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 and essential hypertension.

Table 1. Microvascular brain disease associates

<table>
<thead>
<tr>
<th>Microvascular associate</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical picture</td>
<td>Stroke, TIAs, multi-infarct dementia, essential hypertension, depression, parkinsonism</td>
</tr>
<tr>
<td>Metabolic, endocrinal changes</td>
<td>Type VI hyperlipidaemia, hyperuricaemia, diabetes, truncal obesity</td>
</tr>
<tr>
<td>Vascular pathology</td>
<td>Lipohyalinosis, astrogliosis and interstitial edema, etc</td>
</tr>
<tr>
<td>Haemorheological changes</td>
<td>Increased whole blood viscosity</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 hyperuricaemia.

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

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.
The haemorheological changes associated with microvascular brain disease include increase in the whole blood viscosity and thrombotic tendency of the blood.

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 aggregability also increases whole blood viscosity.

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.

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.

CEREBRAL PARENCHYMAL CONSEQUENCES OF MICROVASCULAR BRAIN DISEASE

- Central and cortical atrophy

This is secondary to chronic global reduction of brain perfusion.

Figure 6. Central and cortical atrophy secondary to chronic global reduction of brain perfusion, Notice the associated lacunar infarctions

- 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. These changes are frequently associated with arteriosclerotic vasculopathy and, in more severe cases, with frank lacunar infarction. 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. 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. Leukoaraiosis may also be related to histologic characteristics of the normal frontal horn subependymal region (fasiculus 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 spaces permeate the basal ganglia bilaterally.](image)

![Figure 9. Neurologically normal patient with leukoaraiosis affecting the basis pontis and tegmentum.](image)

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

Pathophysiology of leukoaraiosis

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

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

The extent to which the more common and histologically milder forms of leukoaraiosis can also be explained by ischemic mechanisms is currently unclear. The term "incomplete white matter infarction" has been proposed to designate regions of mild demyelination, 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 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. 

- 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 (sparring 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 midsized 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 magentic 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.
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\textsuperscript{111,112}. 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\textsuperscript{113}.

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\textsuperscript{114}.

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\textsuperscript{115}. 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\textsuperscript{116}.

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 outermost gray matter.
Figure 19. Cortical laminar necrosis. Sagittal T1-weighted MR image (A) depicts the gyriform increased signal area in right temporal and parietal region. T2-weighted MR and FLAIR images show these areas as dark signal areas.

- Basal ganglionic calcifications

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

The ischaemic microvascular brain disease is the interaction between the haemorheological changes, the vascular arteriolar pathology and the neuronal diminished glucose and oxygen entry

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>
</tr>
</thead>
<tbody>
<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.</td>
</tr>
<tr>
<td>Granular atrophy</td>
<td>Granular atrophy is defined pathologically as infarctions localized to the cerebral cortex and not extending to the subcortical white matter.</td>
</tr>
<tr>
<td>Basal ganglionic calcifications</td>
<td>These are calcification of the the arteriolar wall of the microcirculation within the basal ganglia.</td>
</tr>
</tbody>
</table>

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). 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.

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

Table 3. MICROVASCULAR BRAIN DISEASE & CARDIOVASCULAR ASSOCIATES

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

SUMMARY
The medications used in the management of lacunes are not specific to this subtype of stroke.

**Drug Category: Fibrinolytics** - Used to improve stroke outcome. The National Institute of Neurological Disorders and Stroke (NINDS) study on recombinant tissue-type plasminogen activator (rt-PA) showed an 11-13% absolute increase in the number of ischemic stroke patients with a favorable outcome at 3 months with tissue plasminogen activator (TPA).

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>CT SCAN</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lacunar infarctions</strong></td>
<td><img src="image1" alt="CT Scan" /></td>
<td><img src="image2" alt="MRI" /></td>
</tr>
<tr>
<td><strong>Leukoaraiosis</strong></td>
<td><img src="image3" alt="CT Scan" /></td>
<td><img src="image4" alt="MRI" /></td>
</tr>
<tr>
<td><strong>Central and cortical atrophy</strong></td>
<td><img src="image5" alt="CT Scan" /></td>
<td><img src="image6" alt="MRI" /></td>
</tr>
<tr>
<td><strong>Basal ganglionic calcifications</strong></td>
<td><img src="image7" alt="CT Scan" /></td>
<td><img src="image8" alt="MRI" /></td>
</tr>
</tbody>
</table>
Drug Category: **Antiplatelet agents** - Secondary stroke prevention, if commenced within 48 hours of stroke onset, confers a small survival benefit.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Aspirin (Anacin, Ascriptin, Bayer Aspirin)- Alternatives to aspirin include ticlopidine and clopidogrel. These drugs and combination of aspirin and dipyridamole may be marginally superior to aspirin alone.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Dose</td>
<td>30-1300 mg/d; in US, usual dose is 325 mg PO qd</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>Not established</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity; liver damage, hypoprothrombinemia, vitamin K deficiency, bleeding disorders, asthma; due to association of aspirin with Reye syndrome, do not use in children (age &lt;16 years) with flu</td>
</tr>
<tr>
<td>Effects</td>
<td>Effects may decrease with antacids and urinary alkalinizers; corticosteroids decrease salicylate serum</td>
</tr>
</tbody>
</table>
### Drug Category: Anticoagulants
- **For prophylaxis of deep venous thrombosis and pulmonary embolism.**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Heparin (Hep-Lock)- Can be used in conjunction with compression stockings or pneumatic stockings. Augments activity of antithrombin III and prevents conversion of fibrinogen to fibrin. Does not lyse actively but can inhibit further thrombogenesis. Prevents reaccumulation of clot after spontaneous fibrinolysis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Dose</td>
<td>5000 U SC bid</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>Not established</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity, subacute bacterial endocarditis, active bleeding, and history of heparin-induced thrombocytopenia</td>
</tr>
<tr>
<td>Interactions</td>
<td>Digoxin, nicotine, tetracycline, and antihistamines may decrease effects; NSAIDs, aspirin, dextran, dipyridamole, and hydroxychloroquine may increase toxicity</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>C - Safety for use during pregnancy has not been established.</td>
</tr>
<tr>
<td>Precautions</td>
<td>In neonates, preservative-free heparin is recommended to avoid possible toxicity (gasing syndrome) by benzyl alcohol, which is used as preservative; caution in severe hypotension and shock</td>
</tr>
</tbody>
</table>

### Drug Category: Angiotensin-converting enzyme inhibitors (ACE inhibitors)
- **For secondary stroke prevention.**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Ramipril- The recently published Heart Outcomes Prevention Evaluation (HOPE) study showed the benefit of ramipril in patients with vascular disease and diabetics with vascular risk factors. It is not known whether this is a class effect.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Dose</td>
<td>Initial dose: 2.5 mg PO qd; titrate up to 10 mg PO qd</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>Not established</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity; history of angioedema</td>
</tr>
<tr>
<td>Interactions</td>
<td>Ramipril may increase digoxin, lithium, and allopurinol levels; probenecid may increase ramipril levels; coadministration with diuretics, increase hypotensive effects; the hypotensive effects of ramipril may be</td>
</tr>
</tbody>
</table>
References


34. George AE, de Leon Mj, Gentes Cl, et. al: Leukoencephalopathy in normal and pathologic aging: 1. CT of...


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


---

**Addendum**

- A new version of this PDF file is uploaded in my web site every month (it remains for a month and is changed with the monthly update of the neurology bulletin at: [http://neurology.yassermetwally.com](http://neurology.yassermetwally.com))
- To download the current version follow the link "[http://neurology.yassermetwally.com/topic.zip](http://neurology.yassermetwally.com/topic.zip)"
- You can also download the current version from within the publication or go to my web site at: "[http://yassermetwally.com](http://yassermetwally.com)" to download it.
- At the end of each year, all the publications are compiled on a single CD-ROM, please author to know more details.
- Screen resolution is better set at 1024*768 pixel screen area for optimum display
- For an archive of the previously reported cases go to [www.yassermetwally.net](http://www.yassermetwally.net), then under pages in the right panel, scroll down and lick on the text entry "topic of the month"

---

**The author:** Professor Yasser Metwally, professor of neurology, Ain Shams university, Cairo, Egypt

[www.yassermetwally.com](http://www.yassermetwally.com)