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Mechanisms underlying sporadic cerebral small vessel disease: insights from neuroimaging

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Abstract

The term “cerebral small vessel disease” (SVD) describes a range of neuroimaging, pathological and associated clinical features. The latter range from none, to discrete focal neurological symptoms (stroke), to insidious global neurological dysfunction and dementia. The public health burden is considerable. The pathogenesis is largely unknown. Although associated with vascular risk factors, and generally considered to result from an intrinsic cerebral arteriolar occlusive disease, the pathological processes leading to the arteriolar disease, how these result in brain disease, how SVD lesions contribute to neurological or cognitive symptoms and the relationship to risk factors, have been the subject of much speculation. Pathology often reflects end-stage disease making determination of the earliest stages difficult. Neuroimaging provides considerable insights: the small vessels are not easily seen themselves, but the effects of their malfunction on the brain can be tracked on detailed brain imaging. We review the growing evidence for the most likely mechanisms.

Introduction

‘Cerebral small vessel disease’ (SVD) is the term now commonly used to describe a syndrome of clinical, cognitive, neuroimaging and neuropathological findings that are thought to arise from disease affecting the perforating cerebral arterioles, capillaries and venules and the resulting brain damage in the cerebral white and deep grey matter.¹ These perforating vessels are essential for maintaining optimal functioning of the brain’s most metabolically active nuclei and complex white matter networks.²

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SVD has only recently been recognised for the serious problem that it is. It is very common, causes substantial cognitive,³ psychiatric,⁴ and physical disabilities⁵ in older people,⁶ about a fifth of all strokes⁷ more than doubles the future risk of stroke,^{8,9} and contributes to up to 45% of dementias.¹⁰ The cost to society is huge. The cause is unknown therefore prevention and treatment, still mostly empirical, are probably suboptimal^{11,12} or even hazardous.¹³ Lack of awareness until now may have resulted from i) the large attention given to other stroke mechanisms (i.e. cortical atherothromboembolic and cardioembolic stroke), ii) the cognitive component being overshadowed by Alzheimer's disease, and iii) most research focusing on individual features of SVD rather than recognising the combined components as one problem.

Why do we know so little about such an important problem? Small vessels are difficult to visualise and investigate in vivo.¹⁴ The clinical manifestations are diverse and include sudden onset stroke symptoms or syndromes, recently recognised covert neurological symptoms that include mild, largely ignored, neurological symptoms, signs¹⁵ and self-reported cognitive difficulties¹⁶ and progressive cognitive decline,⁶ dementia, depression,⁴ and physical disabilities.⁵ Reliance on clinical features and CT scanning to differentiate lacunar from non-lacunar stroke is imprecise and has probably confounded epidemiological and observational studies of risk factor associations.¹⁷ Many trials have not differentiated ischaemic stroke subtypes explicitly, potentially overlooking any differences in treatment response between subtypes.¹⁸ Death resulting directly from lacunar stroke is rare, so most pathology reflects late stage disease,¹⁹ there are few studies of human lacunar stroke pathology,¹⁹ and few pathology-imaging correlations.²⁰ Backtracking from a late stage 'scar' to the initiating pathology is difficult. Much of SVD is largely clinically silent until late and experimental models are limited by lack of a mechanism to mimic.^{21,22} Terminology for clinical, imaging²³ and pathology²⁴ of SVD is highly varied. For all these reasons, lack of understanding of SVD mechanisms is hardly surprising. Fortunately, standardisation of terminology for imaging features is currently the subject of an international collaboration of experts and due to report in 2013.²⁵ In the meantime, for the purpose of this review, we will use some traditional terms as these were used in the reports that formed the basis for this review.

The pathogenesis of the microvascular and brain abnormality in most SVD is still undetermined and is the focus of this review. We here define SVD as *a sporadic intrinsic process affecting small cerebral arterioles, capillaries and sometimes venules*. Features of SVD probably develop over many years before becoming clinically evident. The core mechanism underlying SVD-related brain injury is usually assumed to be *ischaemia*, acting through *arteriolar narrowing or occlusion* either structural or functional (e.g. vasospasm, impaired autoregulation, or hypotension). However, arteriolar occlusion may be a late stage phenomenon and does not explain the early pathology. Some discussion of specific SVD imaging features will help put the commonest suspected mechanisms in perspective: then we will focus on what we suggest may be a key problem: diffuse cerebrovascular endothelial failure. Specifically, we will summarise evidence suggesting that endothelial damage leads to increased permeability with leakage of material into the vessel wall and perivascular tissue, damage to the vessel wall, inflammation, demyelination, glial scarring, vessel wall thickening and stiffness, impaired autoregulation and at a late stage, luminal narrowing and occlusion, precipitating discrete focal brain parenchymal ischaemia/infarction.

Methods used in this review

We have used systematic reviews where available, searched Medline and Embase extensively for papers on lacunar stroke, for all SVD components in imaging or pathology studies, on the role of reduced blood flow and inflammation, the endothelium, other

potential mechanisms, risk factors, in human and animal studies, population-based, cohort studies and clinical trials. The literature search included in our prior systematic reviews extended to the early 1900s. Articles were also identified through searches of the authors' own files, from conferences, abstract presentations and web sources such as www.strokecentre.org/trials. We included English and non-English language publications where possible. Our focus is on common "sporadic" SVD. We will not discuss any of the rare hereditary forms of SVD (CADASIL, CARASIL, COL4AI, Fabry's, HERNs) except where these have immediate relevance to sporadic SVD. Nor, for space reasons, will we discuss details of amyloid-associated angiopathy (cerebral amyloid angiopathy) as this has been the subject of recent reviews.²⁶ The final reference list reflects key papers that are most relevant to the broad scope of this review, as space limitations precluded inclusion of many other aspects of potential relevance to pathogenesis of SVD (eg genetic predisposition, or an extensive review of blood pressure).

Recent history of concepts about SVD pathophysiology

Modern concepts concerning aetiology and pathogenesis derive from the seminal post-mortem work of C. Miller Fisher undertaken between 1955 and 1973. His work was based on detailed clinicopathological-vascular post-mortem examinations of 20 patients in whom he studied between one and 50 individual lesions (lacunes, lacunar infarcts, perforating arterioles).²⁷⁻³¹ After the introduction of CT scanning in 1973, pathological examination of the brain in patients with lacunar stroke virtually completely ceased.³¹ Fisher's pathological studies, mostly conducted long after the original stroke, focused on the lacune (fluid filled cavity) that was thought to represent the originally symptomatic lacunar infarct. The lacune still dominates the field,⁹ being much more likely to be recognised as responsible for a clinical lacunar stroke than are non cavitated lesions.²³

Features of SVD on MR imaging

The main *imaging features of SVD*, now recognised all to be inter-related, visible on conventional magnetic resonance (MR) imaging (MRI) at 1.5 or 3T, include acute lacunar (or small subcortical) infarcts or haemorrhages, lacunes (fluid-filled cavities thought to reflect old infarcts, many clinically silent),⁹ white matter hyperintensities (WMH, in which many investigators include small deep grey matter hyperintensities, also mostly clinically covert),³² visible perivascular spaces (PVS),³³ microbleeds,³⁴ and brain atrophy (Figure 1).³⁵ Other emerging features detectable at higher field strengths include microinfarcts.^{36,37} Additional "sub-visible" damage detectable on advanced MRI (e.g. diffusion tensor imaging, DTI, magnetization transfer ratio, MTR) includes altered white matter integrity and disrupted axonal connections,^{38,39} increased brain water content,⁴⁰ altered myelination,³⁹ and secondary focal thinning of the cortical grey matter.⁴¹ We will briefly describe the imaging and the related clinical components of SVD that are particularly germane to understanding the underlying pathophysiology. We will start with lacunar stroke and acute lacunar infarction because, by causing sudden discrete focal neurological symptoms, it provides a useful 'alert' to the presence of SVD and might allow the disease to be caught earlier in its development than in patients presenting with late stage global brain dysfunction.

Lacunar infarction

The lesion underlying most lacunar strokes⁴² is an infarct, rounded, ovoid or tubular in shape, less than 20 mm in axial diameter. Tubular lesions seem to be more likely in the basal ganglia/internal capsule, as noted by Fisher³¹ (Figure 2, Supplementary Figure 1). A small proportion (5%) are due to a small deep haemorrhage. An acute lacunar infarct is of increased signal on diffusion weighted imaging (DWI), reduced signal on apparent diffusion

coefficient (ADC) map, and of increased signal on FLuid Attenuated Inversion Recovery (FLAIR), T2-weighted imaging, reduced signal on T1-weighted MRI, and low attenuation on CT scanning, compared to normal grey or white matter. Only about 50% of recent infarcts are visible on CT,⁴³ whereas at least 70% are visible on MR DWI.⁴⁴ Stroke subtyping on clinical features alone is imperfect, misdiagnosing about 20% of acute lacunar clinical syndromes as cortical stroke and vice versa,¹⁷ and will lead to 'noise' in studies that do not include DWI. The original size definition was established from pathology which, being late stage, underestimated the size of acute lesions (Figure 3). Imaging shows that acute lesions are usually larger than old lesions, has questioned the maximum permissible sizes of acute lacunar infarcts⁴⁵ and emphasised the importance of noting the age of the lesion (Figure 3). Acute infarcts generally shrink to either leave a small cavity (lacune) or a small lesion of similar signal characteristics to a WMH or occasionally disappear (Figure 3). Acute lesions larger than 20mm axial diameter are likely to be striatocapsular, i.e. due to middle cerebral artery (MCA) embolism/occlusion or atheroma occluding multiple perforating arterioles.⁴⁶ However lesions that were quite definitely striatocapsular infarcts when acute can shrink markedly to leave only a small lacunar-like cavity. Thus, it is easy to see why pathology or late stage imaging studies would associate atheromatous or embolic disease with lacunar infarction (Supplementary Figure 2). Probability mapping shows that the main location of acute DWI-proven symptomatic lacunar infarcts is in the primary motor and sensory pathways (note distribution in all images shown),⁴⁷ explaining why such small lesions present as stroke whereas other SVD lesions accumulate 'silently' but otherwise have very similar long term appearances. Fisher also found that location in the internal capsule and not size determined whether the lesion had been symptomatic in life or not.¹⁹

Lacunes are small cerebrospinal fluid-containing cavities located in the deep grey or white matter, typically larger than 3mm and (most consider) smaller than 15mm in diameter (Figure 1 and 3). Lesions larger than 15mm in some literature are considered as lacunes, but in general the larger the lesion the more likely that the lesion was caused by mechanisms other than SCD (Supplementary Figure 2). Many lacunes were never symptomatic but appear silently in the brain (Supplementary Figure 3 for pathology examples).⁹ The proportion of definite DWI-confirmed acute lacunar infarcts that progress to lacunes varies from about 28% to 94%^{48,49} depending on how cavitation is defined and other as yet undetermined factors including duration of follow-up. Whatever the true proportion, not all lesions cavitate: some quite large acute DWI-confirmed lacunar infarcts disappear completely (Figure 3) while others appear long term like a non-cavitated WMH.

White matter hyperintensities (WMH) are rounded areas of decreased attenuation on CT, increased signal on T2-weighted and FLAIR, often decreased on T1-weighted MR imaging with respect to normal brain, but not as attenuated or intense as CSF (Figure 1 and 3). They are distributed in the periventricular and deep white matter of the cerebral hemispheres, in the basal ganglia (i.e. deep grey matter), in the pons and occasionally in other parts of the brainstem and cerebellar white matter. They are almost always symmetrically distributed and are usually numerous in the cerebral hemispheres before appearing in the brainstem. Eventually, when very numerous, they coalesce. It is unclear whether differential periventricular or deep distribution reflects distinct mechanisms or just different disease stages. WMH are more common and more extensive in patients with acute lacunar stroke (vs. other stroke subtypes),³² associated with lacunes,⁵⁰ perivascular spaces,³³ microbleeds³⁴ and brain atrophy.³⁵

Virchow-Robin, or visible perivascular spaces (PVS) surround the small deep perforating arterioles as they pass through the deep grey and white matter, made visible on T2- or T1-weighted MR by containing increased fluid of similar signal to CSF. On MR imaging, PVS appear round where perpendicular to and linear where parallel to the imaging plane, so

typically on axial imaging are round in the basal ganglia and linear in the subcortical white matter of the lateral parts of the temporal, parietal and frontal lobes (Figures 1 and 4). While a few visible PVS may be normal at any age,⁵¹ many are not normal.^{33,52,53} Visible PVS around perforating arterioles, although observed for many years histologically in older people often in association with other SVD features, were often dismissed as an artefact of tissue processing (Figure 4). The relevance of PVS to SVD is illustrated by their presence in larger numbers in association with WMH^{33,53} and with symptomatic lacunar ischaemic stroke.^{33,54} An increase in their number also indicates active inflammation, e.g. in multiple sclerosis (where their diameter also increased during active inflammation)⁵⁵ and in lacunar stroke.⁵⁶ They are not simply a consequence of global brain atrophy⁵³ as they are frequently seen in patients who have little atrophy, although they might be an alternative manifestation of atrophy.

Other features of SVD include *microbleeds*, which are small punctuate areas of hypointensity on T2* or susceptibility-weighted imaging measuring up to 10mm in diameter corresponding to small collections of haemosiderin-laden macrophages around small perforating vessels.^{20,57} Microbleeds are associated with lacunar stroke and WMH,^{34,58} and are clearly part of the spectrum of SVD. As the focus of this review is the aetiology of the non-haemorrhagic components of SVD, space precludes detailed consideration of microbleeds. However, we refer the reader to several excellent recent comprehensive reviews of microbleeds⁵⁹ and cerebral amyloid angiopathy.²⁶

Mechanisms underlying most acute lacunar infarcts, lacunes and WMH

The commonest abnormality described pathologically^{19,27,30,31} is a diffuse, intrinsic disease of the smaller (40-200 μ m diameter) arterioles, referred to by Fisher as arteriolosclerosis, lipohyalinosis or fibrinoid necrosis depending on its severity, which he thought largely to result from hypertension. The vessel wall changes include infiltration of plasma components and inflammatory cells into the vessel wall and perivascular tissue with resulting vessel wall and perivascular brain tissue damage (Figure 5). Many of these features were recognised over 100 years ago.⁶⁰ The mechanisms are largely unknown but this process has been variously attributed to 'microatheroma' (ie diffuse deposition of lipid in arteriolar walls, hence 'lipohyalinosis'), or to be entirely a consequence of hypertension, vasospasm, or more recently to be a consequence of subtle endothelial failure. We will return to consider these mechanisms shortly, but first we will discuss what role, if any, there is for the well established ischaemic stroke mechanisms of embolism, atheroma, and for vascular risk factors, in causing lacunar infarcts and WMH.

Fisher suggested that atherosclerosis and embolism affected the largest perforating arterioles (200-850 μ m diameter).³¹ The size of the lacunar infarct was thought to be related to the size of the affected arteriole and, as the larger lesions were thought to be more likely to cause symptoms, it seemed logical that the symptomatic lacunar infarcts would be due to atherosclerosis or embolism in the larger arterioles and the silent ones would be smaller and due to lipohyalinosis or fibrinoid necrosis in the smaller arterioles. However, as suggested above, that conclusion may have resulted from interpreting a small cavity left after a striatocapsular infarct as the sequelae of a lacunar infarct (Supplementary Figure 2).

Emboli

An acute lacunar infarct can be caused by embolism, but no more than 10-15% of lacunar infarcts and few WMH can be traced to emboli across a range of individual cohort studies and meta-analyses.⁶¹⁻⁶³ In experimental models, very few emboli (<6%) injected into the carotid arteries enter the perforating arterioles.^{21,64} Compared with non-lacunar ischaemic stroke, lacunar stroke is much less likely to be associated with overt embolic sources (atrial

fibrillation or proximal ipsilateral carotid stenosis).^{61,62} Tight internal carotid and intracranial artery stenosis is equally frequent on the contralateral as on the ipsilateral side to an acute lacunar stroke suggesting that the stenosis is unlikely to have caused the infarct.⁶² Similarly, there is little if any direct association between ipsilateral carotid stenosis and WMH.⁶³ The few acute lacunar infarcts that are due to emboli are more likely to be in the basal ganglia, but in all other respects appear similar to acute lacunar infarcts due to intrinsic arteriolar disease.⁶⁵

Atheroma of the parent artery or perforating arteriole

Amongst his 20 detailed clinico-pathological examinations, Fisher described 10 lacunar infarcts in the MCA territory of which six were attributed to atheroma in a perforating arteriole, two to lipohyalinosis and two to embolism (because the arteriole appeared normal and the embolus was assumed to have dissolved).³¹ To put this in perspective, he also described 45/50 lacunar infarcts where the supplying arteriole showed lipohyalinosis or fibrinoid necrosis. Infarct patterns associated with atheromatous MCA stenosis vary between studies, perhaps related to patient selection; many appearing large enough to be striatocapsular rather than true lacunar.⁶⁶ In the Warfarin Aspirin Symptomatic Intracranial Disease (WASID) trial to reduce recurrent stroke in patients with intracranial artery stenosis, only 38/347 (11%) were randomised in the trial following a lacunar stroke the rest being cortical territorial; all recurrent strokes in the 11 patients entering WASID with a lacunar index stroke were non-lacunar.⁶⁷ Thus while MCA stenosis may occasionally lead to lacunar stroke,^{68,69} most strokes (>90%) in patients with intracranial stenosis are non-lacunar.⁶⁷ Intracranial stenosis, although apparently common in some ethnic groups, is very uncommon (<1-2%) in Caucasians⁷⁰ and yet 25% of ischaemic strokes are lacunar in type in Caucasians. A potential association with atheroma has led to the suggestion that there may be two different subtypes of lacunar stroke,^{71,72} those due to proximal perforating arteriolar atheroma and those due to lipohyalinosis/arteriolosclerosis, the former thought to be more likely if the infarct is larger, in the proximal basal ganglia, associated with progressing symptoms,⁷³ a perfusion abnormality on MRI⁷⁴ and poor prognosis, and the latter when there are additional features of SVD (WMH, lacunes, e.g. see Supplementary Figure 1).⁷⁵ Whether or not there are two different subtypes of lacunar stroke, and how reliably they can be differentiated, is at present, unclear. However it may be important to differentiate any due to focal atheroma from non-atheromatous lacunar ischaemic stroke as patients without atheroma may get less long term benefit from anti-atheromatous treatments.^{13,18,76} We found that lacunar infarct size (</>15mm), shape (ovoid/tubular) or location (basal ganglia/centrum semiovale)⁶⁵ did not vary with a range of vascular risk factors (e.g. hypertension, hypercholesterolaemia, diabetes), although basal ganglia lesions more often had any proximal embolic source (e.g. carotid stenosis, atrial fibrillation; 13 vs 4%) than centrum semiovale lesions (although note that the absolute proportion, 13%, is still very low). The perforating arteriolar lumen and atheroma in the perforating arteriole wall are difficult to identify on conventional imaging. High field MR (7T) may identify microatheromatous perforating arteriolar plaques⁴⁵ but the reliability and relevance is yet to be determined.⁷⁷ However, high definition imaging of perforating arterioles to identify mini atheromatous plaques in the proximal perforating arterioles or around the arteriolar ostium, or follow longitudinal changes in arteriolar patency, will be a powerful tool both to diagnose microatheroma where it is likely to be causative in acute lacunar ischaemic stroke and for research into SVD mechanisms.

'Traditional' vascular risk factors

Here, relationships with SVD are still not completely understood. Hypertension, diabetes mellitus, hypercholesterolaemia and smoking are equally common in cortical atherothromboembolic as in lacunar stroke.⁶¹ Many patients with SVD are not hypertensive,

e.g. amongst 70 consecutive autopsies in patients with pathologically-verified SVD, vascular risk factors were mostly absent.⁷⁸ Many sporadic cases and the monogenetic variants of SVD occur in normotensive patients. Hypertension is a key risk factor for WMH⁷⁹⁻⁸³ but the relationship with blood pressure (BP) is complex. Elevated BP some years previously appears to be more strongly associated with WMH in some studies than concurrent BP, although it is unclear whether diastolic^{84,85} or systolic⁸² BP are more important. Both prior and concurrent systolic and diastolic BP predict WMH progression in some⁸¹ but not other⁸⁶ studies. Effective antihypertensive treatment is associated with reduced progression of WMH in observational studies.^{79,80,83} However in randomised controlled trials, antihypertensive treatment has shown limited,⁸⁷ or no¹¹ effectiveness in slowing WMH progression. This may be related to the short intervention period or youngish age range of the included patients. Both white matter tract integrity^{88,89} and WMH burden⁹⁰⁻⁹³ are highly heritable. It is possible that the association between SVD and BP is at the genetic locus level rather than being directly causal.^{94,95} However this finding in a study of SVD-gene associations in families has yet to be replicated. Nonetheless, hypertension is likely to add harm and is at least modifiable. The point is not to devalue the role of BP in SVD, but rather not to overlook other mechanisms. If the apparent WMH-hypertension relationship is partly explained by genetic co-association, then antihypertensive treatment may not be as effective in preventing SVD as is hoped, even if it is very effective in preventing large artery atheromatous disease. On the other hand, risk factors like hypertension and smoking may particularly exacerbate SVD in those with any vulnerability.⁹⁶ Hence prevention of exacerbating risk factors like hypertension and stopping smoking may be particularly effective if SVD vulnerability can be identified.

In terms of other common vascular risk factors, concurrent smoking also appears to be a key risk factor for WMH and their progression,⁹⁷ whereas statins did not prevent WMH progression.¹² Clopidogrel plus aspirin versus aspirin alone caused an excess of haemorrhage (mostly systemic) and death in patients with lacunar stroke,^{13,76} possibly because patients with lacunar as opposed to other ischaemic stroke subtypes lacked any large artery atheromatous disease to prevent (eg myocardial infarction, large artery stroke, etc),¹⁸ further evidence of the largely non-atheromatous nature of SVD. The role of homocysteine, B12 and folate are complex. While homocysteine appears not to be related to large artery atherothrombotic disease (eg myocardial infarction), there may be an association with SVD.⁹⁸ There is some evidence of slowing of WMH progression with B12/Folate supplementation in patients with more severe WMH.⁹⁹ Further data on homocysteine, B12 and folate are needed.

If not ‘traditional’ ischaemic mechanisms, then what?

Some years ago we observed that in the centre of an acute symptomatic lacunar infarct it was sometimes possible to see an abnormal perforating arteriole.¹⁴ The arteriolar wall appeared thickened as it passed through the ‘infarct’ not proximal to it (as one might expect with a typical cortical atherothromboembolic infarct), with signal indicating thrombus in the lumen and blood products in and around the arteriole wall. This led to scrutiny of Fisher’s original descriptions of the microvascular pathology.¹⁰⁰ This suggested that a diffuse process that started in the endothelium and consisted of failure of the cerebral arteriolar and capillary endothelium to function effectively as a barrier, could explain the observed arteriolar wall infiltration, thickening and perivascular tissue changes. The concept emerging from these new observations was that the loss of normal endothelial function would result in leakage of plasma fluid components and migration of cells into the vessel wall with disruption of the normal architecture including damaged arteriolar smooth muscle and fibrin deposition (recognised as lipohyalinosis and fibrinoid necrosis, Figure 5).¹⁰¹ The arteriolar wall changes would be patchy and diffuse and result both in vessel lumen dilation and

narrowing, as described by Fisher, and stiffened vessels with loss of normal autoregulation, as long suspected in SVD.^{102,103} In earlier stages, the perivascular oedema, which is toxic to neurons, glia, astrocytes, in fact all brain cells,^{101,104} would lead to insidious perivascular cumulative tissue damage resulting eventually in the rarefaction and demyelination seen pathologically in WMH on pathology¹⁰⁵ and imaging.¹⁰⁶ It is interesting that the pathological appearance of non-cavitated lacunar lesions (Supplementary Figure 3b) has long been interpreted as infarction even when the arteriole in the centre of the lesion was not occluded and there was little *specific* indication of ischaemia. In capillaries, where there is no smooth muscle layer, the endothelial failure and leakage of plasma components into the tissue would result more directly in oedema and tissue damage. In arterioles, the endothelial disruption, vessel wall thickening and luminal distortion would lead eventually to secondary perforating arteriolar thrombosis, luminal occlusion and traditional 'infarction' (Figure 5). Loss of the normal autoregulatory ability in the thickened, stiffened vessels would contribute further to tissue damage through reduced ability to vasodilate when required, leading to "ischaemic" changes¹⁰⁷ superimposed on the endothelial failure.¹⁰⁸

Proposed role for early endothelial failure

Since then, much more evidence for this hypothesis as a primary precipitant of sporadic SVD has accumulated. At the capillary level, the endothelium forms a key part of the blood-brain barrier (BBB),¹⁰⁹ a phylogenetically important structure for conserving neuronal function present from drosophila to man.¹¹⁰ The BBB is commonly regarded as a nuisance¹¹¹ because, by impeding the passage of many drugs into the brain, it limits potential therapeutic approaches. This, combined with a paucity of methods for studying its activity in vivo, means that our understanding of the role of cerebrovascular endothelium including the BBB in disease pathogenesis is really only in its infancy.¹¹²

The cells of the cerebrovascular endothelium are joined together by tight junctions made up of the occludins and claudins. The BBB is functionally a more complex structure than just the endothelium, encompassing various basement membranes, associated with the perivascular space,¹¹³ pericytes,¹¹⁴ the glia limitans and astrocyte end feet.^{109,115} These components are all inter-related, contribute to the barrier function and are important to consider when trying to understand the aetiopathogenesis of SVD (Figure 6). Autoregulation largely occurs at arteriolar level, but local rapid blood flow responses to neuronal activity also involve capillary responses mediated through pericytes.^{114,116} In this context, it is worth remembering that there are more glia, endothelial cells and pericytes in the brain than there are neurons, the surface area of the cerebrovascular endothelium approximates that of a tennis court and around 20% of the cardiac output at rest is required to service the metabolic demands of the brain.¹¹⁴ It should therefore be no surprise that minor changes occurring over many years could have profound effects on the cerebrovascular endothelium and in turn on brain function.¹¹⁷ In many regards it is more surprising that the impact is not greater.

Two points may help explain how SVD might produce apparently different lesions in different brain and vascular tree locations (Figure 6). First, the endothelial tight junctions are tightest in capillaries where the barrier function is most important, and relatively looser in arteriolar and venular endothelium.¹⁰⁹ The hypothetical consequence is that the effects of endothelial failure would be seen earlier in the larger proximal perforating arterioles than in capillaries, leading for example as seen in some patients, to differential development of proximal arteriolar disease and lacunar infarcts in the basal ganglia in advance of more diffuse WMH in the centrum semiovale where tissue is served by smaller arterioles and capillaries. The second related point concerns how the anatomy of the perivascular spaces differs by location, the basal ganglia perforating arterioles having two leptomeningeal layers

whereas arterioles entering the deep white matter from the superficial cortex having one leptomeningeal layer.^{118,119} Perivascular spaces drain interstitial fluid (Figures 4, 6).¹²⁰ MR imaging demonstrates that basal ganglia and centrum semiovale visible PVS are highly correlated with each other; additionally, basal ganglia PVS are associated with lacunar stroke, while total brain PVS (ie basal ganglia and centrum semiovale combined) are associated with WMH.^{33,54} The regional differences in PVS anatomy could explain this complex association, with SVD pathology leading to visible PVS as well as perforating arteriolar damage and lacunar infarcts mainly in the basal ganglia, whereas multiple WMH tend to form mainly in the centrum semiovale.

Why should the endothelium fail?

As exemplified by the BBB, the cerebrovascular endothelium becomes increasingly permeable with normal ageing.¹²¹ normal subjects aged 70-80 have a near two-fold more permeable BBB compared with younger subjects. Up to age 60, the increase in BBB permeability per decade is probably less marked, suggesting that, as with many ageing-related features, loss of endothelial integrity may start in different people at different ages and progress at different rates, with some evidence of an exponential rather than linear decline in function with advancing age.¹²¹ Any process that aggravates endothelial failure or contributes to damage outside the endothelium may also have progressively worse effects with advancing age.¹²²

In addition to advancing normal age, a range of non-specific stimuli, as yet not well understood, affect the cerebrovascular endothelium.¹¹⁷ For example, in experimental models, non specific peripheral pain, e.g. pain to a foot pad in the rat, opens the BBB.¹²³ Amyloid increases BBB permeability,^{124,125} a possible explanation for the altered BBB permeability detected in AD.¹²¹ Inflammation affects the BBB,¹²⁶ and is a prominent, long-observed although poorly understood component of SVD: inflammatory cell infiltrates were noted pathologically over 110 years ago in the penetrating arterioles and perivascular tissue in SVD,⁶⁰ and consistently ever since (Figure 5, Supplementary Figure 3);¹⁹ plasma inflammatory markers are elevated in lacunar stroke^{56,127} and also associated genetically with WMH progression and lacunar infarcts.¹²⁸ However the cause of the inflammation, whether indicating non-specific responses to peripheral systemic stimuli,¹¹⁷ or systemic inflammation, or brain specific,^{103,109,129} is unknown. High dietary salt intake raises blood pressure and increases stroke risk,¹³⁰ although the salt-stroke association is non-linear and not wholly accounted for by hypertension.¹³¹ High dietary salt exacerbates oxidative stress in salt-sensitive people;¹³² reduced salt intake not only reduced BP but also reduced oxidative stress and vascular stiffness.¹³² Salt affects human vascular function by reducing nitric oxide and impairing vasodilatation.¹³³ In an animal model of spontaneous SVD, even modest short term salt exposure exacerbated inflammation, oxidative stress and small vessel pathology and to a lesser but nonetheless measureable extent in control rats without raising BP.^{134,135} Perivascular spaces drain interstitial fluid from the brain parenchyma¹²⁰ and dilate visibly on MR in overt inflammatory neurological disorders like MS,^{55,136} in SVD (Figure 1),⁵⁶ and associate with increased endothelial permeability in SVD.¹²² Interestingly, WMH appear around PVS on imaging (Figure 4), suggesting focal failure of interstitial fluid drainage¹³⁶ with increased focal brain water,³⁹ or some effect of focal inflammatory cell activity as in multiple sclerosis.⁵⁵ Ischaemia, which might occur secondary to endothelial dysfunction and impaired autoregulation,¹⁰² e.g. in stiffened vessels unable to respond to vasodilatory stimuli during exertion, induces matrix metalloproteinase activity which damages the endothelial tight junction proteins claudins and occludins, and could accelerate endothelial damage.^{137,138} Interstitial fluid drainage along the perivascular spaces may be dependent on 'milking' of fluid by pulsation of the

adjacent arterioles.¹³⁹ The ‘milking’ could become less effective as arterioles stiffen e.g. with SVD.¹³⁹

Changes in BBB permeability also occur in dementia, particularly in vascular dementia versus Alzheimer’s disease or normal age-matched subjects.¹²¹ SVD is the commonest cause of vascular dementia¹⁴⁰ and SVD commonly occurs with Alzheimer’s disease. Most of these meta-analytic data¹²¹ were determined using the CSF/plasma albumin ratio which has limitations. More recently it has been possible to show, using gadolinium contrast-enhanced MR imaging, that the background BBB in white matter remote from any acute infarct is more permeable in patients with lacunar than with large artery cortical stroke (Figure 7),¹²² in WMH than in normal appearing white matter,¹⁴¹ and in WMH in patients with vascular dementia.¹⁴² Interestingly, although the gadolinium signal detected in the brain with these MR techniques is very low, nonetheless it was still possible to demonstrate increasing BBB permeability with increasing age and with increasing numbers of PVS¹²² consistent with the other evidence for associations between advancing age, SVD and PVS described above. In earlier work, where the subject was lying supine in the MR scanner for more than half an hour, we identified an increasing gradient of gadolinium from the frontal to the occipital white matter suggesting some gravity-dependence of BBB permeability¹⁴³ and offering some explanation for the tendency for microbleeds to cluster in the occipital lobes in patients with amyloid angiopathy¹⁴⁴ (amyloid being another cause of increased BBB permeability¹²⁵). In a small longitudinal study, greater BBB permeability soon after non-disabling stroke was associated with dependency at three year follow-up, older age, and having more WMH at initial stroke presentation, suggesting that BBB may predate progression of SVD, but larger studies are required.¹⁴⁵ Diffusion tensor imaging demonstrates that decreasing white matter integrity in normal appearing white matter (notably changes in mean diffusivity indicating altered water content) correlate with increasing WMH.^{38,39}

Evidence for endothelial dysfunction in SVD also comes from CADASIL, a hereditary SVD caused by Notch3 mutations,¹⁴⁶ where extensive WMH were associated with increased brain volume on MRI suggesting an increase of brain water content¹⁴⁷ and CSF/plasma albumin ratios were increased,¹⁴⁸ in keeping with BBB failure. Studies in CADASIL transgenic mice found no evidence for BBB dysfunction,¹⁴⁹ but these mice also develop very little brain parenchymal pathology. In contrast, the most relevant experimental model of sporadic SVD, the spontaneously-hypertensive stroke prone rat (SHRSP),^{21,22,135} has multiple modest endothelial and perivascular tissue defects in early life,²¹ including impaired endothelial tight junctions, poor myelination, overactive microglia, and tendency to glial scarring detectable in protein expression.¹³⁴ The SHRSP shows inflammation (again non-specific) and increased BBB permeability early in life,²¹ predating any rise in BP or development of overt vessel wall or tissue damage.¹⁵⁰ Other models of human SVD using quite different mechanisms such as induction of mild carotid stenosis with external carotid coils¹⁵¹ also show evidence of BBB failure early after induction predating brain damage and consistent with the notion that various stimuli might induce SVD through effects on the cerebrovascular endothelium.

Insights from pathology of SVD

In the study of SVD so far, for reasons outlined above, pathology has had a relatively minor although pivotal role. Patients rarely die in the acute phase; the SVD pathology is often observed at post mortem almost as an incidental finding (Figure 5). Rarely, subacute lesions are observed (Supplemental Figure 3) which, on the basis of size and in the absence of any significant relevant clinical dysfunction in life, are assumed to be asymptomatic lacunes (Supplemental Figure 3a). Imaging correlation is rarely available. The need to develop a

unified approach to the description of vascular pathology for use by research groups has recently been highlighted,²⁴ and a scoring system has been suggested.¹⁵²

Parenchymal changes associated with SVD range from PVS (Figure 4) and areas of relatively subtle white matter rarefaction through to cavitated cystic lesions (Supplemental Figure 3). In general, while tissue pathology changes seen at post mortem are frequently interpreted as “ischaemic”, there are changes that also support the endothelial dysfunction concept. While some, particularly larger lacunar lesions with cystic degeneration may be a consequence of end-stage occlusive SVD, as suggested by Fisher, the pathophysiology of PVS and localised white matter changes is less well understood. PVS have been ascribed to the pulsatile effects of hypertensive arterioles¹⁵³ or changes in interstitial fluid handling,¹¹⁹ amongst others. The latter hypothesis is of particular interest, especially in light of the evolving literature around fluid drainage in the perivascular spaces and development of cerebral amyloid angiopathy.¹³⁶ Perivascular rarefaction is poorly studied. Damaged endothelium, passage of plasma proteins into the vessel wall and vessel wall damage,¹⁵⁴ leakage of fluid,^{78,101} albumin,¹⁰⁸ other plasma proteins, inflammatory cells^{120,155,156} into the perivascular tissue have long been observed (Figure 5). Loss of normal vascular integrity was the only factor associated with increasing WMH score on MRI amongst several potential components examined neuropathologically, including myelin degradation, microglial activation, vascular density and vascular integrity.¹⁵⁵ Additionally BBB was impaired in WMH, and there was increased astrocyte staining with IgG, suggesting BBB failure in deep white matter.¹⁵⁵ These observations support the concept that, while pathological changes seen at post mortem are frequently interpreted as “ischaemic”, based on their histological similarities to thromboembolic infarcts, there are changes that also support the altered BBB permeability concept. Increased endothelial expression of endothelial thrombomodulin is seen in arterioles in SVD, possibly indicating a protective mechanism against local thrombosis due to changes in blood flow secondary to altered arteriolar structure.¹⁵⁷ The presence of hypoxia-inducible factors in WMH at autopsy in elderly patients may be secondary to impaired autoregulation due to SVD, as vessel walls were thickened without luminal reduction; but capillary endothelial and microglial activation were also observed.¹⁰⁷

Other mechanisms suspected from imaging

Falling cerebral blood flow (CBF) has been suggested as a cause of SVD, but why might CBF fall? Earlier, we described the general lack of association between acute lacunar infarcts or WMH and carotid stenosis, suggesting that carotid stenosis is not a *common* mechanical cause in humans. Relatively few studies have measured CBF in SVD: these have produced conflicting results. CBF and blood flow velocities fall with normal ageing. A reduction in CBF was observed using MR imaging methods in patients with more WMH in some,¹⁵⁸ but not other¹⁵⁹ studies; both found associations between CBF and atrophy suggesting that declining CBF might occur secondary to tissue loss, rather than that tissue loss and WMH occur secondary to falling CBF. Increasing age and WMH scores were independently associated with lower MCA flow velocities (on average, a 0.2 cms⁻¹ fall in velocity per year increase in age, p=0.045; a 3.75 cms⁻¹ fall in flow velocity per point increase in WMH score, p=0.004). This suggests that increasing brain tissue loss with advancing age and damage due to increasing WMH result in declining blood flow levels as there is less tissue to supply, rather than the other way round.⁷⁰ Clearly larger longitudinal studies are needed that examine cerebrovascular reactivity and not just resting CBF.¹⁶⁰

Recently, jugular venous reflux was suggested as a further potential mechanism for WMH.¹⁶¹ Jugular venous reflux increases with advancing age as do WMH. Elderly subjects with more WMH had more jugular venous reflux detected on Doppler ultrasound not

accounted for by hypertension, diabetes, hyperlipidaemia or smoking. However other factors that might be associated both with jugular venous reflux and WMH, such as lung disease, were not evaluated. More studies of vascular dynamics and SVD are required.

Current clinical implications

Until we know more, we should continue clinically with careful management of vascular risk factors, particularly hypertension.¹⁴⁰ Multiple combined antiplatelet agents should be used cautiously in patients with pure SVD without other large artery risk factors.¹⁸ We should avoid referring to WMH as 'ischaemic' – why not just call them 'WMH' or 'ageing-related WMH' or 'WMH of presumed vascular origin' until we understand their cause. We should stop considering the individual components of SVD as different disorders until we have better evidence that they are different; having a few lacunes may have similar impact in terms of cognition or stroke or dementia risk as do having some WMH. Stroke should be subtyped as accurately as possible to avoid confounding due to misdiagnosis of lacunar as cortical stroke and vice versa.

Future research

We need standard terminology and definitions for vascular pathology on neuroimaging with standards for image acquisition, analysis, and reporting to facilitate interpretation and meta-analyses. A unified effort to agree on such standards is currently underway.²⁵ We further need more studies matching detailed pathology with individual SVD lesions on MRI, combined with detailed vascular, cognitive, medication and other health-related data in life. We need better ways of assessing subtle endothelial and BBB function in vivo, preferably using imaging, as that allows localisation of affected tissues that can be followed over time. This should include general and specific markers of endothelial function, such as markers of active and passive transport mechanisms and cerebral blood flow at rest and in response to stimuli. The foregoing work in humans is based on changes in non-specific, largely passive, endothelial function detected by intravenous gadolinium contrast agents and MRI (Figure 7): we need better information about how other aspects of endothelial dysfunction might contribute – how failing vasodilatation might contribute to disease pathogenesis and whether this can be modified by specific drug or lifestyle interventions. Research to determine the relative contributions of largely *ischaemic* SVD pathologies (arteriolosclerosis) versus largely *haemorrhagic* SVD pathologies (amyloid angiopathy) are required. Other mechanisms for ageing-related WMH, such as jugular venous reflux or abnormal vascular reactivity, should be tested in replication studies.¹⁶¹ Methods to assess the 'total SVD load' on imaging are required to avoid over-reliance on single features as has been the case in most previous studies. Trials and observational studies should aim to subtype (lacunar) stroke according to underlying mechanism (e.g. intrinsic SVD vs. atheroma) while avoiding risk-factor based definitions.⁶¹ Where possible, MR DWI soon after stroke should be used to identify the acute infarct. We should be cautious not to assume causation between vascular risk factors and SVD until proven by randomised trials. We need more information on the role of homocysteine, B vitamins and inflammation. Most importantly, we need to test interventions that target suspected mechanisms such as ways to improve endothelial function, to prevent the effects of oedema and inflammation on the brain, to prevent increasing endothelial permeability, to manage platelet activity without increasing risks of haemorrhage. The sooner we start thinking of SVD as a disorder of the endothelium together with the surrounding glia, astrocytes, pericytes and last but not least the neurons, the faster we will progress towards effective prevention and treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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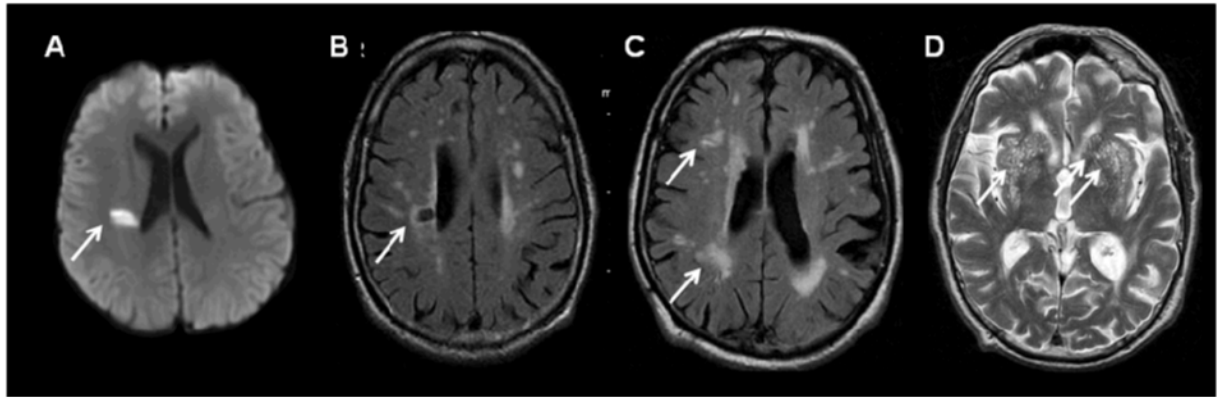


Figure 1.

Key imaging characteristics of features of SVD. A) diffusion-weighted image of an acute small deep ('lacunar') infarct (arrow): <2cm diameter, hyperintense on diffusion imaging, FLAIR and T2-weighted imaging, hypointense on T1-weighted imaging. B) Lacune on FLAIR imaging: a CSF-containing cavity, >3mm and <1.5cm diameter, in white or deep grey matter or brainstem, signal characteristics of CSF on other sequences. C) WMH on FLAIR imaging: hyperintense areas on FLAIR and T2 in white and deep grey matter and brainstem, occasionally hypointense on T1 but often not visible, may coalesce when numerous. D) Perivascular spaces on T2-weighted imaging, hyperintense due to containing CSF-like fluid, <3mm diameter, round or linear in white or deep grey matter, visible on T1-weighted imaging when prominent.

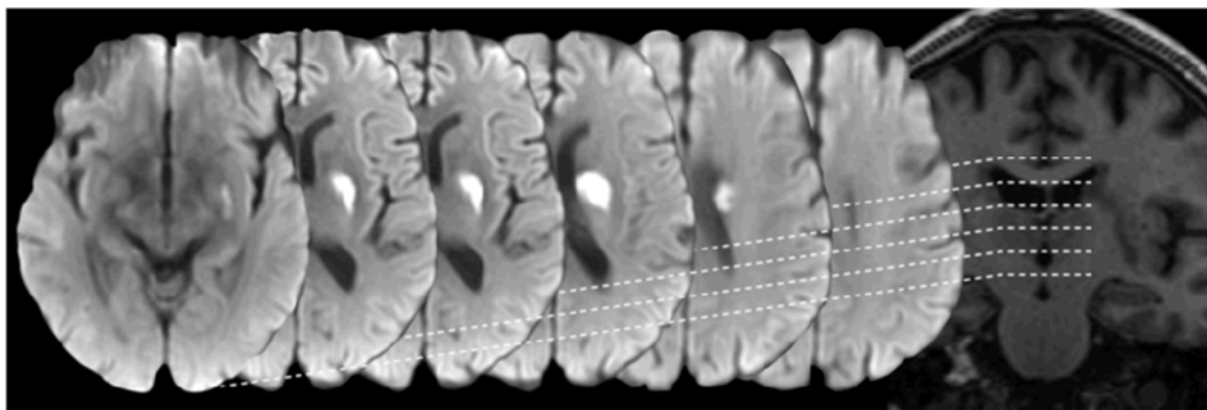


Figure 2.

An acute small deep (lacunar) infarct on diffusion imaging (serial axial views from basal ganglia to centrum semiovale, left to right) and T1-weighted imaging (coronal view, right). Note the tubular shape in the coronal plane as the infarct follows the line of a perforating arteriole. A wider range of examples of acute small deep (lacunar) infarcts is shown in Supplementary Figure 1.

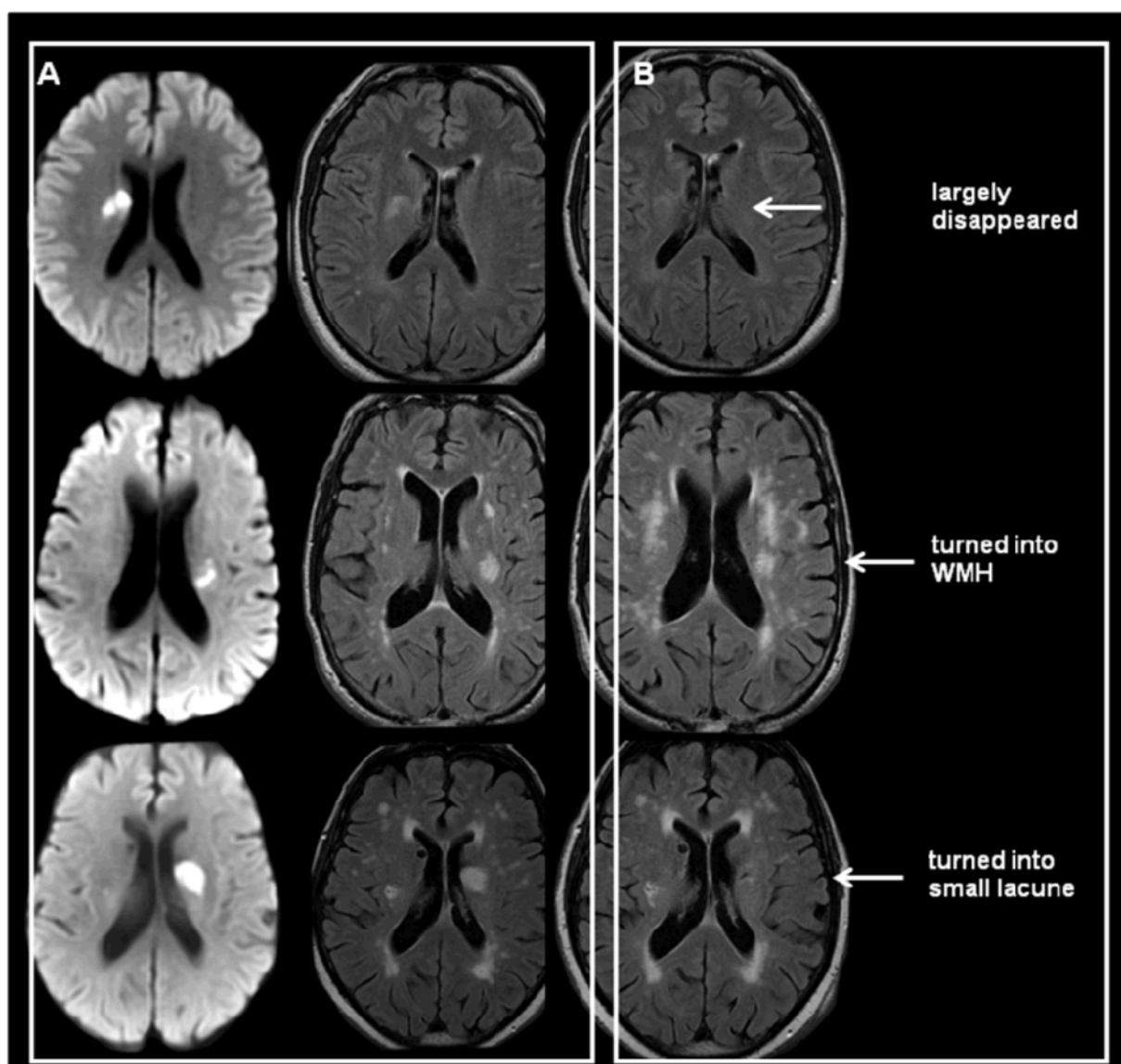


Figure 3. Illustrating common late sequelae of acute small deep (lacunar) infarcts. Acute stage DWI (left column), FLAIR (middle column) and about one year later FLAIR (right column). These can: disappear (top), look like a WMH indefinitely (middle), or cavitate to create a lacune (bottom).

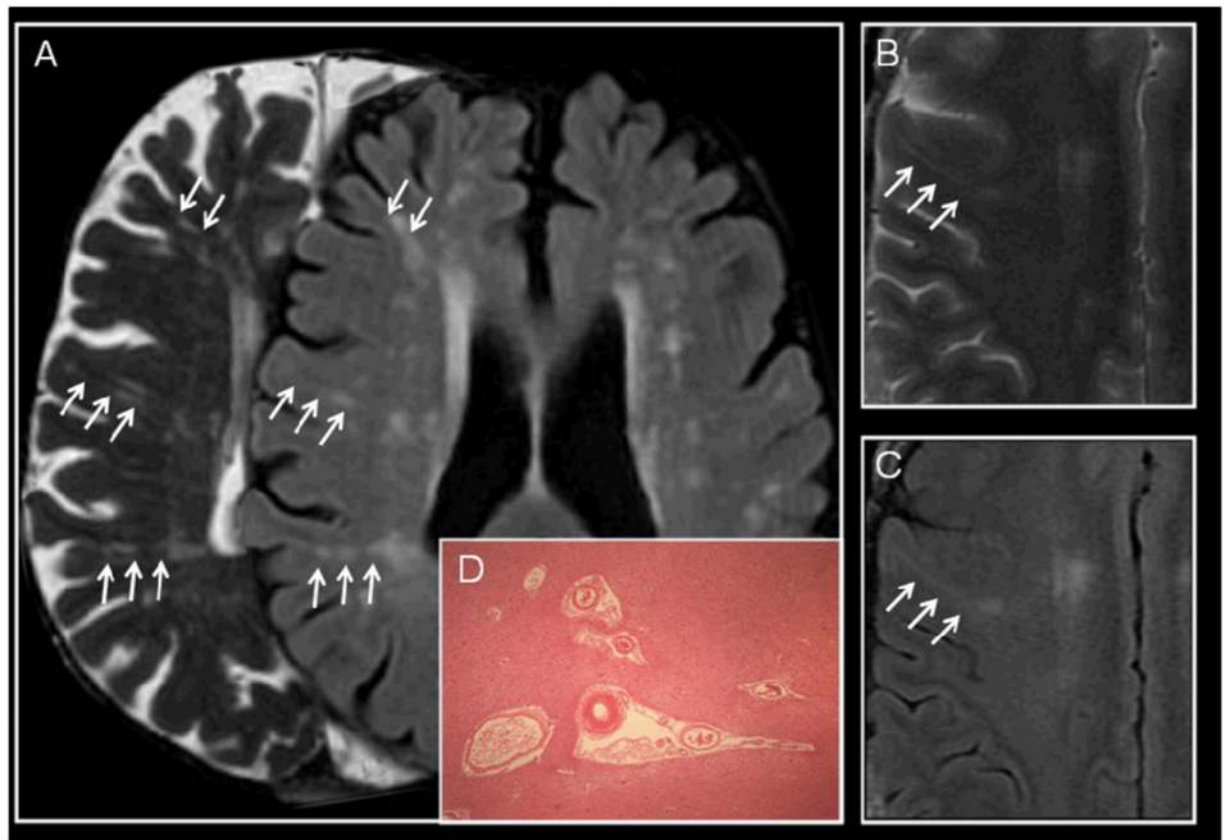


Figure 4.

Examples of perivascular spaces (PVS) on MRI and histology. (a) 72 year old asymptomatic subject, right, T2-weighted image shows linear PVS in the plane of the image, and on left FLAIR shows WMH around the PVS; (b) 49 year old man with left internal capsule acute small deep infarct (not shown) on T2-weighted imaging shows a perivascular space extending from the periventricular to subcortical tissues and (c) on the corresponding FLAIR image, one WMH running longitudinally around the PVS. (d) PVS on histology (H&E x40) showing parenchymal tissue retraction from around small perforating vessels; these have been dismissed as a processing artefact but are typically seen in ageing brain sections, and often associated with SVD.

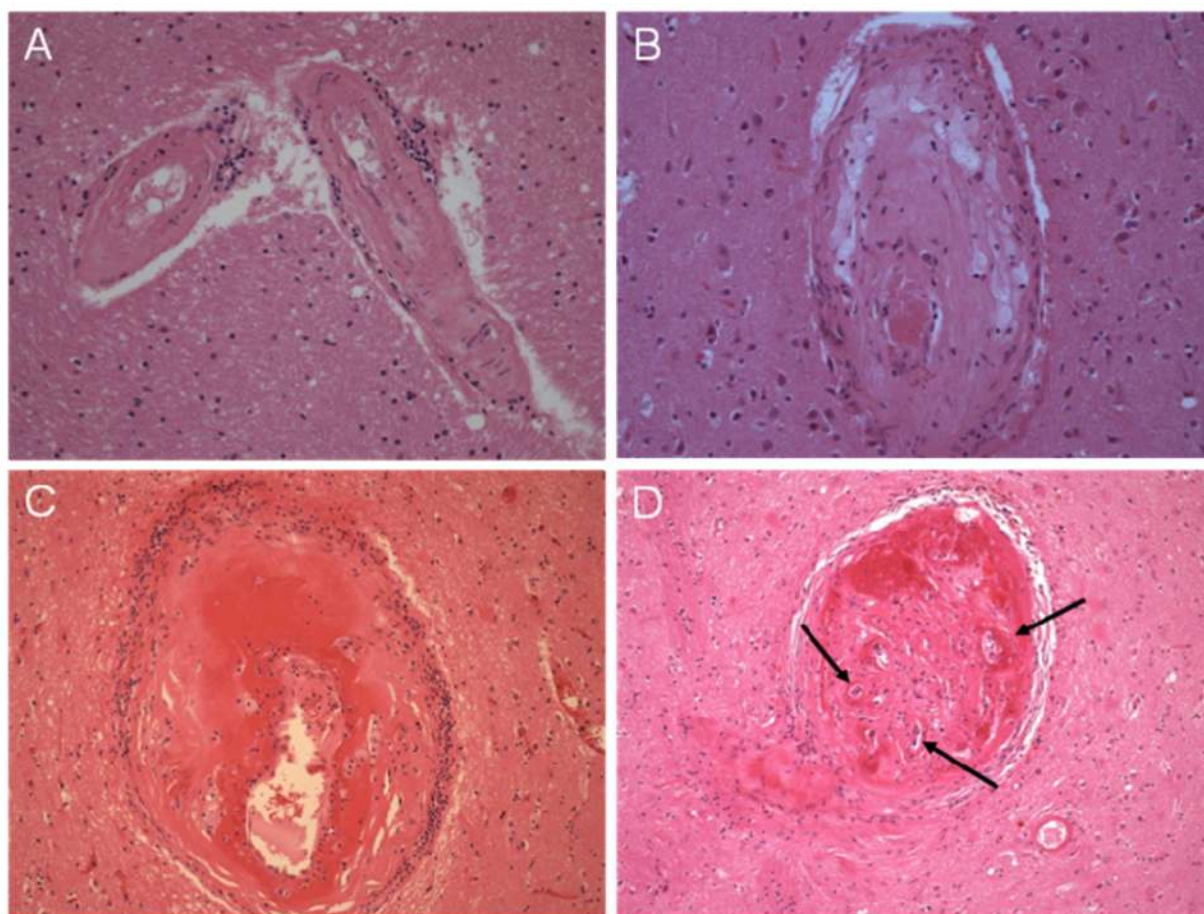


Figure 5.

Histological appearances typical of arterioles affected by SVD pathology, from early arteriolosclerosis through to fibrinoid necrosis (all H&E x200). a) Arterioles where the smooth muscle is being replaced by collagenous tissue and there are small clusters of perivascular inflammatory cells. B) Lipohyalinosis with collagenous thickening of the vessel wall, foamy macrophage deposition and inflammatory cell infiltrate; the residual lumen contains some post mortem thrombus. C) Fibrinoid necrosis with segmental vessel wall destruction and prominent surrounding inflammation; the endothelium is not visible and there is some aneurysmal vessel wall dilatation. d) Severely disrupted arteriole with evidence of previous occlusion and recanalisation, arrows.

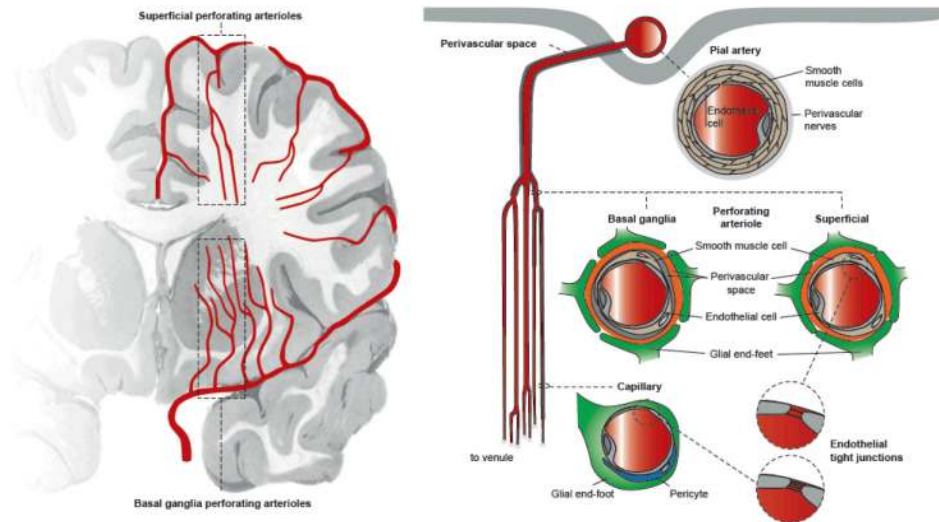


Figure 6.

Schematic diagram of the basal ganglia and superficial perforating arterioles showing key features of the arteriolar and capillary wall. Perforating arterioles show a branching pattern that resembles that of poplar trees rather than oak trees. Arterioles have a smooth muscle layer and are surrounded by perivascular spaces that are delineated by membranes related to pial membranes: there are two layers around basal ganglia arterioles but one layer around superficial perforating arterioles.^{118,119} The capillary endothelium forms the blood-brain barrier and is closely related via pericytes, microglia, astrocytes and glial cells to neurons; the endothelium continues in the arterioles but at the arteriolar level, the endothelial cell tight junctions are less 'tight' than at the capillary level.¹⁰⁹ Hence arteriolar walls are less protected from the consequences of endothelial failure than are capillary walls; tissue around the basal ganglia arterioles is more protected from the effects of vascular disease than is tissue around the superficial perforating arterioles. The figure was prepared by Antonia Weingart, Institute for Stroke and Dementia Research, University of Munich.

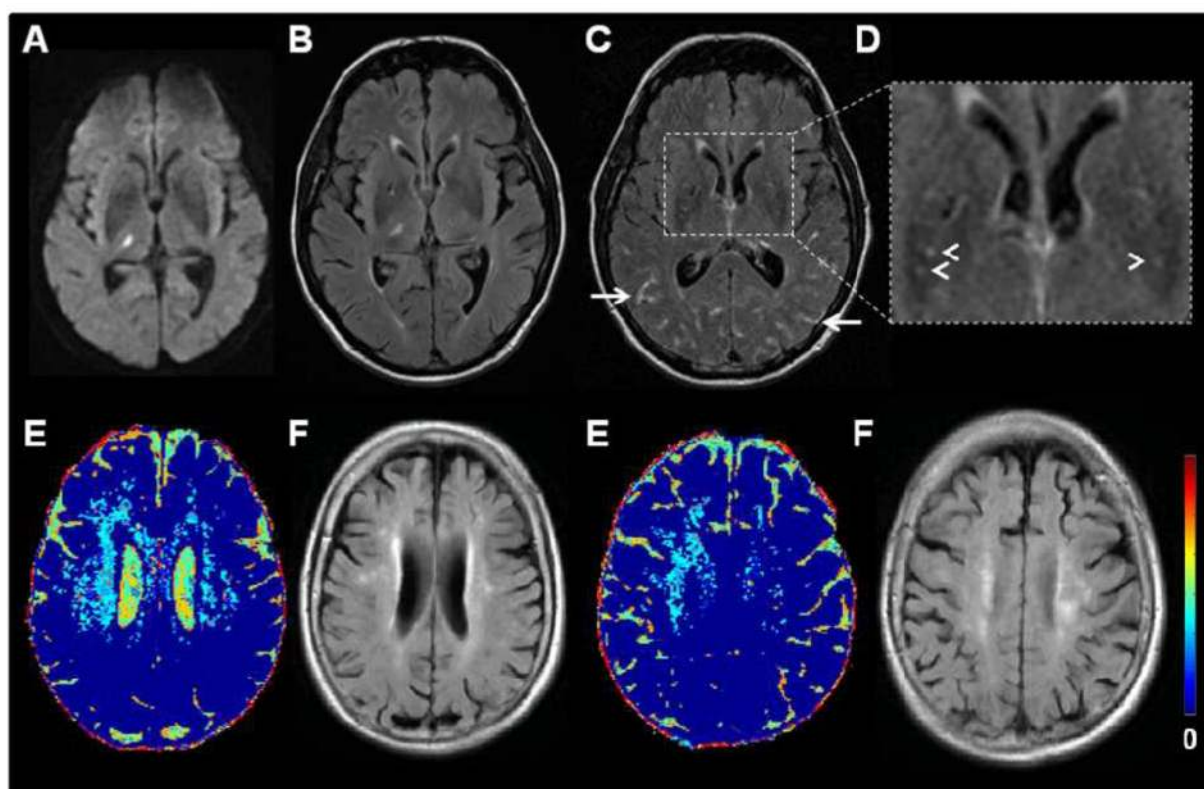


Figure 7.

MR imaging of cerebrovascular endothelial permeability. Top row: 56 year old patient with a right thalamic lacunar infarct: A) DWI, B) FLAIR two days after symptom onset. C) Two months later, FLAIR image after iv. gadolinium (Gd) showing Gd in the perivascular spaces (arrowheads) and sulci (arrows) and (D) inset magnified image of (C). Bottom row: Older patient with left internal capsule lacunar infarct (not shown): E) colour mapping of cerebrovascular permeability following intravenous Gd and F) corresponding FLAIR images showing WMH. Blue indicates low cerebral vascular endothelial permeability, yellow and red indicate increasing permeability. Permeability changes are diffuse. (E) courtesy of Dr Maria Valdes Hernandez.