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INTRODUCTION & PATHOGENESIS

NEUROIMAGING

CORRELATION OF STRUCTURAL PATHOLOGY OF MICROVASCULAR BRAIN DISEASE

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VERTEBROBASILAR ECTASIA (FUSIFORM ANEURYSM)

SUMMARY

INTRODUCTION & PATHOGENESIS:

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

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

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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)](image)

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.

**Figure 2. The cerebral microcirculation**

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

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

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 micro vascular 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.

![Central and cortical atrophy secondary to chronic global reduction of brain perfusion, Notice the associated lacunar infarctions](image)

- 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.
Figure 8. Etat cribe seen in a cognitively and neurologically normal 81-year-old woman. Fast spin echo: A, Proton density image. B, Second echo: dilated perivascular space permeate the basal ganglia bilaterally.

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

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

Rarely, patients with extensive leukoaraiosis can be diagnosed as having Binswanger's disease. This condition, sometimes referred to as lacunar dementia, etat lacunaire, or subcortical arteriosclerotic encephalopathy, is characterized pathologically by extensive athero and arteriosclerosis, multiple foci of white matter infarction, diffuse white matter demyelination with sparing of the subcortical "U" fibers, and variable evidence for cortical

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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 11. Postmortem specimen. Note the topographically extensive periventricular white matter changes in a hypertensive case with evidence of leukoaraiosis on MRI study
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, oligodendrogial 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 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 (eg, the middle cerebral artery, anterior choroidal artery, anterior cerebral artery, posterior cerebral artery, posterior communicating artery, cerebellar arteries, basilar artery). Their small size and proximal position predispose them to the development of microatheroma and lipohyalinosis.

Figure 13. 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**

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.
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 gyrimonform 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 progress sclerosis, hyalinosis, lipid deposits, and regional loss of smooth muscle in the vessel wall associated with lacunar spaces that are histologically seen to consist of three subtypes. Type 1 lacunes are small, old cystic infarcts; type 2 are scars of old hematomas; and type 3 are dilated Virchow-Robin Spaces (129). Grade 3 microangiopathy represents the most severe stage and is especially related to severe chronic hypertension. Typical changes described in lower grades are accompanied by fibrotic thickening vessel wall with onion skinning, loss of muscularis and elastic lamina, and regional necrosis in the vessel walls. The brain parenchyma contains multiple lacunae, and diffuse abnormality of myelin is present in the deep hemispheric white matter.

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

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

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

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

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

- **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\textsuperscript{154, 155} and in patients diagnosed with Alzheimer's disease (AD).\textsuperscript{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.\textsuperscript{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.\textsuperscript{157} In comparison, these rates are doubled in patients attending a memory clinic.\textsuperscript{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).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{microbleed_imaging.png}
\caption{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.}
\end{figure}
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

| Central and cortical atrophy | This is secondary to chronic global reduction of brain perfusion. |
| Leukoaraiosis (diffuse periventricular white matter disease) | 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. |
| Lacunar infarctions | 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. |
| Granular atrophy | Granular atrophy is defined pathologically as infarctions localized to the cerebral cortex and not extending to the subcortical white matter. |
| Basal ganglionic calcifications | These are calcification of the the arteriolar wall of the microcirculation within the basal ganglia. |
| Dilated Virchow-Robin Spaces | Dilation of Virchow-Robin Spaces provides a potential alternative biomarker of microvascular disease (small vessel disease). |
| Cerebral Microbleeds | 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). |

**VERTEBROBASILAR ECTASIA (FUSIFORM ANEURYSM, VERTEBROBASILAR DOLICHOECTASIA)**

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 unfailing 1:1 relationship.

Table 3. MICROVASCULAR BRAIN DISEASE & CARDIOVASCULAR ASSOCIATES

| • LACUNAR INFARCTION | • LEUKOAARAIOSIS |
| • CENTRAL & CORTICAL ATROPHY | • GRANULAR ATROPHY |
| • SPONTANEOUS HYPERTENSIVE CEREBRAL HAEMORRHAGE | • BASAL GANGLIONIC CALCIFICATION |
| • DUPLEX SCANNING OF CAROTID ARTERIES SHOWS NORMAL FINDINGS OR NON SIGNIFICANT CHANGES |
| • LEFT VENTRICULAR HYPERTROPHY WITH STRAIN PATTERN |

Figure 28. Left ventricular hypertrophy with strain pattern
### SUMMARY

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