (Cortical) Border Zone Infarcts

Anterior external border zone infarcts are more common than posterior ones because of the high prevalence of internal carotid artery disease. Vertebrobasilar system disease with superimposed fetal circulation (ie, a fetal-type posterior cerebral artery) may lead to posterior external border zone infarcts. Unilateral posterior external border zone infarcts have been related to cerebral emboli either of cardiac origin or from the common carotid artery, whereas bilateral infarcts are more likely to be caused by underlying hemodynamic impairment (vascular stenosis) (27).
INTERNAL WATERSHED (BORDER ZONE) INFARCTS

- Imaging Appearance

Internal border zone infarcts appear in multiples, in a rosarylike pattern. In one report, this pattern was described as a series of three or more lesions, each with a diameter of 3 mm or more, arranged in a linear fashion parallel to the lateral ventricle in the centrum semiovale or corona radiata (19). Internal border zone infarcts are classified on the basis of their radiologic appearance as either confluent or partial (8). Partial infarcts are usually large, cigar shaped, and arranged in a pattern resembling the beads of a rosary, parallel and adjacent to the lateral ventricle. The duration of hemodynamic compromise has been postulated as the cause of the varied radiologic appearances, with a brief episode of compromise leading to a partial infarct, and a longer period of compromise, to confluent infarcts (22). Confluent internal border zone infarcts may be manifested by a stepwise onset of contralateral hemiplegia. They also may be associated with a poorer recovery than is typical for partial infarcts.
Figure 4. FLAIR and MRI T2 images showing examples of Internal border zone infarcts

Internal border zone infarcts must be differentiated from superficial perforator (medullary) infarcts, which may have a similar appearance on MR images. Superficial perforator infarcts, which are caused by the occlusion of medullary arteries from pial plexuses, are smaller, superficially located, and widely scattered, whereas internal border zone infarcts tend to localize in paraventricular regions (23). Superficial perforator infarcts are associated with less severe vascular stenoses and a better prognosis than internal border zone infarcts. Because of the difficulty of differentiating between the two types of infarcts on radiologic images, they have sometimes been collectively described as subcortical white matter infarcts, but that term is diagnostically nonspecific.
Causal Mechanisms

In contrast to external border zone infarcts, internal border zone infarcts are caused mainly by arterial stenosis or occlusion, or hemodynamic compromise. The greater vulnerability of internal border zones to hemodynamic compromise has been explained on the basis of anatomic characteristics of the cerebral arterioles within these zones. The internal border zones are supplied by medullary penetrating vessels of the middle and anterior cerebral arteries and by deep perforating lenticulostriate branches. The medullary penetrating arteries are the most distal branches of the internal carotid artery and have the lowest perfusion pressure. The deep perforating lenticulostriate arteries have little collateral supply, and there are no anastomoses between the deep perforators and the white matter medullary arterioles. Therefore, the centrum semiovale and corona radiata are more susceptible than other regions to ischemic insults in the setting of hemodynamic compromise.
Clinical Course

Internal border zone infarcts are associated with a poor prognosis and clinical deterioration (21,22). Patients may undergo prolonged hospitalization, and they have an increased likelihood of remaining in a disabled state during clinical follow-up. The results of diffusion-weighted imaging studies suggest that patients with internal border zone infarcts have an increased risk for stroke during the first few days after infarction (24). Perfusion studies in patients with such infarcts have shown a far greater area of misery perfusion than is reflected on diffusion-weighted images. Involvement of the adjacent cortex also has been found on perfusion images (25). Thus, the typically small internal border zone infarcts represent the “tip of the iceberg” of decreased perfusion reserve and may be predictive of impending stroke. This hypothesis was tested further with quantitative carbon 11–flumazenil positron emission tomography (PET), which showed a decrease in benzodiazepine receptors, a finding suggestive of neuronal damage beyond the region of infarction seen on MR images (26).

Conclusions

Internal (subcortical) border zone infarcts, which typically appear in a linear rosarylike pattern in the centrum semiovale, are caused mainly by hemodynamic compromise. External (cortical) border zone infarcts are believed to be caused by embolism, sometimes with associated hypoperfusion. External border zone infarcts usually follow a benign clinical course, whereas internal border zone infarcts are associated with higher morbidity and a higher risk for future stroke. Different therapeutic approaches may be required to prevent early clinical deterioration in patients with different types of border zone infarcts.
CORTICAL LAMINAR NECROSIS

Cortical laminar necrosis occurs as a consequence of oxygen or glucose depletion in the watershed intracortical area in the third cortical layer, as in anoxia, hypoglycaemia, status epilepticus, ischaemic stroke CNS vasculitis, neuro-lupus and drugs (46). Cortical pseudolaminar necrosis, also known as cortical laminar necrosis and simply laminar necrosis, is the (uncontrolled) death of cells in the (cerebral) cortex of the brain in a band-like pattern, (46) with a relative preservation of cells immediately adjacent to the meninges. Pathologically Cortical laminar necrosis represents cytotoxic oedema affecting a particular layer of cerebral cortex (third grey matter layer) at the acute stage and is neuropathologically characterized by delayed selective neuronal necrosis at the acute stage followed by reactive change of glia and deposition of fat-laden macrophages. In particular the characteristic high intensity on precontrast T1-weighted images in Cortical laminar necrosis, which generally begins to appear about 2 weeks after the ictus, becomes prominent at 1-2 months and began to fade at 3-11 months, is due to the deposition of fat-laden macrophages or methemoglobin representing intracortical microhemorrhages.

Chronic brain infarcts are typically seen as low-intensity lesions on T1-weighted and high-intensity lesions on T2- weighted images due to prolonged T1 and T2 values (46). In some infarcts, high-intensity lesions are observed on precontrast T1-weighted images. Haemorrhagic infarcts show characteristic changes of the signal intensity, similar to those of haemorrhage, due to deoxyhaemoglobin, methohaemoglobin, and haemosiderin (52,53). Petechial haemorrhage may occur in cortical infarcts (cortical laminar necrosis) but cannot explain the high-intensity laminar lesions in all patients on precontrast T1 images (46,47). In general high intensity on precontrast T1-weighted images (T1 shortening) can be due to methaemoglobin, mucin, high protein concentration, lipid or cholesterol, calcification and cortical laminar necrosis (51). In ischaemic stroke, high intensity laminar lesions can be cortical laminar necrosis, haemorrhagic infarcts (microhaemorrhage), or a combination of the two.

The grey matter has six layers. The third is the most vulnerable to depletion of oxygen and glucose (watershed intracortical zone). When a relatively mild ischaemic or hypoglycaemic insult occurs, the vulnerable layers are selectively injured (selective neuronal vulnerability) (64).

Because the third grey matter layer is the most vulnerable to anoxia and hypoglycemia, Cortical laminar necrosis is a specific type of cortical infarction, usually seen in the setting of anoxic encephalopathy. Other etiologies like hypoglycemia, status epilepticus and immunosuppressive chemotherapy have been implicated. (55,56) The appearance of the MR images in the setting of diffuse cortical laminar necrosis can be deceptive. Properly windowed diffusion weighted imaging can be very helpful in detecting cortical laminar necrosis, especially in the setting of anoxic-hypoxic encephalopathy in the early subacute phase. (57) Cortical laminar necrosis in the setting of anoxic encephalopathy has a universally poor prognosis, with most patients either progressing to brain death or remaining in a persistent vegetative state. (56).
Boyko et al. (51) described cortical laminar necrosis in brain infarcts as linear high on precontrast TI images signal based on the cortical surface and becoming less intense over time (months). In hypoxic brain damage, Precontrast TI-weighted images revealed a laminar hyperintensity lesion in the cortex in the late subacute stage (21-28 days) which tended to fade after 2 months but persisted up to 11 months (46). In laminar cortical necrosis, cortical high intensity on precontrast TI-weighted images generally begins to appear about 2 weeks after the ictus, became prominent at 1-2 months and began to fade at 3 months, although it could persist up to 11 months. FLAIR images are more sensitive than T1 weighted images to the cortical laminar lesions. Early cortical changes on day 1 showed high intensity on T2-weighted images and low intensity on T1-weighted images, which later became high intensity on precontrast T1 images. This early change is due to prolonged T1 and T2 values caused by acute ischaemic change (tissue oedema).

The cortical laminar necrosis, seen as a laminar high signal lesion on precontrast T1-weighted images, was first described by Sawada et al. (55) in a patient with anoxic encephalopathy. The cortical lesion is usually in the watershed region (watershed intracortical zone) in this condition (46). Cortical laminar necrosis is also reported in ischaemic stroke (46,47,48,49). Although Nabatame et al. (50) thought the high intensity on precontrast T1-weighted images was due to methohaemoglobin in haemorrhagic tissue, pathological studies revealed no haemorrhage (46,50,51). Takahashi et al. (54) reported a patient with a cortical laminar lesion showing low intensity on T2-weighted images in the chronic stage, which they thought due to haemosiderin.
Color plate 4. **Cortical laminar necrosis.**

Color plate 5. **Cortical laminar necrosis.** Early in the disease, gross findings will be characterized by edema and swelling. Note the swollen glistening appearance of the cerebral cortex. Note the vague line between cortex and subcortical white matter (arrows). Histologically this line would correspond to an early (laminar) band of cortical necrosis.
Figure 7. A 60-year-old woman with an anti phospholipid antibody syndrome. All images 1 month after ictus. a A T1 weighted image shows a high-intensity right occipital laminar lesion, with low intensity in white matter. b There is intense contrast enhancement of the grey matter, none of the white matter. c A T2-weighted image demonstrates an isointense laminar lesion, while the white matter shows very high intensity. d A proton-density image demonstrates the high-intensity laminar cortical lesion.
Figure 8. A 73-year-old man with speech disturbance. a At 1.5 months after the ictus, a precontrast T1-weighted image demonstrates a high-intensity left parietal laminar lesion (arrow). B, At 6 months, there is no high intensity and no contrast enhancement (C), but a FLAIR image (D) still shows a high-intensity laminar lesion.
Figure 9. Precontrast T1 image showing cortical laminar necrosis demonstrated as a laminar linear cortical hyperintensity.

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INTRODUCTION

Cortical laminar necrosis occurs as a consequence of oxygen or glucose depletion in the watershed intracortical area in the third cortical layer, as in anoxia, hypoglycaemia, status epilepticus, ischaemic stroke CNS vasculitis, neuro-lupus and drugs [1]. Cortical pseudolaminar necrosis, also known as cortical laminar necrosis and simply laminar necrosis, is the (uncontrolled) death of cells in the (cerebral) cortex of the brain in a band-like pattern,[1] with a relative preservation of cells immediately adjacent to the meninges. Pathologically Cortical laminar necrosis represents cytotoxic oedema affecting a particular layer of cerebral cortex (third grey matter layer) at the acute stage and is neuropathologically characterized by delayed selective neuronal necrosis at the acute stage followed by reactive change of glia and deposition of fat-laden macrophages. In particular the characteristic high intensity on precontrast T1-weighted images in Cortical laminar
necrosis, which generally begins to appear about 2 weeks after the ictus, becomes prominent at 1-2 months and began to fade at 3-11 months, is due to the deposition of fat-laden macrophages or methemoglobin representing intracortical microhemorrhages.

Chronic brain infarcts are typically seen as low-intensity lesions on T1-weighted and high-intensity lesions on T2-weighted images due to prolonged T1 and T2 values [3, 4]. In some infarcts, high-intensity lesions are observed on precontrast T1-weighted images. Haemorrhagic infarcts show characteristic changes of the signal intensity, similar to those of haemorrhage, due to deoxyhaemoglobin, methohaemoglobin, and haemosiderin [7, 8]. Petechial haemorrhage may occur in cortical infarcts (cortical laminar necrosis) but cannot explain the high-intensity laminar lesions in all patients on precontrast T1 images [9]. In general high intensity on precontrast T1-weighted images (T1 shortening) can be due to methaemoglobin, mucin, high protein concentration, lipid or cholesterol, calcification and cortical laminar necrosis [6]. In ischaemic stroke, high intensity laminar lesions can be cortical laminar necrosis, haemorrhagic infarcts (microhaemorrhage), or a combination of the two.

The grey matter has six layers. The third is the most vulnerable to depletion of oxygen and glucose (watershed intracortical zone). When a relatively mild ischaemic or hypoglycaemic insult occurs, the vulnerable layers are selectively injured (selective neuronal vulnerability) [1].

Because the third grey matter layer is the most vulnerable to anoxia and hypoglycemia, Cortical laminar necrosis is a specific type of cortical infarction, usually seen in the setting of anoxic encephalopathy. Other etiologies like hypoglycemia, status epilepticus and immunosuppressive chemotherapy have been implicated.[11,12] The appearance of the MR images in the setting of diffuse cortical laminar necrosis can be deceptive. Properly windowed diffusion weighted imaging can be very helpful in detecting cortical laminar necrosis, especially in the setting of anoxic-hypoxic encephalopathy in the early subacute phase.[13] Cortical laminar necrosis in the setting of anoxic encephalopathy has a universally poor prognosis, with most patients either progressing to brain death or remaining in a persistent vegetative state.[12].

Boyko et al. [6] described cortical laminar necrosis in brain infarcts as linear high on precontrast T1 imag signal based on the cortical surface and becoming less intense over time (months). In hypoxic brain damage, Precontrast T1-weighted images revealed a laminar hyperintensity lesion in the cortex in the late subacute stage (21-28 days) which tended to fade after 2 months but persisted up to 11 months [9]. In laminar cortical necrosis, cortical high intensity on precontrast T1-weighted images generally begins to appear about 2 weeks after the ictus, became prominent at 1-2 months and began to fade at 3 months, although it could persist up to 11 months. FLAIR images are more sensitive than T1 weighted images to the cortical laminar lesions. Early cortical changes on day 1 showed high intensity on T2-weighted images and low intensity on T1-weighted images, which later became high intensity on precontrast T1 images. This early change is due to prolonged T1 and T2 values caused by acute ischaemic change (tissue oedema).
The cortical laminar necrosis, seen as a laminar high signal lesion on precontrast T1-weighted images, was first described by Sawada et al. [10] in a patient with anoxic encephalopathy. The cortical lesion is usually in the watershed region (watershed intracortical zone) in this condition [9]. Cortical laminar necrosis is also reported in ischaemic stroke [5, 6]. Although Nabatame et al. [5] thought the high intensity on precontrast T1-weighted images was due to methohaemoglobin in haemorrhagic tissue, pathological studies revealed no haemorrhage [6, 11]. Takahashi et al. [9] reported a patient with a cortical laminar lesion showing low intensity on T2-weighted images in the chronic stage, which they thought due to haemosiderin.

Figure 1. Cortical laminar necrosis.
Figure 2. Cortical laminar necrosis. Early in the disease, gross findings will be characterized by edema and swelling. Note the swollen glistening appearance of the cerebral cortex. Note the vague line between cortex and subcortical white matter (arrows). Histologically this line would correspond to an early (laminar) band of cortical necrosis.

Figure 3. A 60-year-old woman with an anti phospholipid antibody syndrome. All images 1 month after ictus. a A T1 weighted image shows a high-intensity right occipital laminar lesion, with low intensity in white matter. b There is intense contrast enhancement of the grey matter, none of the white matter. c A T2-weighted image demonstrates an isointense laminar lesion, while the white matter shows very high intensity. d A proton-density image demonstrates the high-intensity laminar cortical lesion.
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Figure 5. Precontrast T1 image showing cortical laminar necrosis demonstrated as a laminar linear cortical hyperintensity.

In cortical laminar necrosis, CT does not demonstrate haemorrhage or calcification, and MRI also fails to demonstrate haemorrhage. Although the mechanism of T1 shortening (precontrast T1 hyperintensity) in the cortical laminar necrosis remains unclear, high cortical intensity on precontrast T1-weighted image (generally begins to appear about 2 weeks after the ictus, becomes prominent at 1-2 months and began to fade at 3 months) is believed to occur by neuronal damage and reactive tissue change, (reactive change of glia and deposition of fat-laden macrophages) [9, 10]. On FLAIR images, cortical laminar necrosis is demonstrated as linear cortical hyperintensity due to increased mobile protons in the reactive tissue. A less likely explanation is that microhaemorrhage in the cortical laminar lesion can occur in some patients, which may contribute to T1 shortening.

On CT cortical laminar necrosis shows contrast enhancement due to disruption of the blood-brain barrier, where loss of neurons and vascular proliferation occur [11]. On MRI contrast enhancement occurs in the cortical lesion with disruption of the blood-brain barrier. Parenchymal enhancement in brain infarcts is common and is generally maximal between 3 days and 3 weeks; it disappears by 3 months [13-15]. The greater sensitivity of MRI to changes in the blood-brain barrier results in prolonged detection of blood-
brain barrier disruption in the cortical lesion, at up to 8 months in our series.

Figure 6. MR (diffusion weighted imaging) showing gyriform increased signal suggestive of cortical laminar necrosis

- **Epilepsy, metabolic disorders and Neuro-lupus**

Transient radiological changes, such as hyperintense cortical lesions in T2, FLAIR, and diffusion weighted images, have been reported in patients with focal Neuro-lupus. Radiologically, Cortical laminar necrosis is characterised by high intensity cortical lesions on T1 weighted and FLAIR images following a gyral distribution, associated with volume loss over the underlying cortex. Cortical laminar necrosis has been described associated with hypoxia, metabolic disturbances, drugs, infections, and Neuro-lupus. Cortical laminar necrosis associated with Neuro-lupus is mostly due to severe hypoglycaemia or hypoxia or significant decreases in blood pressure during the episodes of focal Neuro-lupus. The hypothesis that the necrosis observed in these patients is primarily a consequence of repeated seizures is further supported by the fact that Cortical laminar necrosis is seen in the same areas as those displaying acute cortical oedema and hyperperfusion during the acute phase of Neuro-lupus. Furthermore, these hyperintense lesions did not involve separate vascular territories and occurred at a distance from the structural lesions. The location of Cortical laminar necrosis is also concordant with the location of continuous epileptic activity shown by surface EEG during Neuro-lupus.
• **Hypoglycemia**

First described in a patient with anoxic encephalopathy, it was found later that laminar cortical necrosis represented cytotoxic oedema affecting a particular layer of cerebral cortex neuropathologically characterised by delayed selective neuronal necrosis and is a consequence of hypoxic-ischaemic encephalopathy, hypoglycaemic encephalopathy, status epilepticus and ischaemic stroke. Mechanisms of laminar cortical necrosis are not well elucidated.

![Figure 7](image1.png)

**Figure 7.** Cortical laminar necrosis in a patient with hypoglycemia. (A) Diffusion-weighted MRI shows linear hyperintensities in a gyral pattern in right parietal and insular cortices (white arrow). (B) MRI Apparent diffusion coefficient image showing hypointensities in these areas suggestive of restriction of diffusion. (C) Susceptibility weighted image shows hyperintensities within the right parietal and insular cortices without blooming artifacts.

![Figure 8](image2.png)

**Figure 8.** Cortical laminar necrosis in a patient with hypoglycemia. (A) MRI coronal T2-weighted image of brain showing hyperintense signals from medial temporal lobe (thick white arrow) of right side sparing cerebellar hemispheres. (B) MRI FLAIR images showing hyperintensities in the hippocampal region and parahippocampal gyrus right more than the left. (C) MRI brain coronal
section T2-weighted images showing hyperintensities bilaterally in the hippocampal region.

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RADIOLOGICAL PATHOLOGY OF MICROVASCULAR CEREBRAL HAEMORRHAGE:

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 endocrinological 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.

Figure 1. Microaneurysms of the small penetrating arterioles

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).
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.
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 6. Cerebral (A) and pontine (B) acute haemorrhage, C, acute cerebellar hemorrhage

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

Figure 8. A, Subacute caudate hemorrhage, B, apoplectic cyst, C, Hypertensive hemorrhage into basal ganglia region (specifically: internal capsule).

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 putamenocapsular 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].

![Figure 11. CT appearance of hemorrhage. Serial CT scans of right thalamic hematoma. (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 magnetically 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 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. 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 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 from the susceptibility effect of hemosiderin within macrophage lysosomes.
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 T1-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>
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<td>Paramagnetic intracellular methemoglobin</td>
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</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.

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**SUMMARY**

Table 2. The biochemical stages of cerebral hematomas

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hyperacute stage</strong></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><strong>Acute stage</strong> [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><strong>Subacute stage</strong> [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><strong>Chronic stage</strong> [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 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, methemoglobin</td>
<td>T1 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 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 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 osmotically active proteins</td>
<td>• Activation of the coagulation cascade and thrombin synthesis</td>
<td>• Hemoglobin induced neuronal toxicity</td>
</tr>
<tr>
<td></td>
<td>• Complement activation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Perihematomal inflammation and leukocyte infiltration</td>
<td></td>
</tr>
</tbody>
</table>

References


Created by Professor Yasser Metwally

http://yassermetwally.com
INTRODUCTION

In the last decade or so, cerebral microbleeds (CMBs) – tiny perivascular hemorrhages seen as small, well-demarcated, hypointense, rounded lesions on MRI sequences that are sensitive to magnetic susceptibility – have generated increasing interest among neurologists and clinical stroke researchers. As MRI techniques become more sophisticated, Cerebral microbleeds are increasingly detected in various patient populations (including all types of stroke, Alzheimer’s disease and vascular cognitive impairment) and healthy community-dwelling older people. Their presence raises many clinical dilemmas and intriguing pathophysiological questions. Cerebral microbleeds are emerging as an important new manifestation and diagnostic marker of cerebral small-vessel disease.
Cerebral microbleeds are defined radiologically as small, rounded, homogeneous, hypointense lesions on T2*-weighted gradient-recalled echo (T2*-GRE) and related MRI sequences that are sensitive to magnetic susceptibility.[2] Scharf et al. were the first to report on small, intracerebral black dots of signal loss on T2-weighted spin-echo MRI in patients with hypertensive cerebrovascular disease and intracerebral hemorrhage (ICH) associated with ischemic white matter disease and lacunar infarcts.[3] They called these lesions ‘hemorrhagic lacunes’, and their further characterization using T2*-GRE MRI sequences led to the current radiologic definition of ‘microbleeds’, a term coined by Offenbacher and colleagues in 1996.[4] A key feature of Cerebral microbleeds is that they are not seen well on conventional computed tomography or MRI scans. Available histopathological studies suggest that Cerebral microbleeds radiological lesions are due to tiny bleeds adjacent to abnormal small vessels, being mainly affected by hypertensive angiopathy (arteriolosclerosis – usually lipohyaline degeneration related to hypertension) or cerebral amyloid angiopathy (CAA).[5]

- **Cerebral amyloid angiopathy**

Cerebral amyloid angiopathy (CAA), also known as congophilic angiopathy, affects exclusively the cerebral vasculature, without involvement of other areas of the body. The amyloid substance is deposited in the media and adventitia of small and medium diameter arteries, as well as in veins, of the cortical surface and leptomeninges. The histological diagnosis is made by showing areas of the vessel wall that stain with Congo red and show a characteristic apple green birefringence under polarized light.

Cerebral amyloid angiopathy characteristically affects the elderly, with a linear increase in frequency with age. In routine autopsy studies, the frequency of Cerebral amyloid angiopathy has been 5-13% in those patients aged 60-69, 20-40% in patients aged 70-79, 35-45% in patients aged 80-89, and 45-58% in individuals older than 90 years of age. The main clinical manifestation of Cerebral amyloid angiopathy is Intracerebral hemorrhage, but an association with Alzheimer's disease and with a leukoencephalopathy are now well recognized as well.
Figure 1. Lobar hemorrhage due to amyloid angiopathy, B Microscopic section of the brain cortex, section has been stained with Congo Red for amyloid viewed with polarized light. The section shows relatively preserved cortical neurons and the blood vessels shows birefringence with polarized light. In some areas the walls of the blood vessels are yellow-green (arrow). Diagnosis: Amyloid angiopathy, also known as congophilic angiopathy.

Table 1. The Intracerebral hemorrhages that occur in the setting of Cerebral amyloid angiopathy have several characteristic features. These include:

- A lobar location, due to the cortical and leptomeningeal distribution of the angiopathy.
- A frequently irregular, variegated appearance on a computed tomography (CT) scan, which results from extension of the superficially-located haemorrhage into the adjacent subarachnoid space.
- A tendency to be recurrent, on occasion with multiple episodes of lobar Intracerebral hemorrhage over periods of months or years, a feature that is exceptionally rare in Intracerebral hemorrhage due to hypertension.
- The occasional presence of multiple simultaneous haemorrhages, is also a distinct rarity in Intracerebral hemorrhage of hypertensive mechanism.
Figure 2. Precontrast CT scan showing irregular variegated putameno-capsular haemorrhage [left two images] and a lobar subcortical haemorrhage [right]

The Intracerebral hemorrhage in patients with Cerebral amyloid angiopathy can occasionally be related to preceding head trauma or a neurosurgical procedure, raising the possibility that mechanically-induced vascular rupture may be at times involved in its pathogenesis. Similarly, the use of anticoagulant and fibrinolytic agents is being increasingly suspected as a potential risk factor in instances of Intracerebral hemorrhage in the elderly, presumed to harbour Cerebral amyloid angiopathy as a local vascular lesion predisposing to Intracerebral hemorrhage.

The actual mechanism of bleeding in Cerebral amyloid angiopathy has not been elucidated. A factor that may be related to bleeding is the association of this angiopathy with other vascular changes, notably fibrinoid necrosis. Such vascular lesion has been found with high frequency (71%) in instances of Cerebral amyloid angiopathy associated with Intracerebral hemorrhage, while it is not present in patients with Cerebral amyloid angiopathy but without Intracerebral hemorrhage. These data suggest that despite the high prevalence of Cerebral amyloid angiopathy in the elderly, the relatively low frequency of Intracerebral hemorrhage may be explained by the need to have the associated changes of fibrinoid necrosis in the affected vessels, in order to result in rupture and Intracerebral hemorrhage.

Figure 3. Precontrast CT scan showing lobar subcortical haemorrhage
CA with Intracerebral hemorrhage is a sporadic condition, but two rare familial forms have been described only in specific geographical locations in Iceland and in Holland. The latter form of familial Cerebral amyloid angiopathy with Intracerebral hemorrhage has been characterized as a biochemical abnormality in the precursor protein of amyloid, which is also present in Alzheimer's disease and Down's syndrome.

Figure 4. Precontrast CT scan showing simultaneous cerebral and cerebellar haemorrhage in a single patient

Other associations of Cerebral amyloid angiopathy include Alzheimer's disease and a leukoencephalopathy. The histological features of Alzheimer's disease are present in approximately 40% of patients with Cerebral amyloid angiopathy-related Intracerebral hemorrhage, and 30-40% of patients with Cerebral amyloid angiopathy have clinical features of dementia. The leukoencephalopathy of Cerebral amyloid angiopathy affects the white matter of the cerebral hemispheres, with preservation of the 'U' fibres, corpus callosum, internal capsule, optic radiation, and white matter of the temporal lobes. The imaging diagnosis of this leukoencephalopathy is greatly facilitated by the use of magnetic resonance imaging (MRI), which shows hyperintensity of the white matter in T2-weighted sequences.

Box 2. Cerebral microbleeds are increasingly recognized in patients with the following neurological disorders

1- Cerebrovascular disease (including first-ever and recurrent ischemic or hemorrhagic stroke),[6,7]

2- Alzheimer’s disease,[8,9]

3- Vascular cognitive impairment[10]

4- Normal elderly populations. [11]

Cerebral microbleeds are emerging as a manifestation and diagnostic marker of cerebral small-vessel disease (along with lacunar infarcts, leukoaraiosis, ).[13–17] They are a potential predictor of Intracerebral hemorrhage risk, a possible contributor to cognitive
impairment and dementia and may provide a new imaging tool to understand the links between vascular and degenerative pathologies.[2]

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. Histologically, these small black dots on MR imaging represent hemosiderin-laden macrophages that are clustered around small vessel. 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. 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. 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 5. Cerebral Microbleeds. (A) An axial T2-weighted MRI. (B) A T2*-weighted gradient-recalled echo (T2*-GRE) MRI. Note the microbleeds – small, dark dot-like lesions (arrow) visible only on the T2*-weighted gradient-recalled echo (T2*-GRE) MRI.](image)

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. 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). Furthermore, some reports show that presence of microbleeds,
and particularly those in lobar locations, relates to worse cognitive function, both in healthy elderly individuals and in patients diagnosed with Alzheimer's disease (AD). 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. 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. In comparison, these rates are doubled in patients attending a memory clinic.

Table 2. Location of cerebral microbleeds and clinical significance

<table>
<thead>
<tr>
<th>Location</th>
<th>Clinical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>lobar locations</td>
<td>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.</td>
</tr>
<tr>
<td>Deep or infratentorial microbleeds</td>
<td>Deep or infratentorial microbleeds in aging individuals are primarily linked to classic cardiovascular risk factors and are more likely caused by hypertensive vasculopathy and small vessel disease.</td>
</tr>
</tbody>
</table>

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 6. A postmortem section of the brain showing a cortical microbleed (arrow) in a patient with Alzheimer’s disease and CAA.

Figure 7. 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 8** Microbleed location. T2-weighted MR images showing microbleeds (arrows) in lobar (left), deep (middle), and infratentorial (right) locations.

**Table 3. Pathology of ischemic microvascular brain disease**

<table>
<thead>
<tr>
<th>Central and cortical atrophy</th>
<th>This is secondary to chronic global reduction of brain perfusion.</th>
</tr>
</thead>
<tbody>
<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 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>
Physical Principles of Microbleed MRI Detection

The available data suggest that Cerebral microbleeds are composed of small collections of blood-breakdown products (in particular hemosiderin) contained within perivascular macrophages. Hemosiderin is an extremely paramagnetic material; this property, known as magnetic susceptibility, describes the degree to which a tissue (or any material) responds magnetically when placed in an exogenous magnetic field.[20] Consequently, when hemosiderin deposits are brought into the magnetic field of an MRI scanner, microscopic local magnetic fields develop, which create significant macroscopical inhomogeneities in the magnetic field surrounding Cerebral microbleeds, leading to fast decay of the local MRI signal, a phenomenon called the ‘susceptibility effect’. [12] Similar distortions of the magnetic field are also caused by the close proximity of tissues with different magnetic susceptibilities (e.g., at the interface of soft tissues, bone and air).
Figure 10. Example of incident microbleeds on 3-dimensional T2*-weighted gradient-recalled echo MRI in an 80 years old man. The microbleeds are lobar in location.

Figure 11. 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 12. Example of incident microbleeds on 3-dimensional T2*-weighted gradient-recalled echo MRI in an 80 years old man. The microbleeds are mainly lobar in location. The patient is presented clinical with the clinical picture of Alzheimer dementia.

MRI Criteria for Microbleed Identification & Differential Diagnosis

Cerebral microbleeds are defined as small, rounded or ovoid, blooming, homogeneous signal voids on T2*-GRE and related MRI sequences that are sensitive to susceptibility effects. A precise size definition does not appear to substantially influence the detection of Cerebral microbleeds: although the upper size limit is usually taken to be between 5 and 10 mm, a recent analysis revealed that the volume of microbleeds and macrobleeds (at least in a cohort of patients with Cerebral amyloid angiopathy) is not a continuum, but shows a bimodal distribution.[32] Blood vessels in the subarachnoid space, calcifications of the basal ganglia or cavernous malformations can all give rise to small, dot-like, low-signal areas on T2*-GRE MRI. Careful inspection of contiguous slices using different imaging modalities (CT, T2 MRI, FLAIR or DWI) and lesion geometry and location facilitates the identification of Cerebral microbleeds.
• Histopathological Correlates of Cerebral microbleeds

Neuroimaging–pathological correlation studies, as well as other histopathological analyses of Cerebral microbleeds ,[38,44–47] show that Cerebral microbleeds are commonly associated with two different small-vessel pathologies: hypertensive vasculopathy (Lipohyelinosis) and Cerebral amyloid angiopathy. Moreover, these two microangiopathic disorders seem to influence Cerebral microbleeds topography. Typically, hypertensive vasculopathy results in Cerebral microbleeds in the basal ganglia, thalamus, brainstem and cerebellum, while Cerebral amyloid angiopathy is characterized by a lobar, cortical–subcortical distribution.[2]

• Risk Factors & Associations

Apart from being associated with specific underlying vasculopathies, Cerebral microbleeds are strongly associated with a number of clinical syndromes including ischemic and hemorrhagic stroke, Alzheimer’s disease and vascular cognitive impairment.[12]
Patterns of Cerebral Microbleed Distribution. (A) Axial T2*-weighted gradient-recalled echo of an elderly individual without a history of hypertension, showing microbleeds in strictly lobar.

Pathophysiology of Cerebral microbleeds

Cerebral microbleeds are unique among the MRI manifestations of cerebral small-vessel disease, in that they seem to provide direct evidence of microvascular leakiness, causing blood-breakdown products to extravasate through the vessel wall. By contrast, Leukoaraiosis (in small vessel disease) lack pathological specificity and may result from a wide range of both vascular and inflammatory conditions. In the setting of small-vessel disease, the vascular endothelium of small arterioles and capillaries seems to become permeable to elements such as red blood cells, inflammatory cells and plasma proteins,[66] which are normally excluded by the BBB.[67] Thus, it seems highly plausible that endothelial/BBB derangement could play a key role in Cerebral microbleed formation,[68] although direct evidence for this hypothesis is limited so far.

Clinical Implications of Cerebral microbleeds

It is now becoming evident that Cerebral microbleeds can contribute to neurologic dysfunction, long-term disability and cognitive impairment. A population-based study of elderly people (n = 435) with or at high risk of cardiovascular disease investigated the prognostic value of Cerebral microbleeds regarding overall, cardiovascular-related and stroke-related mortality.[87] Compared with subjects without any Cerebral microbleeds, subjects with more than one Cerebral microbleed had a sixfold risk of stroke-related death (hazard ratio: 5.97; 95% CI: 1.60–22.26; p = 0.01).[87] However, the most striking findings were that deep Cerebral microbleeds were found to be significantly and independently
associated with cardiovascular mortality (hazard ratio: 2.67; 95% CI: 1.23–5.81; p = 0.01), whereas strictly lobar Cerebral microbleeds were significantly associated with stroke-related mortality (hazard ratio: 7.20; 95% CI: 1.44–36.10; p = 0.02).[87] Also in a previous study, the presence of Cerebral microbleeds (especially multiple Cerebral microbleeds) was the strongest predictor of mortality (among other MRI markers of vascular damage, such as WMCs) in a memory clinic population of 1138 patients.[88]

As well as affecting mortality and stroke risk, the accumulation of multiple Cerebral microbleeds could have a cumulative effect on brain functions subserved by distributed networks, such as gait or cognition. It is important to note that there are many potential confounders in the study of how Cerebral microbleeds could affect brain function and cause clinical impairment. Their close relationship and overlap with other imaging correlates of cerebral small vessel disease such as lacunes and white matter damage, as well as all types of clinical stroke syndromes, makes it challenging to dissect their independent effects.

- Cerebral microbleeds & Neurological Function
  - Gait.

In a cross-sectional study, De Laat et al. reported the first indications that Cerebral microbleeds (especially in the temporal and frontal lobe, basal ganglia and thalamus) may be associated with gait disturbances, independently of other coexisting markers of cerebral small-vessel disease.[89] In addition, in a prospective cohort of elderly patients (n = 94) presenting with spontaneous lobar Intracerebral hemorrhage, Greenberg and colleagues showed that a high number of Cerebral microbleeds at baseline was associated with a high 3-year cumulative risk of cognitive impairment, functional dependence or death (being more than 50% in individuals with more than six Cerebral microbleeds).[90] Cerebral microbleeds have also been associated with clinical disability in cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy.[91]

  - Cognition.

There has been increasing attention given to Cerebral microbleeds in relation to cognition. Werring and colleagues systematically examined the cognitive impact of Cerebral microbleeds [92] in a neurovascular clinic population. Consecutive patients with Cerebral microbleeds (n = 25) were compared with a control group without Cerebral microbleeds (n = 30) that was closely matched for age, leukoaraiosis severity, prevalence and location of cortical infarctions and ischemic stroke subtype (i.e., factors likely to influence cognition).[92] A striking difference in the prevalence of executive dysfunction was found between the two groups: 60% of patients with Cerebral microbleeds were impaired in frontal executive function (i.e., initiation, planning and higher-order problem-solving behaviors among others), compared with only 30% of nonmicrobleed patients (p = 0.03).[92]
Cerebral microbleeds as Prognostic Markers of Recurrent Stroke

Whether Cerebral microbleeds are a marker of increased future stroke risk (particularly intracerebral hemorrhage) is one of the most clinically relevant questions at present, yet few longitudinal data of good quality are available. A previous systematic review demonstrated that Cerebral microbleeds were more prevalent among patients with recurrent stroke rather than patients with a first-ever stroke.[6] Although this general conclusion was derived from a small number of patients (n = 1021), it suggests that Cerebral microbleeds may be a useful imaging marker of ongoing cerebrovascular damage,[6] which can add additional information about stroke recurrence (to that obtained using standard MRI sequences).

Overall, the association of Cerebral microbleeds with spontaneous intracerebral hemorrhage raises a clinical dilemma concerning the safety of antithrombotic treatments. Since Cerebral microbleeds provide direct evidence of blood leakage from pathologically fragile small vessels, their presence may be a risk factor for antithrombotic-associated intracerebral hemorrhage, raising the important question of whether Cerebral microbleeds may shift the risk–benefit balance away from antithrombotic use in some patients.

Cerebral microbleeds & Treatment: Balancing the Risks
  - Cerebral microbleeds & Antithrombotic Treatment.

Antiplatelet and anticoagulant treatments are widely used in patients at high risk of cardiovascular or cerebrovascular disease (e.g., ischemic stroke, ischemic heart disease or atrial fibrillation). In our aging population, the lifetime risk for developing atrial fibrillation is one in four people over the age of 40 years.[125] If left untreated, atrial fibrillation increases the risk of ischemic stroke fivefold, with the highest risk seen in elderly patients who have had a previous stroke or transient ischemic attack. In this setting, anticoagulation reduces ischemic stroke risk by approximately 65%. However, this benefit has to be balanced against an increased risk of intracerebral hemorrhage, which is the most feared complication of anticoagulation, causing death or severe disability in up to 75% of patients.[126] A recent observational inception cohort study of patients treated with anticoagulation (of whom a quarter had a previous history of stroke) reported a 2.5% (95% CI: 1.1–4.7%) risk of Intracerebral hemorrhage in 1 year.[127] Over the last decade, increasing use of warfarin to prevent cardioembolic stroke due to atrial fibrillation has led to a fivefold increase in the incidence of anticoagulant-related intracerebral hemorrhage, which now accounts for approximately 15% of all intracerebral hemorrhage.[128] This trend is set to continue and will be a huge future healthcare, social and economic challenge. With the potential availability of new oral anticoagulants such as dabigatran,[129] it is likely that even more acute cardioembolic stroke patients will be using oral anticoagulation for secondary stroke prevention. It is a paradox that many of these elderly patients at the highest risk of cardioembolic stroke are also at the highest risk of Intracerebral hemorrhage. In many patients, this makes it extremely difficult to balance the antiocclusive and prohemorrhagic effects of antithrombotic drugs; improving this risk–benefit assessment for individual patients remains a major goal of research in cerebrovascular medicine.
Because anticoagulation-related intracerebral hemorrhage is associated with increased age and previous stroke, and it often occurs with anticoagulation intensity within the therapeutic range,[130] it is likely that the mechanism underlying this high risk is related to individual patient factors (e.g., an age-related disorder of small brain vessels, such as Cerebral amyloid angiopathy or hypertensive small-vessel disease). In keeping with this hypothesis, some studies suggest that WMCs (a marker of small-vessel disease) increase the risk of anticoagulant-related Intracerebral hemorrhage.[131,132] Because they provide direct evidence of blood leakage from pathologically fragile small vessels, Cerebral microbleeds might be a stronger independent predictor of anticoagulation-associated Intracerebral hemorrhage. The available studies on Cerebral microbleeds and anticoagulation-associated Intracerebral hemorrhage risk have many limitations, with most being cross-sectional studies in Asian cohorts, so their findings cannot clearly show causative relationships and may not be generalizable to other populations.[120,133–146] Nonetheless, existing data support the hypothesis that the presence of Cerebral microbleeds increases the risk of Intracerebral hemorrhage as a complication of antithrombotic medication.[135,142,145] A prospective study reported Cerebral microbleeds in 87% of patients with Intracerebral hemorrhage following warfarin treatment for atrial fibrillation,[142] while a recent case–control study also reported more Cerebral microbleeds in warfarin-associated Intracerebral hemorrhage than in matched warfarin users without Intracerebral hemorrhage.[141]

- **Cerebral microbleeds in the Setting of Other Treatments**
  - **Thrombolysis**

Another relevant question is whether there is an increased risk of intracerebral hemorrhage after thrombolysis of patients with ischemic stroke when Cerebral microbleeds are present. Some studies that explored the association between Cerebral microbleeds and the risk of hemorrhagic transformation following intravenous tissue plasminogen activator in patients who have had ischemic stroke have indicated possible links,[143,152] while more recent studies have questioned these findings.[153,154] The BRASIL study (the largest prospective, multicenter study to date), which included 570 ischemic stroke patients, found that symptomatic Intracerebral hemorrhage occurred in 5.8% of patients with Cerebral microbleeds versus 2.7% of patients without Cerebral microbleeds (p = 0.170).[153] However, all of the studies were underpowered to provide reliable data of such an effect[6,155] and leave unanswered the questions of the role of strictly lobar microbleeds (reflecting underlying Cerebral amyloid angiopathy pathology) and multiple Cerebral microbleeds on the shaping of the risk.[49]

  - **Statins**

Some neurologists have raised concerns over the use of statins in patients with Cerebral microbleeds. In the Rotterdam study, low serum cholesterol levels were found to be strongly associated with the presence of strictly lobar microbleeds.[56] However, this association was not replicated in the recent update of the study.[85] Lee and colleagues also found a relationship between low cholesterol concentrations and higher microbleed burden in the 172 patients they studied.[156] In a more recent retrospective analysis of 349 patients
with acute ischemic stroke or transient ischemic attack, previous statin therapy was not associated with either the prevalence or the degree of Cerebral microbleeds.[157] The role of statins and low serum cholesterol in patients with microbleeds needs further exploration, particularly in light of the results of a randomized controlled trial of atorvastatin in patients with stroke, which showed a small increase in the incidence of Intracerebral hemorrhage among patients receiving high doses of the drug.[158] The increased risk of Intracerebral hemorrhage may be due to pleiotropic effects of statins other than the lipid-lowering effects.[159]

References


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CEREBRAL HAEMORRHAGE

Intracerebral haemorrhage (ICH) accounts for approximately 10-15% of strokes. Although its frequency is relatively low in comparison with that of atherothrombotic (20%) and embolic (25%) strokes, its importance stems from the generally severe neurological deficits it causes and its often grave prognosis. In addition, ICH can be the result of several mechanisms, and their identification implies important differences in management and prognosis. All these features make ICH a challenge to the clinician involved in the care of these patients.
MECHANISMS & AETIOLOGY OF CEREBRAL HAEMORRHAGE

ICH has traditionally been considered to be primarily related to chronic hypertension. This notion is based on the high frequency (89%) of history of hypertension in patients with ICH, along with a high incidence of left ventricular hypertrophy at autopsy. As defined in this manner, the hypertensive mechanism accounts for approximately 47-66% of ICH, depending to some extent on the topography of the ICH, the highest frequency of hypertensive mechanism occurring in the pontine variety. Lobar ICH, on the other hand, has been found to have the lowest frequency of hypertension.

The sources of arterial bleeding in hypertensive ICH are primarily located in the deep portions of the cerebral hemispheres and, to a lesser extent, in the cerebellum and brainstem. This causes haemorrhages that are most frequently located in the deep gray nuclei of the hemispheres (basal ganglia, thalamus) and in the subcortical white matter of the cerebral lobes. These locations correlate with the distribution in the brain of the hypertension-related arterial lesions that are thought to be the cause of ICH. These include lipohyalinosis and microaneurysms, lesions that often coexist in a given pathological specimen, and which have their highest concentration in the deep hemispheric areas and in the gray/white matter interface of the cerebral lobes, explaining the sites of predilection of ICH. Other, not primarily hypertensive, mechanisms are often documented as the cause of ICH. see table 1

Table 1. Non-hypertensive causes of intracerebral haemorrhage.

<table>
<thead>
<tr>
<th>Cerebral hg</th>
<th>Cerebral amyloid angiopathy</th>
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<tr>
<td></td>
<td>Vascular malformations</td>
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<td>Intracranial tumours</td>
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<td>Anticoagulants</td>
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<td>Thrombolytic agents</td>
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<td>Sympathomimetic drugs</td>
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<td></td>
<td>Vasculitis</td>
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- Cerebral amyloid angiopathy

Cerebral amyloid angiopathy (CAA), also known as congophilic angiopathy, affects exclusively the cerebral vasculature, without involvement of other areas of the body. The amyloid substance is deposited in the media and adventitia of small and medium diameter arteries, as well as in veins, of the cortical surface and leptomeninges. The histological diagnosis is made by showing areas of the vessel wall that stain with Congo red and show a characteristic apple green birefringence under polarized light.

CAA characteristically affects the elderly, with a linear increase in frequency with age. In routine autopsy studies, the frequency of CAA has been 5-13% in those patients aged 60-69, 20-40% in patients aged 70-79, 35-45% in patients aged 80-89, and 45-58% in individuals older than 90 years of age. The main clinical manifestation of CAA is ICH, but
an association with Alzheimer's disease and with a leukoencephalopathy are now well recognized as well.

Figure 1. Lobar hemorrhage due to amyloid angiopathy, B Microscopic section of the brain cortex, section has been stained with Congo Red for amyloid viewed with polarized light. The section shows relatively preserved cortical neurons and the blood vessels shows birefringence with polarized light. In some areas the walls of the blood vessels are yellow-green (arrow). Diagnosis: Amyloid angiopathy, also known as congophilic angiopathy.

The ICHs that occur in the setting of CAA have several characteristic features. These include:

- A lobar location, due to the cortical and leptomeningeal distribution of the angiopathy.
- A frequently irregular, variegated appearance on a computed tomography (CT) scan, which results from extension of the superficially-located haemorrhage into the adjacent subarachnoid space.
- A tendency to be recurrent, on occasion with multiple episodes of lobar ICH over periods of months or years, a feature that is exceptionally rare in ICH due to hypertension.
- The occasional presence of multiple simultaneous haemorrhages, is also a distinct rarity in ICH of hypertensive mechanism.
The ICH in patients with CAA can occasionally be related to preceding head trauma or a neurosurgical procedure, raising the possibility that mechanically-induced vascular rupture may be at times involved in its pathogenesis. Similarly, the use of anticoagulant and fibrinolytic agents is being increasingly suspected as a potential risk factor in instances of ICH in the elderly, presumed to harbour CAA as a local vascular lesion predisposing to ICH.

The actual mechanism of bleeding in CAA has not been elucidated. A factor that may be related to bleeding is the association of this angiopathy with other vascular changes, notably fibrinoid necrosis. Such vascular lesion has been found with high frequency (71%) in instances of CAA associated with ICH, while it is not present in patients with CAA but without ICH. These data suggest that despite the high prevalence of CAA in the elderly, the relatively low frequency of ICH may be explained by the need to have the associated changes of fibrinoid necrosis in the affected vessels, in order to result in rupture and ICH.

CA with ICH is a sporadic condition, but two rare familial forms have been described only in specific geographical locations in Iceland and in Holland. The latter form of familial CAA with ICH has been characterized as a biochemical abnormality in the precursor protein of amyloid, which is also present in Alzheimer's disease and Down's syndrome.
Other associations of CAA include Alzheimer's disease and a leukoencephalopathy. The histological features of Alzheimer's disease are present in approximately 40% of patients with CAA-related ICH, and 30-40% of patients with CAA have clinical features of dementia. The leukoencephalopathy of CAA affects the white matter of the cerebral hemispheres, with preservation of the 'U' fibres, corpus callosum, internal capsule, optic radiation, and white matter of the temporal lobes. The imaging diagnosis of this leukoencephalopathy is greatly facilitated by the use of magnetic resonance imaging (MRI), which shows hyperintensity of the white matter in T2-weighted sequences.

- **Vascular malformations**

These are a common cause of ICH in non-hypertensive patients, especially in the young adult. These lesions include the arteriovenous malformations (AVMs), cavernous angiomas, capillary telangiectasias, and venous angiomas. Of these, only the first two carry a significant risk of bleeding, especially AVMS.

Vascular malformations account for approximately 4.5% of ICHs in autopsy series, but their frequency in clinical series is higher, as they are frequently non-fatal. A ruptured AVM is the main cause of ICH in individuals younger than 45 years of age, a group in which this mechanism may account for as many as 40% of haemorrhages that have their mechanism documented.

The ICHs due to ruptured AVMS, are at times caused by malformations that are too small to be detected by cerebral angiography. In addition, those due to cavernous angiomas cannot be documented angiographically due to the low flow of blood within the small malformation. Due to these facts, these small malformations (AVMs or cavernous angiomas) that are invisible to angiography, were once labeled as cryptic, their diagnosis depending exclusively on pathological documentation, either at autopsy or after biopsy of the wall of a haematoma that had been drained surgically. However, this term has become obsolete since the introduction of CT and especially MRI, as these malformations, ruptured or unruptured, can now be readily demonstrated by their characteristic aspect.

AVMs appear as tangles of blood vessels shown as flow voids in TI-weighted sequences, often with a prominent adjacent draining vein, whereas cavernous angiomas are
characterized, in T2-weighted sequences, by a mixed (i.e. bright and low) signal center with a surrounding low-signal ring of haemosiderin, indicative of prior bleeding at the periphery of the malformation. On CT, both malformations can show areas of calcification, and post-contrast enhancement is characteristic in AVMs but is not generally seen in the low-flow cavernous angiomas.

Cavernous angiomas probably have a lower tendency to bleeding, in comparison with AVMS. However, their presence should be sought in patients with otherwise unexplained ICH, especially in the young adult. Cavernous angiomas represent 5-13% of the vascular malformations in the central nervous system, and occur with equal frequency in males and females. Their diagnosis is generally made in patients in their 20s and 30s. Their location is predominantly supratentorial (60-75%), favouring the temporal over the other cerebral lobes, whereas the infratentorial ones (25-40%) favour the pons over the cerebellum. Most malformations are single (70-90%), but occasional examples of multiple malformations occur, in which case familial incidence is likely. Their clinical presentation is with seizures (in 25-70% of the cases, in the supratentorial compartment), haemorrhage (10-30%), or a progressive neurological deficit (35%), the latter occurring more often in infratentorial than supratentorial cavernous angiomas. In cases with gradual progression of symptoms, which are probably due to repeated episodes of small haemorrhage at the periphery of the malformation, the usual diagnoses have been brainstem glioma or multiple sclerosis.

Figure 5. A, Single axial non-contrast-enhanced CT image demonstrates a large heterogeneous-appearing lesion in the right frontal region that primarily is hyperdense centrally with a more diffuse area of increased density peripherally resulting from calcification and small areas of hemorrhage. B, Non-contrast-enhanced axial CT image demonstrates findings of a large primarily hyperdense mass in the left occipital region. Note the relative lack of mass effect on the surrounding parenchyma on both CT images. C, T1-weighted axial MRI image at a slightly different slice angle from the CT scan demonstrates both cavernomas on the same image. These two heterogeneous masses have a reticulated core of high and low signal intensities surrounded by a hypointense rim of hemosiderin. D, Gradient-echo axial MRI image demonstrates increased conspicuity of both lesions. The hemosiderin rim demonstrates a blooming artifact as a result of its increased magnetic susceptibility effects.
Figure 6. Cavernous angioma. Images A-C demonstrate increased sensitivity of gradient-echo sequences over T1-weighted and T2-weighted images in the detection of smaller lesions. A, This T1-weighted image fails to demonstrate the multiple tiny cavernomas demonstrated on a gradient-echo image. B, A corresponding T2-weighted axial MRI image does not demonstrate well the multiple tiny cavernomas seen on a gradient-echo sequence. C, Cavernous angioma. Gradient-echo pulse MRI sequence demonstrates multiple punctate and rounded areas of hypointensity within the periventricular and subcortical white matter bilaterally. The largest lesion is seen within the periventricular frontal white matter just anterior to the frontal horn of the left lateral ventricle near the genu of the corpus callosum. Multiple smaller lesions are seen both anteriorly and posteriorly.

Figure 7. Cavernous angioma. A, T1-weighted MRI image demonstrates a small hyperintense lesion in the left temporal cortex with a hypointense rim. This smaller lesion is demonstrated better and is more apparent on a T2-weighted image (see B) and on a gradient-echo image (see C). B, T2-weighted image demonstrates the hypointense blooming artifact within the lesion in the left temporal lobe, although the blooming is not nearly as marked as seen on a gradient-echo image (see C). C, The lesion becomes obvious on this gradient-echo image (see B). Even this relatively small temporal lobe lesion is detected easily on pulse sequence. Since cavernous angiomas are often multiple, a gradient-echo sequence should be performed in addition to standard T1-weighted and T2-weighted sequences to carefully identify all concomitant lesions as clinically indicated.
Intracranial tumours

Intracerebral bleeding secondary to a brain tumour occurs in approximately 6-10% of patients presenting with ICH. This form of presentation of a brain tumour is characteristic of the malignant varieties, primarily glioblastoma multiforme and metastases. A benign tumour which is associated with haemorrhage relatively frequently is the pituitary adenoma, which presents with the picture of pituitary apoplexy. Bleeding from brain metastases is most frequently observed in instances of melanoma, choriocarcinoma, renal-cell carcinoma, and bronchogenic carcinoma.

In a patient presenting with ICH, the suspicion of an underlying tumour should be suggested by the following:

<table>
<thead>
<tr>
<th>Brain tumour</th>
<th>The finding of papilledema at the time of presentation with the acute ICH.</th>
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<tbody>
<tr>
<td>Brain tumour</td>
<td>An atypical location of the haemorrhage, in an area such as the corpus callosum, which exceptionally is involved in non-tumoural haemorrhages and, on the other hand, can occur in instances of tumours that infiltrate that structure, such as glioblastoma multiforme.</td>
</tr>
<tr>
<td>Brain tumour</td>
<td>Multiple and simultaneous haemorrhages.</td>
</tr>
<tr>
<td>Brain tumour</td>
<td>A CT image of a ring-like hyperdensity surrounding a low density center, as a result of bleeding from tumoural vessels at the interface between the tumour and the adjacent parenchyma.</td>
</tr>
<tr>
<td>Brain tumour</td>
<td>A disproportionate amount of white matter oedema and mass effect around an acute ICH.</td>
</tr>
<tr>
<td>Brain tumour</td>
<td>Nodular post-contrast enhancement at the periphery of the ICH</td>
</tr>
</tbody>
</table>
Any of these features should raise the possibility of an underlying tumour, and the work-up should proceed with MRI and, eventually, cerebral angiography. In the event of negative results of this test, if the diagnostic suspicion persists, consideration should be given to surgical removal of the haematoma with biopsy of its cavity, in order to establish the diagnosis, since the treatment and prognosis of this form of ICH is different from that of non-tumour related ICH.

- **Anticoagulants**

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.

- The clinical features of ICH in patients receiving oral anticoagulants include:

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

Other features related to the occurrence of anticoagulant-related ICH are less consistently observed, and include:

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**

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.

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

  - 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.
  - Predominantly lobar location, with rare examples of bleeding into the posterior fossa and putamen.
  - Multiple simultaneous haemorrhages in about one-third of the cases.
  - 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.

- Sympathomimetic drugs

The use of sympathomimetic drugs has been associated with the occurrence of ICH, often shortly after exposure to the drug. The agents most commonly implicated include the amphetamines, phenylpropanolamine, and cocaine.

The amphetamines have been long known to promote ICH. Intravenous methamphetamine has been the most commonly Responsible agent, and the ICH occurs within minutes to a few hours from drug exposure. The ICHs are usually lobar, but occasional examples of basal ganglionic haemorrhage have been reported. Their pathogenesis possibly includes transient hypertension (documented in about 50% of the reported cases), and an angiographic abnormality characterized by alternating areas of constriction and dilatation of intracranial arteries, or beading. This probably corresponds to a form of multifocal vasospasm related to the effects of the sympathomimetic agent on the arterial wall, and in only rare occasions a true vasculitis has been histologically documented.

Phenylpropanolamine (PPA) is a sympathomimetic agent contained in more than 70 over-the-counter nasal decongestants and appetite suppressants. Its use has been associated with instances of ICH and, less commonly, subarachnoid haemorrhage (SAH). These haemorrhagic strokes have generally affected young adults, women more often than men,
who have had no other risk factors for intracranial haemorrhage. Acute and transient hypertension at presentation with ICH has been a feature in about one-third of the cases. The haemorrhages have occurred after 1-8 hours from the ingestion of the PPA-containing preparations, in about 50% of the patients after first-time use of the drug. The doses of PPA ingested have been approximately equally distributed between those recommended for appetite-suppression (75 mg/day) and excessive ones (100-170 mg). The radiological aspects of the ICHs are similar to those of amphetamine-related haemorrhages, with predominantly lobar haematomas and angiographic beading in the majority of cases studied. In one instance, biopsy obtained at the time of surgical drainage of an ICH showed histological changes consistent with vasculitis. The mechanism of these haemorrhages is thought to be similar to that of amphetamine-related ICH.

Cocaine has become the most common illicit drug related to cerebrovascular complications in young adults. Strokes have been reported after the use of both the pure alkaloidal (free base) form of the drug and the adulterant-containing crack. Intracranial haemorrhages, both ICH and SAH, have occurred after minutes to 1 hour from exposure to crack cocaine. The ICHs are both lobar and deep hemispheric (basal ganglia and thalamus), and occasional patients have had multiple simultaneous haemorrhages.

The mechanism of ICH after cocaine use remains unknown. The angiographic beading reported after amphetamine and PPA exposure is rarely seen in cocaine-related ICH, whereas the latter show a higher association with AVMs and aneurysms as the bleeding mechanism. This observation suggests that the acute hypertension that frequently follows cocaine use may act as a precipitant of ICH in the presence of a pre-existing AVM or aneurysm. Other possible contributors to ICH after cocaine use include vasoconstriction leading to cerebral infarction, with secondary haemorrhage after re-perfusion of ischaemic blood vessels, concomitant heavy alcohol intake and cigarette smoking as possibly additive risk factors, and the rare observation of a true drug-induced vasculitis.

- Vasculitis

Cerebral vasculitis causes cerebral infarction more often than ICH, but occasional examples of ICH have been reported. They have corresponded to examples of granulomatous angiitis of the nervous system (GANS), which is a primary cerebral vasculitis, unassociated with systemic involvement. Its course is acute or subacute, and is characterized by headache, progressive dementia, seizures, and episodes of cerebral infarction. Systemic features of vasculitis, such as fever, malaise, arthralgias, myalgias, weight loss, anaemia, and elevated sedimentation rate, are absent in GANS. The diagnosis is suggested by inflammatory cerebrospinal fluid (CSF) findings, and beading in multiple intracranial arteries, at times with microaneurysm formation. A normal angiogram, however, does not exclude the diagnosis, which ultimately rests in the histological demonstration of vasculitis in the leptomeninges and cerebral cortex.

The rare cases of ICH in association with GANS have generally occurred in the setting of subacute, progressive features of encephalopathy (headache, dementia) or myelopathy, but
occasionally ICH has been its first manifestation. The haemorrhages are isolated, rarely recurrent, and have a predominantly lobar location.

COMMON ANATOMICAL SITES OF CEREBRAL HAEMORRHAGE

- Putamenal haemorrhage

This type of ICH originates in the posterior aspect of the putamen, from where it can extend into the temporal lobe, centrum semiovale, internal capsule, and ventricular system, depending on its size. Its cause is hypertension in over 60% of patients. The severity of the initial clinical picture relates to haematoma size.

The clinical spectrum includes minimally symptomatic patients who present with pure motor hemiparesis and those who are densely hemiplegic, with a hemisensory loss, aphasia, hemianopia, and forced conjugate eye deviation to the side of the haematoma, generally in association with a markedly depressed level of consciousness.
The size of the haematoma relates directly to prognosis, and the presence of intraventricular extension of the haemorrhage is generally indicative of poor functional and vital prognosis, as the haematoma needs to reach a large size in order to track across the internal capsule to gain access into the lateral ventricle.

Figure 10. Hypertensive hemorrhage into basal ganglia region (specifically: internal capsule).

Figure 11. Precontrast CT scan showing putameno-capsular haemorrhage, notice the intraventricular extension.

Figure 12. putameno-capsular haemorrhage, notice the intraventricular extension.
Caudate haemorrhage

This rare form of basal ganglia haemorrhage involves the head of the caudate nucleus, at times extending into the putamen, and virtually always reaching the immediately adjacent frontal horn of the lateral ventricle.

This latter aspect often leads to the misdiagnosis of this condition as primary intraventricular haemorrhage on CT, on account of the small intraparenchymal caudate haematoma and the relatively more impressive amount of blood inside the ventricular system. This in turn is responsible for its clinical presentation with sudden onset of headache, vomiting, and depressed level of consciousness, with minimal or altogether absent focal neurological deficits, a presentation akin to that of SAH from ruptured aneurysm. When focal neurological deficits are present, they are both minimal and transient, generally including ipsilateral Horner's syndrome and contralateral hemiparesis, reflecting extension of the haematoma inferiorly and laterally, respectively.
The cause of caudate ICH is often (50-60%) hypertension, but its differential diagnosis should include rupture of anterior communicating artery aneurysm (with upwards bleeding into the ventricular system and caudate nucleus) and ruptured AVM. The prognosis of caudate ICH is generally good, as the parenchymal haematoma is small and the intraventricular haemorrhage is reabsorbed, at times requiring the insertion of an intraventricular catheter for the treatment of hydrocephalus, which occurs in 75% of patients.

Figure 16. Caudate haemorrhage

- Thalamic haemorrhage

Thalamic haemorrhage often involves the thalamus and the adjacent internal capsule, resulting in severe contralateral sensory and motor deficits. The hemisensory syndrome is often a complete anaesthesia for all sensory modalities, and the whole hemibody is affected, including limbs, trunk, face and scalp.

Figure 17. Thalamic haemorrhage

As is the case with caudate haemorrhage, the proximity of the thalamus to the ventricular system results in the possibility of early extension of the haemorrhage into the third
ventricle and hydrocephalus. The clinical presentation of thalamic haemorrhage differs from that of putaminal haemorrhage in the prominence of the oculomotor findings that characterize the former, and which correspond to the compressive effects of the thalamic haematoma on the tectum of the midbrain. These include: paresis of upward gaze, the eyes often being deviated downward and adducted at rest (as if looking at the tip of the nose); small and unreactive pupils; conjugate horizontal eye deviation toward the affected hemisphere or, less frequently, in the opposite direction (wrong way eye deviation); and occasionally, ipsilateral Horner’s syndrome, skew deviation.

As in other types of ICH, the prognosis of thalamic haemorrhage is strongly dependent on the size of the haematoma. In addition, the presence of obstructive hydrocephalus adds an element of worse prognostic significance, but its reversal by prompt institution of ventricular drainage is at times associated with a dramatic clinical improvement, especially in the level of consciousness and the oculomotor abnormalities.

Figure 18. Precontrast CT scan showing intraventricular haemorrhage

- **Lobar haemorrhage**

The clinical features of lobar ICH differ according to the cerebral lobe involved. In frontal haemorrhages there is prominent bifrontal headache and contralateral weakness, the latter following a pattern of arm or leg predominance depending on the lateral or medial location of the haemorrhage, respectively. In large size haemorrhages, additional features of ipsilateral horizontal gaze preference and decreased level of consciousness occur. In temporal haemorrhages, headache in front of the ear or around the eye occurs ipsilaterally, and dominant hemisphere haematomas present with fluent aphasia with poor comprehension, prominent paraphasias, and severe anomia. In either hemisphere, a contralateral visual field defect, either hemianopic or quadrantanopic, is frequent, but hemiparesis and hemisensory loss are uncommon. Non-dominant hemisphere haematomas often show prominent mental changes in the absence of focal neurological deficits, at times leading to the misdiagnosis of metabolic encephalopathy or confusional state. Parietal haemorrhages are characterized by the onset of headache in the ipsilateral temple area, prominent contralateral sensory and motor deficits, and variable occurrence of visual field defects. Depression of the level of consciousness correlates with haematoma size, as well as with a more medial than lateral location of the haematoma in the parietal lobe.
In occipital haemorrhages the headache is located in or around the ipsilateral eye, the patients often complain of visual blurring, and the most consistent finding on examination is an isolated contralateral homonymous hemianopia. On rare occasions, a syndrome of alexia without agraphia has occurred in the setting of dominant hemisphere occipital haemorrhages.

- **Cerebellar haemorrhage**

Cerebellar haemorrhage has a characteristic onset with abrupt vertigo, headache, vomiting, and an inability to stand and walk, in the absence of hemiparesis or hemiplegia. These features reflect bleeding in the area of the dentate nucleus of the cerebellar hemisphere, with involvement of ipsilateral cerebellar output tracts, along with the potential for mass effect on the adjacent tegmentum of the pons. The clinical findings that suggest the diagnosis include ipsilateral limb ataxia, horizontal gaze palsy, and facial palsy, at times with ipsilateral trigeminal sensory loss, but without limb weakness.

*Figure 19. Acute cerebellar hemorrhage*

*Figure 20. Precontrast CT scan showing cerebellar haemorrhage*
The clinical picture is less well defined in instances of midline (vermian) cerebellar haemorrhage with extension into the fourth ventricle, when the lateralized features are lacking, and the patients present with a syndrome that is indistinguishable from primary pontine haemorrhage. On occasion, a small cerebellar haemorrhage has presented with isolated vertigo and gait instability, leading to the misdiagnosis of Meniere's disease or labyrinthitis, suggesting that a high index of suspicion for the diagnosis is necessary.

Figure 21. 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].

- **Pontine haemorrhage**

This is the form of ICH with the worst prognosis, as patients generally present with features that reflect bilateral destruction of the basis pontis and tegmentum. Its signs include coma, quadriplegia, decerebrate posturing, bilateral horizontal ophthalmoplegia, pinpoint reactive pupils, ocular bobbing, respiratory rhythm abnormalities, and hyperthermia. In less severe forms, when the haematoma is small and is located on one side of the pontine tegmentum, a Syndrome of ipsilateral cranial nerve involvement and ataxia, with contralateral hemiparesis and hemisensory loss results.

Figure 22. Precontrast CT scan studies showing three cases with pontine haemorrhage
Other sites of brainstem haemorrhage

Brainstem haemorrhages outside the pons are rare. Mesencephalic haemorrhage has been reported in about a dozen patients, and has been characterized by the onset of headache and vomiting, along with either contralateral hemiparesis or ipsilateral cerebellar ataxia, and oculomotor findings. The latter have included paralysis of upward gaze, small unreactive pupils, and palpebral ptosis, as well as third nerve palsy in instances of primarily unilateral tegmental haematomas. The cause of the haemorrhage has generally been unknown; sometimes the mechanism was hypertension, and very occasionally ruptured AVM. Medullary haemorrhage as a primary site of bleeding is extremely rare.

It presents with sudden onset of signs of predominantly unilateral tegmental or basal medullary involvement, including vertigo, vomiting, gait imbalance, limb ataxia, and lower cranial nerve palsies. Its clinical findings can at times be similar to those of Wallenberg's lateral medullary syndrome, with the exception of contralateral hemiparesis and ipsilateral hypoglossal nerve palsy, which reflect extension of the medullary haemorrhage ventrally and medially, respectively.
Incidence [in\%] of the common anatomical sites in hypertensive intracerebral haemorrhage

<table>
<thead>
<tr>
<th>Site</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>putaminocapular</td>
<td>50%</td>
</tr>
<tr>
<td>intraventricula</td>
<td>20%</td>
</tr>
<tr>
<td>thalamic</td>
<td>12%</td>
</tr>
<tr>
<td>lobar cortical</td>
<td>12%</td>
</tr>
<tr>
<td>cerebellar</td>
<td>4%</td>
</tr>
<tr>
<td>midbrain</td>
<td>4%</td>
</tr>
<tr>
<td>pontine</td>
<td>4%</td>
</tr>
</tbody>
</table>

**IMAGING DIAGNOSIS OF INTRACEREBRAL HAEMORRHAGE**

- **Computed tomography**

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 (HU).

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.

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.

• Magnetic resonance imaging

MRI has greatly enhanced the yield of imaging in the diagnosis of ICH. This technique not only detects small haematomas in areas where CT is unreliable on account of bony artifacts, such as the brainstem and cerebellum, but can also accurately date the stage of evolution of an ICH, by imaging the various stages of evolution of the haemoglobin molecule. This allows for the distinction of hyperacute (first few hours), acute (days, up to 1 week), early subacute (weeks), late subacute (weeks to months), and chronic (months to years) stages of haematoma evolution, which have distinct MRI characteristics in the various sequences used.
Table 2. 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 TI-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 TI shortening and very high signal intensity on T1-weighted images within the periphery of the hematoma. The intracellular methemoglobin will cause T2 shortening and very low signal on T2-weighted images.</td>
</tr>
<tr>
<td>Extracellular migration of methemoglobin</td>
<td>MR will exhibit the persistent high signal of extracellular methemoglobin on TI - 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 [201 from the susceptibility effect of hemosiderin within macrophage lysosomes.</td>
</tr>
<tr>
<td>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.</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>
</tr>
</tbody>
</table>
Table 3. The MRI biochemical stages of cerebral hematomas

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hyperacute stage [0-12 Hr]</strong></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><strong>Acute stage [4Hr -3 days]</strong></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><strong>Subacute stage [3days-3 weeks]</strong></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><strong>Chronic stage [3 weeks-3 months]</strong></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 4. Effect of blood products on the MRI signal

<table>
<thead>
<tr>
<th>Stage</th>
<th>Blood Product</th>
<th>Effect</th>
<th>Imaging Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hyperacute stage</strong></td>
<td>Oxyhemoglobin</td>
<td>lacks unpaired electrons and thus clot signal is close to normal brain</td>
<td>normal brain parenchyma- normal to slightly lower signal on</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TI-weighted images and slightly higher signal on T2-weighted</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>images</td>
</tr>
<tr>
<td><strong>Acute stage</strong></td>
<td>Deoxyhemoglobin within</td>
<td>No effect</td>
<td>T2 shortening, with areas of very low signal on T2-weighted</td>
</tr>
<tr>
<td></td>
<td>intact, clotted</td>
<td></td>
<td>spin echo and T2 * - weighted gradient echo images</td>
</tr>
<tr>
<td></td>
<td>hypoxic red blood</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Early subacute stage</strong></td>
<td>Strongly paramagnetic</td>
<td>TI shortening and very high signal intensity on TI-weighted images</td>
<td>The intracellular methemoglobin will cause T2 shortening and</td>
</tr>
<tr>
<td></td>
<td>intracellular methemoglobin</td>
<td></td>
<td>within the periphery of the hematoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Late subacute stage</strong></td>
<td>extracellular migration</td>
<td>MR will exhibit the persistent high signal of extracellular methemoglobin</td>
<td>The intracellular methemoglobin will cause T2 shortening and</td>
</tr>
<tr>
<td></td>
<td>of ethemoglobin</td>
<td></td>
<td>very low signal on T2-weighted images for up to a year</td>
</tr>
<tr>
<td><strong>Chronic stage</strong></td>
<td>Focal atrophy is</td>
<td>Focal atrophy is characterized by a decrease in the size of cortical</td>
<td></td>
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<tr>
<td></td>
<td>characterized by a</td>
<td>gyri, with compensatory enlargement of cerebrospinal fluid spaces</td>
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<td></td>
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<td>and dilatation of the adjacent ventricle. Cystic cavities are</td>
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<td></td>
<td>of cortical gyri, with</td>
<td>surrounded by gliosis and hemosiderin scarring.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>compensatory enlargement</td>
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<td></td>
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</tbody>
</table>
Table 5. 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>
<tr>
<td>Chronic</td>
<td>&gt;14 days</td>
<td>Hemosiderin (extracellular)</td>
<td>Iso or hypo</td>
<td>Hypo</td>
</tr>
</tbody>
</table>

References


INTRODUCTION

Cerebral amyloid angiopathy (CAA) refers to the deposition of β-amyloid in the media and adventitia of small- and mid-sized arteries (and less frequently, veins) of the cerebral cortex and the leptomeninges. It is a component of any disorder in which amyloid is deposited in the brain, and it is not associated with systemic amyloidosis. CAA has been recognized as one of the morphologic hallmarks of Alzheimer disease (AD), but it also is found often in the brains of elderly patients who are neurologically healthy. While often asymptomatic, CAA can present as intracranial hemorrhage (ICH), dementia, or transient neurologic events. ICH is the most consistent effect of CAA. Although the vast majority of cases are sporadic, 2 familial forms exist (ie, hereditary cerebral hemorrhage with amyloidosis...
Dutch type and HCHWA-Icelandic type). The severity of CAA is age related; more than 50% of patients in the tenth decade of life have evidence of CAA. Increasing age and the presence of AD are the only identified risk factors for CAA.

Deposition of amyloid damages the media and adventitia of cortical and leptomeningeal vessels, leading to thickening of the basal membrane, stenosis of the vessel lumen, and fragmentation of the internal elastic lamina. This can result in fibrinoid necrosis and microaneurysm formation, predisposing to hemorrhage. Some evidence suggests that the amyloid is produced in the smooth muscle cells of the tunica media as a response to damage of the vessel wall (perhaps by arteriosclerosis or hypertension). Although CAA may be found more commonly in women than men at autopsy, the incidence of ICH is the same in women and men. Hemorrhage occurs at the same age in men and women.

The true incidence and prevalence are hard to specify, as definite CAA can be diagnosed only at postmortem. However, estimates can be made based on autopsy series and the incidence of lobar ICH. A series of 400 autopsies found evidence of CAA in the brains of 18.3% of men and 28% of women aged 40-90 years. In a series of 117 brains of patients with confirmed AD, 83% had evidence of CAA. The prevalence of CAA increases with advancing age; in some autopsy series it has been found in 5% of individuals in the seventh decade but in 50% of those older than 90 years. CAA is estimated to account for up to 15% of all ICH in patients older than 60 years and up to one half of nontraumatic lobar ICH in patients older than 70 years (approximately 15-20 cases per 100,000 people per y). CAA and CAA-related hemorrhage are particularly common in elderly individuals with AD and Down syndrome.

- Conditions associated with cerebral amyloid angiopathy
  - Intracerebral hemorrhage

The most consistent clinical effect of CAA is lobar ICH. Lobar ICH is associated with a lower mortality rate (11-32%) and a better functional outcome than hypertensive deep ganglionic bleeds. Of individuals with CAA-related hemorrhage, 25-40% have a recurrence, with the highest risk in the first year. Recurrent hemorrhages can occur simultaneously or several years later. They are associated with a high mortality rate (up to 40%). Patients with a previous hemorrhage are at greater risk for subsequent hemorrhages than those with no history. Hypertension may exacerbate the tendency to CAA-related hemorrhage and vice versa. Cortical petechial hemorrhage can be epileptogenic. Familial forms of CAA are associated with hemorrhage at younger ages, by the third or fourth decade in the Icelandic form and by the sixth decade among the Dutch kindreds.

- Dementia

Cognitive impairment of Alzheimer type is a common feature of CAA. More than 40% of patients with ICH-related hemorrhage have some degree of dementia. In some cases, the cognitive changes can precede the ICH. The relationship between CAA and AD is close. CAA, which is present in 80-85% of patients with AD, is severe in one third to two thirds of these patients. CAA is the most significant microscopic abnormality in 10-15% of patients.
diagnosed with AD by clinical criteria. CAA and AD coexist pathologically at rates greater than predicted by chance. Arterial β-amyloid in CAA is nearly identical to senile plaque β-amyloid. Vascular lesions can play a significant physiopathologic role and can contribute to the development of dementia in AD. The severity of CAA is correlated with the presence of ischemic or hemorrhagic lesions in the brains of patients with AD, and CAA is associated with gross strokes but not with subcortical lacunae. However, a direct causal link between the 2 disorders has not been established, and the association could be due to shared risk factors such as the presence of apolipoprotein (ApoE) e4. Some patients with CAA present with a progressive dementia that entails rapid cognitive decline over days or weeks. This rapid progression could be due to the additive effects of severe vascular amyloid, cortical hemorrhages and infarctions, white matter destruction, and accumulation of neuritic plaques.

- **Vasculitis**

Few cases of vasculitis of various types (giant cell arteritis, rheumatoid vasculitis, primary angiitis of the CNS) associated with CAA have been reported. No consensus exists as to whether the pathologic abnormalities are related causally or whether the appearance of vasculitis is a reaction to CAA-induced angiopathic changes.

- **Microbleeds in cerebral amyloid angiography**

Cerebral microbleeds are defined radiologically as small, rounded, homogeneous, hypointense lesions on T2*-weighed gradient-recalled echo (T2*-GRE) and related MRI sequences that are sensitive to magnetic susceptibility.[11] Scharf et al. were the first to report on small, intracerebral black dots of signal loss on T2-weighted spin-echo MRI in patients with hypertensive cerebrovascular disease and intracerebral hemorrhage (ICH) associated with ischemic white matter disease and lacunar infarcts.[12] They called these lesions ‘hemorrhagic lacunes’, and their further characterization using T2*-GRE MRI sequences led to the current radiologic definition of ‘microbleeds’, a term coined by Offenbacher and colleagues in 1996.[13] A key feature of Cerebral microbleeds is that they are not seen well on conventional computed tomography or MRI scans. Available histopathological studies suggest that Cerebral microbleeds radiological lesions are due to tiny bleeds adjacent to abnormal small vessels, being mainly affected by hypertensive angiopathy (arteriolosclerosis – usually lipohyaline degeneration related to hypertension) or cerebral amyloid angiopathy (CAA).[14]
Figure 1. A postmortem section of the brain showing a cortical microbleed (arrow) in a patient with Alzheimer’s disease and CAA

CLINICAL PICTURE OF CEREBRAL AMYLOID ANGIOGRAPHY

- **History**

CAA is frequently asymptomatic. However, it can present as one of several clinicopathologic entities. The most frequent are ICH and dementia.

- CAA most often comes to clinical attention because of ICH. Symptoms may range from transient weakness to coma, depending on the size and location of the hemorrhage. Patients may have recurrent episodes.
  - The most common symptom at onset is headache (60-70% of patients). Frontal hematomas produce bifrontal headache pain; parietal bleeds, usually unilateral temple pain; temporal hematomas, ipsilateral eye and ear pain; and occipital bleeds, ipsilateral eye pain.
  - Vomiting (in 30-40%) tends to occur early.
  - Seizures occur at onset in 16-36%. Seizures are most commonly partial, with symptoms determined by the location of the ICH. As many as half of the patients present in status epilepticus.
  - Coma at presentation has been reported in a small proportion of patients (0.4-19%). Decreased level of consciousness, which is related to the size and
location of the hematoma, results from compression of the contralateral hemisphere or brain stem or increased intracranial pressure.

- **Dementia** may be manifested by any of several patterns of cognitive dysfunction. Some patients present with rapid progression from a normal baseline to profound dementia in a couple of years. Other patients can have a more protracted course, which is more typical of that seen in AD.

- **Stereotyped transient neurologic events** commonly consist of focal weakness, paresthesias, or numbness. In some cases, these events may be prodromes to larger hemorrhages.
  - The symptoms spread to contiguous body parts over 2-10 minutes, and they may involve areas in several vascular territories. These events are probably due to small cortical petechial hemorrhages that lead to focal seizures. The rate of spread is akin to that seen in migraine; some have proposed that they may represent spreading depression of neuronal activity.
  - Some patients present with transient confusion or episodes of visual misperceptions.

- **Uncommon presentations of CAA**
  - CAA can be associated with ischemic strokes; in some of these patients, a coexistent vasculitis can be found. The causal relationship with CAA is unclear.
  - CAA is found in patients with autosomal dominant dementia, spasticity, and ataxia without ICH.
  - CAA is reported in patients with vascular malformations, postirradiation necrosis, spongiform encephalopathies, and dementia pugilistica.
  - CAA can present as a mass lesion; this has been related to the existence of an "amyloidoma" with accumulation of amyloid in the brain parenchyma or to edema and gliosis that result from the vascular lesion.

- **Physical**

Physical findings depend on the clinicopathological entity associated with CAA in a particular patient.

- The features of ICH depend on the location of the bleed. Strict isolation of features from each lobe frequently is not possible because of extension of hematoma to other lobes, mass effect, and increased intracranial pressure.
  - Frontal: Depending on the size and location, frontal ICH may present with any symptoms from weakness of one limb to impaired consciousness with contralateral hemiparesis, hemisensory loss, and horizontal gaze palsy. Left hemispheric lesions can present with aphasia, and more anterior lesions lead to an abulic state with frontal release signs.
  - Parietal: Hemisensory loss, homonymous hemianopsia, hemi-inattention, and apraxia are all signs of parietal ICH.
  - Temporal: Dominant hemisphere hematomas lead to aphasia and hemianopia; nondominant hemisphere hematomas produce a confusional state.
Occipital: Unilateral hemianopia or quadrantanopia and visual hallucinations often accompany occipital ICH.

AETIOLOGY OF CEREBRAL AMYLOID ANGIOGRAPHY

- Most cases are sporadic, although genetic predispositions exist. (eg, ApoE subtypes confer different risk profiles.)
- Most cases of CAA-related ICH are spontaneous, but they may be related to vessel wall injury by atherosclerosis and hypertension. The risk of intracranial bleeding following head trauma and neurosurgical procedures is increased in patients with CAA. Some evidence suggests that CAA has a role in a substantial proportion of anticoagulant- and thrombolytic-related hemorrhages.
- Hereditary forms of CAA are due to specific gene mutations.
- Hereditary cerebral hemorrhage with amyloidosis-Dutch type is an autosomal-dominant disorder with complete penetrance.
  - The age of onset of ICH is in the sixth decade (mean, 55 y). Eighty-seven percent of those affected have ICH, and 13% have infarcts (deep).
  - Some patients develop dementia without ICH.
  - Amyloid deposits are found in cortical and leptomeningeal vessels; parenchymal neurofibrillary tangles are not seen. Deposited amyloid protein in these patients is identical to the amyloid protein seen in sporadic cases, and the likely genetic defect is in the amyloid protein precursor protein (APP) gene on chromosome 21.
- Hereditary cerebral hemorrhage with amyloidosis-Icelandic type is also autosomal dominant.
  - Patients present with their first episode of ICH in the third or fourth decade, with some patients dying from ICH aged as young as 15 years. A recent case report has identified a family with late-onset dementia with and without ICH.
  - The amyloid angiopathy is more widely distributed in this type than in other types, involving arteries in the cerebrum, cerebellum, and brain stem.
  - The amyloid protein is a mutant of the cysteine protease inhibitor cystatin C.
- Severity of angiopathy and fibrinoid necrosis closely correlate with the occurrence of ICH.
- The Boston Cerebral Amyloid Angiopathy Group has elaborated guidelines for the diagnosis of CAA associated with ICH. Four levels of certainty in the diagnosis of CAA are considered: definite, probable with supporting pathological evidence, probable, and possible. The first 3 require that no other cause of hemorrhage has been identified; they are yet to be validated but are clinically useful.
  - Definite CAA: Full postmortem examination reveals lobar, cortical, or corticosubcortical hemorrhage and evidence of severe CAA.
  - Probable CAA with supporting pathological evidence: The clinical data and pathological tissue (evacuated hematoma or cortical biopsy specimen) demonstrate a hemorrhage with the aforementioned characteristics and some degree of vascular amyloid deposition.
Probable CAA: Clinical data and MRI findings (in the absence of a pathological specimen) demonstrate multiple hematomas (as described above) in a patient older than 60 years.

Possible CAA: This is considered if the patient is older than 60 years, and clinical and MRI data reveal a single lobar, cortical, or corticosubcortical hemorrhage without another cause, multiple hemorrhages with a possible but not a definite cause, or some hemorrhage in an atypical location.

GENETIC OF CEREBRAL AMYLOID ANGIOGRAPHY

- The severity of the angiopathy is associated with ApoE polymorphism. The ApoE e4 and e2 alleles are risk factors for CAA.
  - The ApoE e2 allele also confers an increased risk of ICH in patients with CAA. The ApoE e4 allele is associated with earlier onset of first hemorrhage and carries a significant risk of concomitant AD.
  - Patients with lobar ICH and the e2 or e4 allele have a greater risk of early recurrence.
  - These tests lack sensitivity and specificity and are not indicated as screening or diagnostic procedures. However, they may be helpful prognostic tools in identifying patients with a greater risk of early recurrence.

- In cases of CAA-related ICH, laboratory studies should rule out other possible etiologies.

IMAGING OF CEREBRAL AMYLOID ANGIOGRAPHY

- CT scan of the brain
  - This procedure is the first choice for patients with suspected acute ICH.
  - A single lobar hemorrhage with superficial location and cortical involvement with or without local extension to the subarachnoid and intraventricular spaces is suggestive of CAA-related hemorrhage. Evidence of multiple hemorrhages restricted to lobar regions may be present.
  - Hemorrhages are most common in the frontal and parietal lobes, involving the cortex and subcortical white matter. Over time, several lobes may be involved. Deep central gray nuclei, the corpus callosum, and the cerebellum are sometimes affected. CAA is rarely the cause of putaminal, thalamic, or brain stem hemorrhage.
  - Pure subarachnoid, intraventricular, and subdural hemorrhages can be seen but are rare. CAA should never be assumed to be the cause of an isolated subarachnoid hemorrhage unless all other causes, particularly aneurysmal, have been excluded.
  - Patients with CAA-associated dementia have a leukoencephalopathy similar to that seen inBinswanger disease. Atrophy also can be detected, particularly in patients with cognitive impairment and a history of prior hemorrhage.
- MRI
  - MRI shows evidence of multiple cortical and subcortical large and small petechial hemorrhages, even in patients without a history that suggests previous hemorrhage.
  - MRI gradient-echo sequences show evidence of iron deposits, which correspond to old hemorrhages. In patients who present with lobar hemorrhages, the evidence of old petechial bleeds and microbleeds can help in the diagnosis of CAA. Gradient-echo MRI also can be used as a marker of disease progression and potentially can evaluate the effect of therapeutic interventions.
  - Leptomeningeal enhancement is seen in patients with associated vasculitis.
  - Cerebral microbleeds are commonly associated with cerebral amyloid angiopathy. Microbleeds are lobar in location in patients with cerebral amyloid angiopathy.

Figure 2. Lobar microbleeds on 3-dimensional T2*-weighted gradient-recalled echo MRI in an 80 years old man with dementia and cerebral amyloid angiopathy.
Figure 3. Example of microbleeds on 3-dimensional T2*-weighted gradient-recalled echo MRI in an 80 years old man with Alzheimer dementia and cerebral amyloid angiopathy. The microbleeds are lobar in location.

HISTOPATHOLOGICAL FINDING IN CEREBRAL AMYLOID ANGIOGRAPHY

Histologic examination is required for definitive diagnosis. Pathologic samples are obtained from hematoma evacuation, cortical biopsy, or postmortem specimens. The disease process may be diffuse, so pathologic data may be lacking even in biopsy cases. The presence of vascular amyloid is a sensitive marker for CAA-related hemorrhage. β-amyloid consists of twisted β-sheet fibrils in vessel wall. It is a homogenous, intensely eosinophilic material that gives a smudged appearance by light microscopy. When stained with Congo red and visualized under polarized light, it gives a characteristic yellow-green (ie, apple green) birefringence. When thioflavin T and S are used and visualized with ultraviolet light, amyloid appears fluorescent. The presence of fibrinoid necrosis in amyloid-laden vessels is relatively specific for CAA-related ICH. CAA, which involves cortical and leptomeningeal vessels, is most common in the parietal and occipital lobes. The microangiopathy spares white matter and deep gray structures. Parenchymal features found in the brains of patients with CAA include patchy demyelination and loss of white matter, cortical hemorrhages and infarcts, and neuritic plaques with or without neurofibrillary tangles. Most patients with CAA-related ICH do not have AD.
Figure 4. Lobar hemorrhage due to amyloid angiopathy, B Microscopic section of the brain cortex, section has been stained with Congo Red for amyloid viewed with polarized light. The section shows relatively preserved cortical neurons and the blood vessels shows birefringence with polarized light. In some areas the walls of the blood vessels are yellow-green (arrow). Diagnosis: Amyloid angiopathy, also known as congophilic angiopathy.

References

INTRODUCTION & PATHOGENESIS:

Microcirculatory brain disease is a collective terminology that comprises vascular arteriolar pathology, metabolic endocrinial 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><strong>Clinical picture</strong></td>
<td>Stroke, TIAs, multi-infarct dementia, essential hypertension, depression, parkinsonism</td>
</tr>
<tr>
<td><strong>Metabolic, endocrinal changes</strong></td>
<td>Type VI hyperlipidaemia (Hypertriglyceridemia), hyperuricemia, type 2 diabetes, Insulin resistance, truncal obesity (The metabolic syndrome)</td>
</tr>
<tr>
<td><strong>Vascular pathology</strong></td>
<td>Lipohyalinosis, astrogliosis and interstitial edema, etc</td>
</tr>
<tr>
<td><strong>Haemorheological changes</strong></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.

*Figure 1. Diabetes, hyperlipidaemia, truncal obesity, depression, parkinson disease, hyperuricaemia hypertension, etc all stem from one and the same root (the genetic root)*

**THE ISCHEMIC MICROVASCULAR BRAIN DISEASE**

As a point of departure a quick over view 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.

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.

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 hyperaggregable 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 collagenosis, 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, astrocytosis, 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.
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 crible originally described by Durand-Fardel in 1843.

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

Figure 8. Etat crible 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.

Figure 9. Neurologically normal patient with leukoaraiosis affecting the basis pontis and tegmentum.
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.
Figure 12. leukoaraiosis, MRI T2 image. The MRI T2 periventricular hyperintensities are mainly due to astrogliosis and interstitial edema.

- 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, 30, 51, 18 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. 45 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, 30 others have seen leukoaraiosis to progress in concert with a severely stenosed ipsilateral carotid that advanced to complete occlusion. 95 In a more recent study, an increased oxygen extraction fraction (OEF) for white matter was found in four nondemented subjects with severe leukoaraiosis. 94 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. 16, 97 Approximately 10% to 20% of CSF may be produced intraparenchymally and transependymally absorbed 47, 78, 81 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, 31,32 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. 74

- **Axonal degeneration**

Ischemic axonopathy may also account for leukoaraiosis. Ball, 7 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 (sparing 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 (e.g., 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](image1.png)  ![Figure 13](image2.png)

**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.

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.
o 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.
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 progression 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.

- **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 154, 155 and in patients diagnosed with Alzheimer's disease (AD). 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. 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. 157 In comparison, these rates are doubled in patients attending a memory clinic. 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>Central and cortical atrophy</th>
<th>This is secondary to chronic global reduction of brain perfusion.</th>
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<tbody>
<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>
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<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>
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<td>Basal ganglionic calcifications</td>
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<tr>
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**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. 140
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.

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 un failing 1-1 relationship.

**Figure 28. Left ventricular hypertrophy with strain pattern**

**Table 3. MICROVASCULAR BRAIN DISEASE & CARDIOVASCULAR ASSOCIATES**

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<td><strong>BASAL GANGLIONIC CALCIFICATION</strong></td>
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- **DUPLEX SCANNING OF CAROTID ARTERIES SHOWS NORMAL FINDINGS OR NON SIGNIFICANT CHANGES**

- **LEFT VENTRICULAR HYPERTROPHY WITH STRAIN PATTERN**
## SUMMARY

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<th>MRI</th>
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<tr>
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<td><img src="image5.png" alt="CT Scan" /></td>
<td><img src="image6.png" alt="MRI" /></td>
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Dilated Virchow-Robin Spaces

Basal ganglionic calcifications

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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
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>
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<td>Periventricular white matter changes (leukoaraiosis)</td>
<td>Common in Egypt</td>
<td>73.8</td>
<td>Low incidence</td>
<td>75%</td>
<td>Microvascular brain disease</td>
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<tr>
<td>Cortical-Subcortical</td>
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<td>Low incidence</td>
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<td>Microvascular brain disease</td>
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<tr>
<td>Watershed</td>
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<td>70.8</td>
<td>High incidence</td>
<td>Low</td>
<td>Carotid bifurcation disease</td>
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<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>
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  - HAEMATOMA
  - INFARCTION
  - HERNIATION
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- CAROTID-CAVERNOUS ANEURYSMS
- VASCULAR ECTASIA (FUSIFORM ANEURYSMS)
Berry Cerebral 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>
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</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.

![Image](image.png)

**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.
Figure 4. Angiography showing a posterior communicating artery aneurysm

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>
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</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 induces 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.
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.

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.

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 front 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.

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%).

Figure 21. A CT scan revealing a left temporal lobe hematoma secondary to rupture of a left PCoA aneurysm rupture.
Relationship Between Aneurysm Site and Hematoma Location

The types of ICH can be 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>
</table>
| Posterior communicating artery aneurysm | 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.  
2. The rupture of aneurysms at the posterior communicating level also produces more ganglionic infarcts than aneurysms at other sites. |
| Internal carotid artery aneurysm | Massive middle cerebral artery infarction.                                      |
| Anterior communicating artery aneurysm | 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. |

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 subuncal hematoma, widening of the space between the anterior cerebral arteries by an interfrontal 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.

![Hematoma along the course of the vertebral-basilar system](image)

**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.
Figure 25. A case with ruptured anterior communicating artery aneurysm showing subarachnoid and intraventricular haemorrhage with acute hydrocephalus

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)

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**
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.
Figure 29. A, MRA, B, postmortem specimen showing basilar ectasia and basilar tip aneurysm

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.

Figure 30. Vertebrobasilar ectasia

- 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

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:.
INTRODUCTION

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>Weight</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 all 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.

Figure 3. Lacunar infarctions

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.
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 coeruleus 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>
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<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).

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).
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>
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<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>
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</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.

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RADIOLOGICAL PATHOLOGY OF CEREBRAL VENOUS & DURAL SINUS THROMBOSIS

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 temporo-occipital 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 diploe 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 (Pacchioni 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.
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.

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.

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,
Figure 3. Coronal contrast enhanced MR venogram MIP image shows many of the dural sinuses and a few of the deep cerebral veins. SSS = superior sagittal sinus; To = torcular herophili or confluence of sinuses; R = basal vein of Rosenthal; L = vein of Labbe; DMV = deep middle cerebral vein; TS = transverse sinus; SG = sigmoid sinus; SPS = superior petrosal sinus; J = internal jugular vein; C = internal carotid artery; V = vertebral artery; JB = jugular bulb; IJ = internal jugular vein; CV = cortical veins.

- **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.
o **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>
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<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>
<tr>
<td>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.</td>
</tr>
<tr>
<td>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</td>
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drainage, there is an increase in cerebellar water, which results in a small fourth ventricle and tonsillar herniation.

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<th>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.</th>
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<tr>
<td>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>
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</tbody>
</table>

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><strong>Stage I</strong></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><strong>Stage II</strong></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><strong>Stage III</strong></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>
</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>
</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>
</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>
</tr>
<tr>
<td>IV</td>
<td>Severe edema, with or without hemorrhage</td>
<td>Hemiparesis, seizure, loss of consciousness, coma</td>
</tr>
<tr>
<td>V</td>
<td>Massive edema and/or hemorrhage</td>
<td>Coma, response to deep pain only</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 I 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.</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.
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.

![Figure 4. 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 parietal 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-url)
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>Diagnosis</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empty delta sign</td>
<td>21%</td>
</tr>
<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 TI-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</td>
<td>The thrombus is isointense to the brain on TI-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>products (days I through 5)</td>
<td></td>
</tr>
<tr>
<td>The subacute extracellular methemoglobin</td>
<td>The thrombus is hyperintense on both TI-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>stage of blood products (from day 5 through</td>
<td></td>
</tr>
<tr>
<td>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.</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.

![Image](image_url)

**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><strong>Edema</strong></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>
</tbody>
</table>
| Affected dural sinuses                   | 1. In the acute stage (days 1 through 5), the thrombus is
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>
</tbody>
</table>
| Pregnancy | C - Safety for use during pregnancy has not been

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<table>
<thead>
<tr>
<th>Precautions</th>
<th>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</th>
</tr>
</thead>
<tbody>
<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, sulfonylureas, 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.

### Pregnancy

| X - Contraindicated in pregnancy |

### 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>

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| **Interactions** | Drugs that alter platelet function (eg, 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 |

breastfeeding
<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>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, sulfinpyrazone, 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>

**Agents**
- antithymocyte globulin
- cefamandole
- cefoperazone
- Ginkgo biloba
- NSAIDs
- platelet inhibitors
- porfimer
- strontium-89 chloride
- sulfinpyrazone
- tranexamic acid
- valproic acid

**Pregnancy**
- B - Usually safe but benefits must outweigh the risks.
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