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Vascular dementia: why pathology is still important

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Summary

Cerebral infarction, as the result of atheroma in large blood vessels, was one of the first explanations for dementia in older people. However, this was a relatively uncommon finding in those presenting with dementia and it was soon realized that subcortical infarctions due to non-atheromatous changes in small blood vessel walls were more important factors in cognitive decline. Furthermore, small vessel disease (SVD) producing lacunar infarcts (LI) and white matter changes increased dementia severity in individuals with only moderate Alzheimer's disease (AD) pathology. Magnetic resonance imaging (MRI) found subcortical (lacunar) 'silent infarcts' and white matter changes were surrogate markers for SVD and increased significantly the likelihood of developing dementia. Detailed histopathological studies of SVD showed it was in fact a range of pathologies, but the aetiology of the most common type (arteriosclerosis/lipohyalinosis) is difficult to explain. Theories to explain SVD include effects of hypertension, a leaky blood–brain barrier (BBB), amyloid accumulation, microbleeds, venous changes and endothelial inflammation. Endothelial expressed inflammatory molecules could represent potential biomarkers of SVD. Many of the risk factors associated with SVD are also present in AD, such as diabetes, systemic hypertension and ageing; all of these can target the endothelium with the potential to initiate SVD, resulting in ischaemic changes and neurodegeneration, including AD pathology.

Key words: dementia, cerebral ischaemia, small vessel, lacunar infarct, leukoaraiosis.

Introduction

Most epidemiological studies of the incidence and prevalence of dementia report that Alzheimer's disease (AD) is the most common dementia, with vascular dementia (VaD) in second place.[1–4] However, prospective pathological-based studies support the view that dementia due to both vascular-based pathology and AD pathology (mixed dementia) is in fact a far more common underlying cause for dementia in elderly people than indicated by the figures based upon epidemiological evidence.[5–14]

Early clinicopathological studies,[15,16] later confirmed by neuroimaging, identified cortical and subcortical infarcts, assumed to be the result of small diameter blood vessel (arteriole) disease (SVD), were important factors in dementia. More recent evidence has shown that large vessel atherosclerosis could also be important in the aetiology of these changes in mainly elderly people.[17–19] Intracranial atherosclerosis (involving large diameter arteries) was regarded as the most likely explanation for multi-infarct dementia[20] and recently intracranial atherosclerosis has been identified as a risk factor for dementia that is independent of cerebral infarction and other risk factors, such as peripheral atherosclerosis, systemic hypertension and age.[18,20–23] Vascular pathology, including SVD, co-existing in the same brain as individuals with only moderate AD pathology, unexpectedly increased the severity of dementia, raising the possibility of a common set of risk factors shared by VaD and AD.[5,25,26] White matter lesions detected by imaging have also been shown to have a strong influence on progression of cognitive decline and are regarded a further surrogate marker of SVD.[27–32]

Despite these detailed clinicopathological studies, there remains a lack of accepted neuropathological criteria to validate clinically identified VaD.[33,34] Similar problems have been encountered in the interpretation of neuroimaging, and the relationship between radiological images and neuropathological findings remain undecided, adding further uncertainty to the efforts to provide an agreed diagnostic criteria (clinical and pathological) to assist with the diagnosis of VaD.[35]

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This review will outline the evidence collected from pathological studies showing that both large and small diameter blood vessels contribute to VaD, not only through focal brain infarction, but as the result of microbleeds, venous changes and also through the endothelium expressing inflammatory cytokines and neurotoxic proteins that cross a damaged blood–brain barrier (BBB) to activate adjacent microglia.[19,36] The emerging concept of injury to the neurovascular unit (endothelium, BBB and neuron) will be discussed with reference to potential biomarkers of SVD pathology in AD and VaD.[37–39] Furthermore, many of the risk factors associated with ischaemic vascular pathology are reversible, making the cerebral circulation an important new target for the treatment and prevention of dementia of both AD and VaD varieties.[40]

Clinicopathological studies rediscover the importance of vascular pathology in dementia

Post-mortem examination of elderly individuals with dementia[41,42] found that a significant proportion of cases were the result of a combination of both AD pathology (neurodegeneration) and arteriosclerosis (ischaemic pathology), hence the probability that multiple pathological processes, rather than a single pathology, were responsible for the cognitive decline.[20]

Hachinski *et al.* did not regard cerebral atherosclerosis as an explanation for mental deterioration in elderly people because it did not produce 'a relentless strangulation of the brain's blood supply' as previously considered.[20] In his opinion, both small and large acute ischaemic cortical infarcts contributed to the entity known as 'multi-infarct dementia'. The majority of cerebral infarcts were due to thromboembolic events originating from extracranial vessels, with a minority due to *in situ* thrombosis of medium/large diameter cerebral vessels. Autopsy studies found that multi-infarct dementia was, however, rare and VaD was not entirely explicable by large vessel atheroma and thromboembolic-related events.[43,44]

The importance of pathologically identified subcortical infarcts for VaD

Autopsy examination of VaD cases (as defined clinically by abrupt onset and stepwise deterioration of cognitive function) found that the vast majority showed multiple infarcts (micro- and macroscopic) with mean loss of brain volume of 39 ml (range 1–229 ml). The location of the infarct(s) with regard to dementia was significant; in those individuals with dementia, 96% had bilateral temporal infarcts and over 80% had subcortical infarcts (basal ganglia, globus pallidus, caudate nucleus).[15]

A more detailed clinicopathological study compared elderly people with VaD (based upon the criteria of insignificant numbers of neurofibrillary tangles (NFT) and neuritic plaques (NP) to satisfy Consortium to Establish Registry for Alzheimer's Disease (CERAD) criteria[45] with those with either no dementia or cerebrovascular disease.[16] The main difference between vascular and non-vascular groups was the frequency of microscopic vascular change, described as SVD. This is not regarded as a single pathological entity in this study, but included cribriform, perivascular, subcortical white matter damage, microinfarction and congophilic material in vessel walls. Ninety per cent of dementia cases had bilateral, multiple, temporal lobe infarcts with subcortical infarction (no infarct diameter dimensions provided). The prevalence of atheroma in the internal carotid arteries and Circle of Willis, and macroscopic infarction in all groups (VaD, non-demented with stroke and control groups) was similar, indicating that large diameter intracranial vessel disease is not necessarily the most important factor producing subcortical infarction and dementia. The emphasis on SVD-associated infarction in subcortical sites as an important underlying cause for VaD was confirmed.[15,16,46]

Interaction between vascular disease and moderate AD pathology results in more severe dementia

The co-existence of subcortical lacunar infarction (LI) and moderate AD pathology results in a more severe dementia than predicted from simple additive effects of ischaemic and neurodegenerative pathology. The Nun study investigated cognitive function in women, with and without AD pathology (based on Khachaturian criteria[47]), in the presence of brain infarction. The prevalence of dementia with subcortical LI (defined as lesions <1.5 mm in diameter) due to SVD was 88%, whereas dementia was present in only

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57% without either lacunes or infarcts.[5] This study concluded that 'a few small infarcts in strategic locations may be sufficient to produce dementia in those individuals made vulnerable by abundant neuropathological lesion of AD in the neocortex'.[5,25] The effect of subcortical LI upon cognition was explained as a disconnection of the already damaged AD neocortex from the subcortical structures by single or multiple subcortical LI. The prevalence of infarction did not increase with severity of AD pathology, and neither lacunes nor large infarcts were associated with APOEε4 status.[5]

The Honolulu-Asia Aging (HAA) Study is a longitudinal, prospective, community study of over 6000 cases with documented cognitive function and 220 autopsies, involving elderly Japanese American men on the island of Oahu. It showed that co-existing vascular-related factors, especially LI (infarcts not exceeding 1 cm), determined the severity of dementia.[6,8,26] Of 68 men with VaD, 50% had small vessel infarcts, 23% had large vessel infarcts and 16% mixed (small and large vessel infarcts).[6] The data showed that vascular lesions increase the likelihood and severity of dementia in men who would otherwise have normal cognition and only moderate AD pathology (CERAD criteria). Similar findings were seen in early clinical AD cases.[11,25,48] The importance of stroke prevention in early stages of AD was therefore confirmed and it was estimated that 24% of cases of dementia in men of Japanese ancestry would be prevented if risk factors such as systemic hypertension were eliminated.[26] The Rush study confirmed the synergistic interaction between subcortical infarcts due to SVD and AD pathology, concluding 'the presence of subcortical infarction implies that subcortical infarcts do not simply add to the deleterious effects of AD pathology (NFT and NP counts), but they somehow lead to a greater than expected cognitive loss'.[48]

A note of caution regarding the significance of subcortical infarcts, SVD and dementia

The clinical significance of SVD and the associated subcortical LIs is not as well established as perhaps implied from the above studies. In the Cardiovascular Health Study, over 20% of individuals (aged over 65 years) had lacunes, of which approximately 90% were clinically silent.[49] Neuropathological studies also found lacunes in 25% of elderly people apparently without evidence of dementia or neurological disability.[14] LI of 1.5 cm in diameter or less, as defined by occlusion or *in situ* SVD of a single deep perforating artery of the middle cerebral artery, cannot be identified radiologically and can only be confirmed at autopsy. Several arterial systems (not all of them end arteries) supply the subcortical structures, so a subcortical infarct cannot be assumed to represent a LI due to SVD unless this is identified microscopically.[19] Furthermore, SVD represents a range of possible pathologies and should not be regarded as a single pathological entity.[16,19] This is discussed in more detail below.

The prospective Baltimore Longitudinal Study of Aging (BLSA) examined 179 brains of 579 participants[18,23] and showed that the number of macroscopic hemispheric infarcts, either obvious or clinically silent, contributed to 35% of the dementia cases in the study. It was the presence of a cerebral infarct and not any associated risk factors, such as coronary artery disease and hypertension, that determined the risk of dementia. The BLSA study found the effect of deep subcortical infarcts on dementia was no longer significant after adjusting for the number of hemispheral infarcts and that the 'presence of hemisphere infarcts remained highly related to the odds of dementia after controlling for number of deep subcortical infarcts'. This evidence does not support the implied major contribution of SVD-related subcortical infarcts to dementia, contradicting the findings of others.[5,16,33,48] Furthermore, another large retrospective study found no association between small vessel arteriosclerosis, plaques and tangles.[50] Conversely, large vessel atherosclerosis was strongly associated with increased frequency of NPs and, by inference, dementia.[51]

The BLSA data also raise the possibility that large diameter vessel intracranial atherosclerosis has a local effect upon the brain to produce dementia that is independent of the presence of cerebral infarction, systemic atherosclerosis (carotid disease) and AD pathology.[18] According to these authors, these data support the view of 'an association between atherosclerosis and cognition that is independent of cerebral infarction'. An explanation for this would be a common mechanism that produces both intracranial atherosclerosis and neurodegeneration (dementia),

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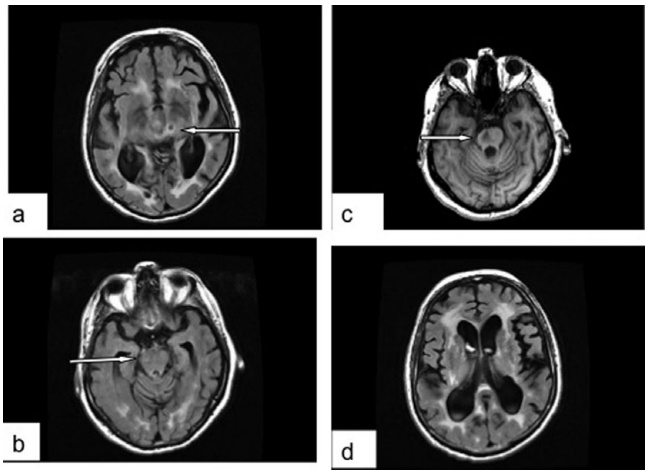


Figure 1. (a) MRI-FLAIR scan image of a lesion (arrow) in the left thalamus corresponding to a lacunar subcortical infarct; (b) MRI-FLAIR scan image of a lacunar infarct in the brainstem (pons); (c) same brain but with T1 weighted MRI scan showing the same lesion in pons (arrow); (d) MRI-FLAIR scan demonstrating perivenular stippling corresponding to Virchoff Robin space dilatation in the thalamus.

such as oxidative stress, disruption of the BBB, or dysfunction of communication between local blood flow and neuron metabolism (neurovascular unit).[38] This conclusion was supported by Roher *et al.*[21] and Beach *et al.*,[22] who proposed that hypoperfusion due to narrowing of large diameter intracranial arteries resulted in a breakdown of brain energy metabolism. However, these findings disagree with the Rotterdam study, where extracranial carotid artery atherosclerosis was positively associated with risk of developing AD and VaD and had an inconsistent relationship with apolipoprotein E genotype.[52,53]

Neuroimaging and SVD

The limitations of neuroimaging for identifying silent (lacunar) infarcts

The variation in scanning techniques and criteria adopted for identifying silent (non-clinically apparent) LI presents problems for estimating their incidence and prevalence, but some general conclusions can be drawn. It should emphasized that MRI cannot detect actual SVD, but detects evidence of surrogate markers of SVD, namely LI and white matter hyperintense lesions (WML).[19] MRI detects more silent infarcts than CT, because LI are only visible on T2-weighted imaging.[31] It is generally accepted that focal lesions greater than 3 mm in diameter on imaging are regarded as LI, whereas autopsy studies generally agree on 1.0–1.5 cm.[54,55] A recent review of MRI studies noted that the distinction between dilated perivascular space and LI is especially difficult when the lesion is less than 3 mm in diameter.[55] To add to the difficulty, a recent MRI study has identified dilated perivascular space as a surrogate marker of brain inflammation and not LI (Figure 1).[56]

Neuroimaging identifies surrogate markers for SVD and their relationship with dementia

The Rotterdam Prospective study, using MRI to initially scan non-demented elderly individuals, found that increasing numbers of so-called silent strokes (subcortical LI > 3 mm) and WML correlated with increasing risk of dementia.[31,54,57]

The prevalence of silent infarcts (8–28% in the general population) is five times greater than clinically obvious stroke and higher in women and in individuals with cardiovascular disease and depression.[31] Silent infarcts also have a five times higher incidence for all age groups than clinically obvious stroke in the same populations.[31,54] The presence of silent infarcts dramatically increases the risk of clinically obvious stroke, especially in those individuals with co-existing WML, providing evidence that SVD is responsible for both silent

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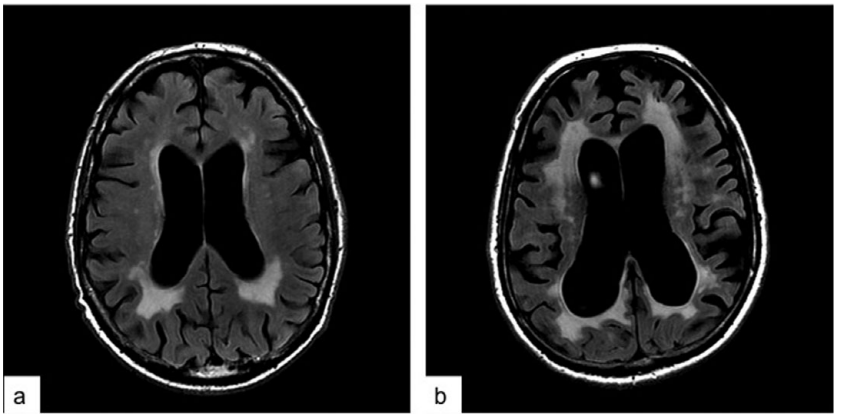


Figure 2. MRI-FLAIR scans showing varying degrees of periventricular leukoaraiosis (LA). In (a) there are moderate periventricular changes of LA, whereas in (b) the extent of periventricular changes is more extensive.

infarcts and WML.[31,58] The risk factors associated with silent infarcts are age, systemic hypertension, retinal microvascular changes, severe white matter changes and a family history of stroke, and these are shared with SVD. Other risk factors, some of which are associated with atheroma formation such as smoking, cholesterol level and surprisingly diabetes, have been found not to be associated consistently with silent infarcts and by inference not to be risk factors for SVD.[31,54]

The Rotterdam study found that the presence of silent infarcts in elderly individuals more than doubles the risk of developing dementia, including AD, and mild cognitive impairment.[31,49] In the same study, the presence of silent infarcts due to SVD reduced information processing and executive memory function.[59] Evidence that SVD is responsible for the majority of silent strokes is also provided by radiological evidence showing that silent infarcts are mainly LI (<3 mm) located in the same subcortical areas (thalamus and putamen)[60] as those assumed to be responsible for dementia in pathological studies.[5,15,16,46] These strategically located subcortical infarcts disturbed urinary retention, motor control and executive function,[61] whereas LIs in the anterior thalamus and putamen inhibited short-term memory.[62]

The mechanism responsible for a silent infarct due to SVD increasing the severity of dementia is not clear. Several possible explanations exist: (1) the accelerated formation of NFT and NP in already 'vulnerable brains',[31] (but this is unlikely in view of Honig *et al.*[51]); (2) white matter damage, especially of periventricular distribution; and (3) a LI resulting in an increased loss of synapses and neurons, even in cases with only moderate numbers of NFT and NP, increasing the severity of dementia.[5,7]

Neuroimaging identified leukoaraiosis in old age and the demented – what does it represent?

The term leukoaraiosis (LA) was a descriptive term, first employed by Hachinski in 1987,[44] to describe diffuse WML in the periventricular or subcortical (centrum semiovale) areas.[63,64] On scans, LA corresponded to poorly defined lesions that were either hypodense on CT or hyperintense ('holes') on T2-weighted or FLAIR (fluid-attenuated inversion recovery) MRI scans (Figure 2); these lesions can be described as white matter hyperintensities (WMH).[32,35] Initially, LA was regarded as of doubtful significance, but with more widespread use of imaging studies it was found to be present in 30–40% of cases of dementia with lacunar strokes and in over 60% of individuals with clinical VaD. The ischaemic aetiology for LA is supported by evidence from the Leukoaraiosis and Disability in the Elderly Study (LADIS),[65,66] showing that age, systemic hypertension, diabetes and lacunar stroke are the major determinants of age-related white matter changes (LA) seen with neuroimaging.[65–68] Neurological features associated with increasing LA load, as for SVD, include bladder control, gait disturbance and information processing, not all of which are necessarily related to cognitive decline.[54] However, as the number of LA lesions from the

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first to subsequent scans increased, so too did the clinical progression to dementia.[59,63,65,66]

The correlation between radiologically identified WML with their pathology and their significance for dementia

As LA lesion size increases, from small punctuate hyperintense lesions to large confluent lesions, they are associated with myelin loss, gliosis and microinfarction, contributing to a decline in cognitive performance. By contrast, the periventricular lesions have a non-ischaemic appearance and are associated with the loss of normal ependymal lining and subependymal gliosis.[27,63,69] In MRI identified areas of brain containing LA, tissue markers of hypoxia are increased in activated microglia, pointing to hypoperfusion as a contributory factor to myelin damage in LA. However, evidence for hypoperfusion as defined by radiological techniques in the same areas is not convincing[70] and as yet any initiating factor triggering hypoxia has not been identified.[71]

The Rotterdam scan study identified that both periventricular and subcortical WML were associated with dementia, but the association was stronger for periventricular changes than for subcortical ones.[59,64,72] The mechanism for this association could be related to the potential ischaemic aetiology of large WML, but the effect of the periventricular lesions was independent of cerebral infarcts and could be the result of interrupting cortico-cortical association fibres. It therefore represents an independent risk for dementia.[30] Neuropathological studies have confirmed MRI identified WML lesions are the result of SVD, including histologically identified arteriosclerosis.[7,73]

The strong correlation between periventricular, and to a lesser extent diffuse WML (both identified by histological staining for myelin) with cognitive decline in individuals with dementia, but no co-existing AD pathology was confirmed by Kovari *et al.*, raising the possibility that periventricular WML identified by MRI is a surrogate marker for non-AD dementia.[30,54,74]

By contrast, the significance of WML (identified by histological staining for myelin) and LIs (that co-existed in 95% of cases) for dementia was investigated prospectively in brains from individuals with no evidence of co-existing macrovascular or AD pathology. The presence of grey matter LIs (1 mm – 1.5 cm) correlated with cognitive decline, but the presence of co-existing WML identified by myelin staining did not correlate with dementia and therefore questions the use of histologically and radiologically identified WML as a surrogate marker for SVD.[75]

White matter vascular changes due to SVD and AD pathology – a possible causal relationship

The Vantaa study found only frontal periventricular and diffuse WML on MRI scan correlated with high Braak stage, raising the possibility of a link between AD pathology in the frontal lobe (NFT formation) and periventricular WML as a consequence of underlying SVD. Large vessel macroscopic infarcts did not correlate with severity of AD pathology in this study, in contrast to several others.[21,23] However, the presence of SVD was proposed as an explanation for both frontal lobe NFT formation and white matter changes because of (1) retrograde axonal degeneration with subsequent NFT formation in frontal lobe neurons and/or (2) neuron loss due to SVD-related ischaemia in the grey matter resulting in anterograde axonal loss in adjacent areas of white matter. On this basis, radiologically detected frontal WMLs are regarded as a surrogate marker of SVD.[76]

Some conclusions?

The evidence for WML influencing cognitive decline is confusing, but the most recent meta-analysis of 46 MRI studies concluded that WML are correlated with increased risk of stroke, dementia, cognitive decline and death.[68] The data from this review were not able to identify the specific vascular basis for white matter disease in stroke and dementia, but suggested that the WML could result from several pathways: (1) disruption of subcortical neural networks, supported by diffusion tensor MRI scan evidence; (2) the same aetiological factors responsible for AD pathology; and (3) the same SVD that is also responsible for LI, reflecting underlying vascular injury.[68]

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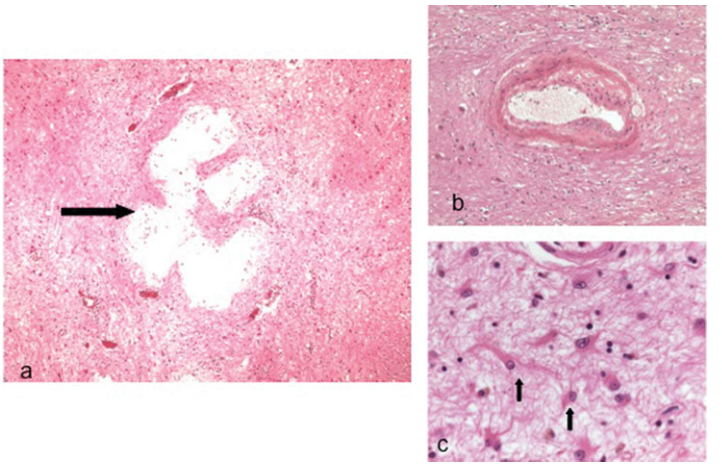


Figure 3. (a), Lacunar infarct (arrow) in the basal ganglia stained with haematoxylin & eosin (H&E). The periphery of the infarct contains macrophages with loss of brain tissue from the centre, forming a so-called lacune. (b), transverse section through a small diameter arteriole in the basal ganglia, stained with H&E with the endothelial, intimal and media layers replaced by pathological changes amounting to arteriosclerosis (note the narrowing of the vessel lumen); (c), the brain surrounding an arteriole with arteriosclerosis contains numerous reactive glial cells (arrows) stained with H&E, some of which are capable of expressing inflammatory cytokines.

SVD – what is the histopathology?

The effects of ageing on cerebral blood vessels

Ageing produces structural changes in small diameter blood vessels, including basal membrane thickening and endothelial changes, both reducing blood flow and preventing efficient transport across the BBB.[77] The change in the density of cerebral capillaries with age has been a controversial topic, but it is now accepted that capillary density is reduced in ageing and AD.[78] Elderly capillaries are unable to respond as efficiently as younger capillaries when exposed to hypoxia, preventing efficient autoregulation of cerebral blood flow. In young animals, tissue hypoxia increases hypoxic inducible factor (HIF), promoting vascular endothelial growth factor (VEGF) expression and endothelial changes. This results in new vessel formation, or angiogenesis, thus restoring blood flow. The HIF-1 response to hypoxia is lost in elderly blood vessels, as is cerebral angiogenesis, preventing new vessel formation after ischaemic conditions.[79,80,81] A combination of age-related changes (capillary density decline) and systemic hypertension prevent normal autoregulation of cerebral blood flow, placing the elderly brain at risk from the effects of hypoperfusion and resulting in ischaemic changes, microbleeds, white matter ischaemia and cognitive decline.[82] Microvascular changes, including endothelial damage, are present in AD, with reduced endothelial CD34 and CD31 demonstrating degeneration of the vessel wall.[82] Accumulation of cerebral arteriole wall β amyloid has also been proposed as a factor preventing efflux of β amyloid from the ageing brain, with neurotoxic consequences.[83]

Vessel pathology, large and small

Atheroma involves the wall of large diameter arteries (e.g. carotid artery, Circle of Willis, coronary arteries) and is responsible for ischaemic infarction through occlusion of the lumen with thrombus formation.[84,85] By contrast, SVD is restricted by definition to small diameter vessels and is associated with pathological and radiological evidence of LIs and white matter changes variously called LA and WML (Figure 3). Whether or not LI and WML are the result of different types of SVD remains to be established.[86]

Arteriosclerosis (thickening), or age-related vascular risk factor type 1, is found in arterioles.[19] This group also includes Fisher's segmental arteriolar disorganization (lipohyalinosis), fibrinoid

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necrosis, microatheroma (plaque-like proteins, plasma cells and macrophages) and microaneurysm formation.[87] The pathology is characterized by age-related loss of smooth muscle cells and replacement by deposits of fibro-lipohyalinosis material producing lumen occlusion and vessel wall thickening, including basement membrane structural changes.[86] Type 1 vessel wall changes have been described in basal ganglia, brainstem (in the same distribution as LIs) and in white matter lesions, but not in cortex.[87]

Cerebral amyloid angiopathy (CAA) type 2[19] involves arteries, veins, arterioles and capillaries (β amyloid in the capillary wall is type 1).[87] This results in vessel wall dilation, disruption and fragmentation, microscopic haemorrhage, haematoma formation and parenchymal damage, as found in AD and β amyloid-related angiitis. CAA does not involve white matter.

Venous collagenosis is a pathological thickening of veins closely located to the lateral ventricles.[19] Thickening of the vessel wall can result in occlusion of the lumen, with a reduction of local venous return increasing the likelihood of WML in periventricular areas.

Atheroma and SVD are different

A systematic review of 25 studies found no difference between risk factors for developing SVD-related LI and non-LI, embolic/atheromanous-related stroke. This included as risk factors high systemic blood pressure and diabetes.[88] One problem with this meta-analysis was the variation in the definition of ischaemic stroke between different studies producing a classification bias. When these data were re-analysed, hypertension and diabetes were found not to be associated with LI and the individual stroke subtypes cannot be distinguished on the basis of these risk factors alone.[88,89]

However, although unable to discriminate SVD from atheroma on the basis of related risk factors, SVD-related LIs are also apparently less likely to be associated with coronary thrombosis, carotid artery atheroma and a previous myocardial infarction than non-LIs due to atheroma.[88] This suggests that SVD pathology does not share the same aetiology as peripheral atheroma and thrombo-embolic disease. In a large prospective study,[89] cerebral non-atheromatous LIs were usually followed by subsequent LIs, rather than atheroma-related ischaemic infarction elsewhere in the brain or heart. This supports the conclusion that SVD and LIs are independent of the disease process responsible for atheroma and thrombus formation.

Causes and consequences of SVD

The lacunar hypothesis and systemic hypertension

Fisher defined clinically significant LIs as 'infarcts caused by occlusion of small penetrating cerebral arteries' (200–800 μm diameter) and he attributed the underlying pathology to narrowing of the lumen of deep perforating arteries. This produced a lacune, more strictly defined as a healing stage of a deep infarct, and these were increasingly found in the brains of hypertensive individuals.[90] The LIs are the basis for radiologically identified subcortical infarcts located in basal ganglia and thalamus, as described in dementia. The pathology of the SVD assumed to be responsible for LIs was initially described as fibrinoid necrosis, lipohyalinosis and miliary aneurysms.[90] The fibrinoid necrosis and lipohyalinosis were regarded as a consequence of hypertension, but a recent study of hypertensive individuals with SVD found these changes are uncommon and the vessel wall pathology is better described by the term hyaline arteriosclerois.[91] In fact, the author recommends that the generic term 'SVD' is a more accurate term, because it does not imply any pathological understanding, but does localize responsibility for LI at the level of the arteriole.

The early explanations for LI involved two possibilities. Embolic occlusion proved to be unlikely because occluded arterioles have been rarely found in autopsy material and emboli would account for only 10–15% of LIs.[89,92,93] Early studies by Fisher proposed hypertension produced either fibrinoid necrosis or vasospasm, which in turn initiated degenerative changes (fibrinoid necrosis lipohyalinosis) in the vessel wall.[92] The Rotterdam silent infarct study provided support for this explanation, identifying hypertension as a risk factor, as did animal models of experimental hypertension.[92,93] However, in humans, typical SVD (hyaline arteriosclerosis) changes were found to be equally prevalent in hypertensive and normotensive non-diabetic brains.[91] This study supports the findings that systemic hypertension

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in the general population is not a risk factor for LI, because it is unlikely to initiate SVD.[88] Furthermore, neither subcortical infarcts due to SVD nor systemic hypertension were identified as risk factors for dementia in the BLSA cohort.[18,23]

The leaky vessel or disrupted BBB hypothesis

An alternative explanation for SVD is that lipohyalinosis and type I arteriole damage are in fact secondary effects, due to injury to the vessel wall endothelial lining resulting in BBB disruption, with leakage into the neuropil of serum proteins.[92] These serum proteins include IgG, coagulation and complement proteins and are capable of activating local microglia in white matter, with secondary small vessel wall changes including perivascular oedema resulting in an 'incomplete' LI (type b).[84,86] Although the leaky hypothesis is plausible, the initiating event(s) provoking prolonged disruption of the endothelium with increasing BBB permeability is not yet known and this could represent a secondary effect following primary local neuron ischaemia. A systemic stimulus, such as oxidative stress, would potentially involve all cerebral arterioles and provide a better explanation for SVD, rather than individual small vessels being occluded by chance embolic events.[92,94,97] This possibility, rather than the effects of systemic hypertension, has been discussed by Dolan *et al*. as an underlying cause for both vascular and AD pathology.[18]

Small vein pathology, white matter lesions and cognitive decline

Periventricular, non-necrotic, white matter hyperintensities (PVH), as detected by MRI scanning, are present adjacent to the ventricle wall and are generally silent. However, if extensive, they can be associated with gait disturbance and cognitive decline.[98] More detailed clinicopathological analysis found that PVH correlated with decline of executive dysfunction as a consequence of interrupting cortico-cortical axons. Pathological analysis of PVH found myelin pallor, astrocytosis and reduced numbers of oligodendroglia due to apoptosis.[98] One explanation for these findings was periventricular intraparenchymal venular disease, due to collagen thickening of vein walls, resulting in stenosis and occlusion considered sufficient to produce vasogenic oedema and eventually chronic hypoperfusion of adjacent periventricular white matter.[98] This is supported by studies showing that glia in post-mortem tissue from MRI-identified PVH regions expressed higher levels of HIF-1a and HIF-2a than in WM controls. This provides evidence that WM tissue hypoxia with activation of microglia, expression of pro-inflammatory cytokines, metalloproteinases and oligodendroglial apoptosis would contribute to the disruption of the BBB.[99,100] The identity of the stimuli initiating venular disease is regarded as ischaemic, but the evidence for localized white matter hypoperfusion is undecided.[70]

Consequences of SVD, microbleeds and cognitive performance

Type 2 vessel wall rupture due to sporadic amyloid deposition results in haemorrhage in the surrounding brain (Figure 4), with an MRI appearance of micro-hyperintense lesions in associated cerebral white matter and micro-infarcts.[19] Approximately 40% of elderly individuals over the age of 80 years will have MRI evidence of microbleeds[101] and there was high association with LA, LIs, systemic hypertension and cognitive decline due to caudate and frontal lobe involvement.[102]

As the result of either acute or chronic ischaemia and vessel wall rupture, serum proteins such as thrombin, a serine protease vital for blood coagulation, will gain access to brain parenchyma.[103] Under physiological conditions, thrombin is synthesized by neurons and astrocytes at low concentrations and this is important for brain repair.[104,105] However, at high concentrations (500 nM) following BBB disruption, thrombin activates microglia via the JAK2-STAT3 signalling pathway, promoting inflammatory cytokine production, myelin damage, apoptosis and axonal injury.[106]

Future prospects and topics for research

Neuropathological criteria – an urgent requirement

At present there is no accepted histological criteria to provide assessment of clinically diagnosed VaD.[34] By analogy with the CERAD, any proposed histological criteria should include small diameter

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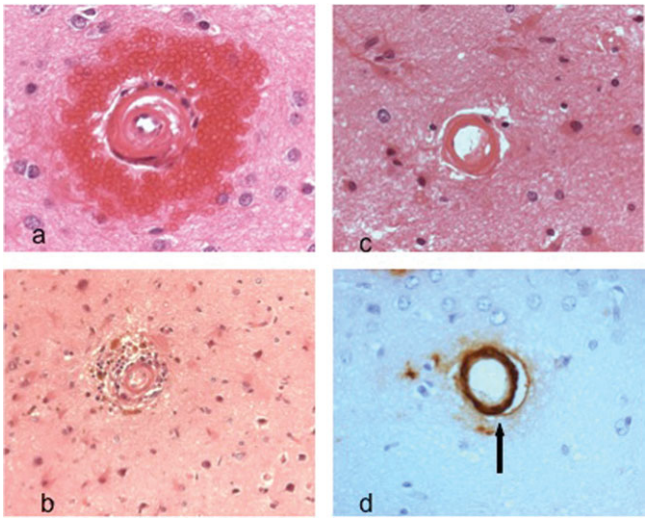


Figure 4. (a), Small diameter arteriole in the basal ganglia surrounded by perivascular haemorrhage – a so-called 'microbleed' stained with H&E; (b), higher magnification shows a small diameter arteriole with vessel wall changes surrounding reactive glia and macrophages containing haemosiderin pigment (iron) originating from the breakdown products of haemoglobin in a perivascular microbleed; (c), cerebral capillary stained with H&E showing a thickened hyalinized wall; (d), the same capillary stained with anti-Aβ4 antibody showing the vessel wall contains Aβ4 amyloid.

vessel wall appearance, white matter changes, infarct localization (subcortical, cortical, thalamic) and take into consideration age, neuroimaging, cognitive status and the presence or absence of risk factors (hypertension, diabetes), in order to provide a qualitative score of possible, probable and definite VaD.

The neurovascular functional unit – a possible explanation for SVD and the co-existence of vascular and amyloid-related dementias?

There is a growing amount of evidence to show that vascular dysfunction is potentially a primary event in both AD and VaD pathology. Neuron metabolism is closely linked with blood flow through cerebral capillaries and the close relationship between neurons and capillaries, as well as the BBB, is regarded as a functional neurovascular unit.[38] Following primary vascular changes due to endothelial injury, initiated by risk factors such as oxidative stress, the capillary endothelium expresses inflammatory cytokines that activate local microglia, disrupt the BBB and inhibit normal neuron metabolism. Oxidative stress is a risk factor for both atheroma and AD pathology and it is possible it has its primary effect upon the cerebral vessel wall, resulting in local neuronal dysfunction, leaky BBB (SVD pathology) and β amyloid deposition (AD pathology), exposure of the brain to potentially neurotoxic systemic proteins and activation of microglia.[107–109]

One serum protease, thrombin, crosses the disrupted BBB and has several potentially neurotoxic effects mediated by thrombin receptor protease activated receptor-1 (PAR-1) distributed on astrocytes and neurons. Thrombin also stimulates the endothelial release of pro-inflammatory cytokines (MCP-1 VEGF), tau aggregation and neuron death, as the result of increasing synthesis of pro-apoptotic proteins triggering NADPH oxidase-mediated oxidative stress and activation of microglia, with release of nitric oxide.[109] *In vitro* thrombin can stimulate amyloid precursor protein production and subsequent cleavage into β amyloid peptides, which in turn increase neurovascular pro-inflammatory cytokine synthesis and endothelial damage.[110] This is summarized in Figure 5.

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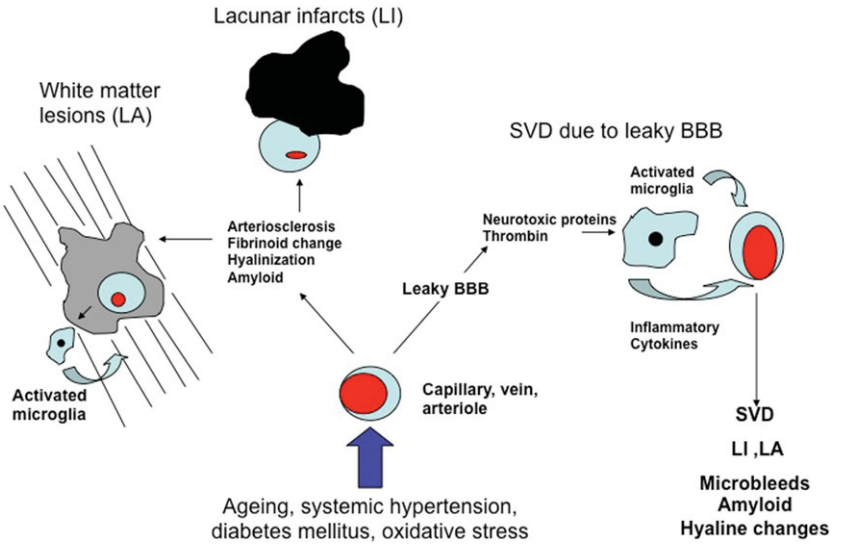


Figure 5. A schematic diagram to summarize the possible pathways producing SVD and associated pathological changes. Various pathological stimuli (systemic hypertension, diabetes mellitus, oxidative stress) combined with ageing produce primary changes in the wall of small calibre cerebral vessels resulting in arteriosclerosis, atheroma, hyalinization, fibrinoid necrosis and amyloid deposition (as documented in SVD). These changes in vessel wall lumen produce white matter pathology (LA) with activation of local microglia; the other main pathology, ischaemic lacunar infarction (LI) found in subcortical sites, is the result of small vessel occlusion. The alternative explanation is that the same initial pathological stimuli, including ageing, produce a 'leaky blood–brain barrier' with systemic neurotoxic proteins entering the brain parenchyma to activate microglia. Microglia express inflammatory cytokines, resulting in secondary pathological changes in small calibre blood vessel walls that amount to SVD.

Endothelial inflammation and potential biomarkers for SVD

Inflammatory molecules synthesized by the endothelium can act as biomarkers of endothelial and BBB dysfunction and provide insight into the evolution of SVD before clinical consequences become apparent.[111] The endothelial cells express a range of proteins present in the serum and associated with coagulation and fibrinolysis, including inter-cellular adhesion molecule 1 (ICAM-1), thrombomodulin (TM), activation of anticoagulant protein C, and tissue factor pathway inhibitor (TFPI). Serum levels of C-reactive protein (CRP), fibrinogen and IL-6 represent biomarkers of tissue inflammation and have been associated with brain infarction and white matter changes.[112] Hassan *et al.* found that serum levels of ICAM-1, TM and TFPI were all elevated in individuals with radiologically detected LIs and LA, supporting the concept of a leaky BBB reflecting endothelial dysfunction.[37] However, a similar study[113] found there was an increase of serum tissue plasminogen activator (tPA) in WML but no difference between LI and non-LI groups for tPa, TFPI or TM, in contrast to Hassan, who found these serum markers increased with severity of LA. TM is also distributed throughout the systemic circulation, so it is unlikely these proteins are suitable specific serum biomarkers for SVD, although they do indicate activation of endothelium in LI.[112,113] More general biomarkers of inflammation, such as CRP and IL-6, have been found to be significantly associated with radiologically detected WML and LIs,[114] as well as cerebral infarcts due to large vessel atherosclerosis.[115]

Therapeutic interventions to target inflammation and coagulation

The role of antihypertensive treatment reducing the risk of dementia as the result of preventing subcortical LI due to SVD is well established. Anti-inflammatory drugs, such as inhibitors of cyclo-oxygenase-2, nitric oxide, tumour necrosis

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factor (TNF) and prostaglandins, have been tried without success in dementia, but this is probably the result of them being administered in the more advanced stages of AD and VaD rather than at the outset.[116] Similarly, anticoagulant agents to prevent the neurotoxic effects of thrombin, TM and TF could be of potential benefit if started sufficiently early. Reliable serum and radiological biomarkers to identify at-risk-of-dementia groups should mean that these drugs can be given at an earlier stage in the evolution of SVD and will have a potentially greater chance of success.

Conclusions

Clinicopathological studies identified small infarcts in subcortical structures and white matter changes were major contributory factors in VaD. This has been confirmed by MRI scanning of individuals with VaD, showing that many have LIs and white matter changes. These radiological lesions are regarded as surrogate markers for SVD, despite disagreement about the radiological criteria with which they are identified.

Although subcortical LIs were easily identified at autopsy, their aetiology was assumed to be the result of hypertension damaging the wall of small calibre arterioles supplying these subcortical structures. Evidence to confirm this explanation has been less than conclusive. Similarly, pathological changes in white matter tracts have been assumed to be the result of ischaemic changes due to arteriole obstruction, but evidence for local hypoperfusion is inconclusive. SVD is not a single pathological process, as it includes arteriosclerosis, amyloid deposition, perivascular space and venous wall thickening, implying that a range of different aetiologies are responsible. The wide range of pathology included in SVD has contributed to the failure to construct a universally agreed scoring system to allow documentation of SVD, making comparisons across different studies difficult and inconclusive. To date the vascular pathology of SVD in AD and VaD is not thought to differ, although this could be a reflection of the failure to adopt a unified classification of SVD, preventing meaningful comparisons.

The favoured explanation for SVD includes primary endothelial injury due to systemic hypertension, metabolic changes and oxidative stress. Injury of capillary wall endothelium will contribute to BBB disruption, with exposure of neurons, capillaries/arterioles and white matter changes due to inflammatory cytokines expressed by activated microglia. Many of the risk factors for SVD are also shared with AD, raising the possibility that AD and VaD share a common aetiology, based upon primary vessel wall changes.

Therapeutic agents designed to reduce endothelial wall inflammation, maintain BBB integrity and inhibit the neurotoxic effects of serum proteins such as thrombin should be developed and prescribed at an early stage to those at high risk of developing VaD, in order to gain maximum benefit. Biomakers of SVD are currently available and, once these have been refined, will allow more accurate identification of 'at-risk groups' to be treated prophylactically, before clinical signs and radiological markers of VaD become apparent.

Perhaps it is now an opportune time to accept that the majority of dementias result from different proportions of both neurodegeneration and ischaemia, because these two apparently different pathologies share many common underlying and reversible vascular-related aetiologies.

Conflicts of interest

The author declared no conflicts of interest

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