Small vessel disease: mechanisms and clinical implications

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Small vessel disease is a disorder of cerebral microvessels that causes white matter hyperintensities and several other common abnormalities (eg, recent small subcortical infarcts and lacunes) seen on brain imaging. Despite being a common cause of stroke and vascular dementia, the underlying pathogenesis is poorly understood. Research in humans has identified several manifestations of cerebral microvessel endothelial dysfunction including blood–brain barrier dysfunction, impaired vasodilation, vessel stiffening, dysfunctional blood flow and interstitial fluid drainage, white matter rarefaction, ischaemia, inflammation, myelin damage, and secondary neurodegeneration. These brain abnormalities are more dynamic and widespread than previously thought. Relationships between lesions and symptoms are highly variable but poorly understood. Major challenges are the determination of which vascular dysfunctions are most important in pathogenesis, which abnormalities are reversible, and why lesion progression and symptomatology are so variable. This knowledge will help to identify potential targets for intervention and improve risk prediction for individuals with small vessel disease.

Introduction

Small vessel disease is a disorder of the brain's small perforating arterioles, capillaries, and probably venules[1] that causes various lesions that are seen on pathological examination or brain imaging with MRI or CT. Typical small vessel disease lesions are white matter hyperintensities of presumed vascular origin, lacunes, microbleeds, superficial siderosis, perivascular spaces, and microinfarcts (panel).[2,3] These lesions might be clinically silent individually, and many affected people do not have symptoms, but increasing numbers of individual lesion types and combinations of lesion types are associated with cognitive impairment, dementia, depression, mobility problems, increased risk of stroke,[4] and worse outcome after stroke.[5] Other typical small vessel disease lesions are recent small subcortical (or lacunar) infarcts and intracerebral haemorrhage, which typically present with stroke.[2] These varied clinical presentations have usually been considered separately in research and in the clinic, and patients have been referred to separate stroke, cognition, or mobility clinics. However, small vessel disease causes about a quarter of ischaemic strokes and most haemorrhagic strokes, is the commonest cause of vascular dementia, often occurs with Alzheimer's disease, and worsens the resulting cognitive impairment,[6,7] thus contributing to about 50% of dementias worldwide, a massive health burden of stroke and dementia.[4,7]

Small vessel disease-related brain damage is not confined to the visible lesions. More sensitive MRI methods show that pathological changes occur in the so-called normal appearing white matter and grey matter, which worsen as the small vessel disease lesions increase,[8,9] and that white matter fibres passing through visible lesions can die back, leading to secondary degeneration in distant cortex or the brain stem and resulting in global brain effects.[8–10] Some MRI methods are exquisitely sensitive to small changes in fluid content, and studies[8,11] suggest that white matter hyperintensities, at least partly or in their early stages, represent areas of increased interstitial fluid, not just demyelination.

Small vessel disease is recognised as being increasingly diverse, including rare familial and common sporadic (ie, non-familial) forms, with apparently different subtypes, even among sporadic forms. For example, cerebral amyloid angiopathy with microbleeds and superficial siderosis has different pathology to predominantly non-haemorrhagic small vessel diseases.[12]

In this Review, we discuss sporadic (ie, non-familial) small vessel disease, the commonest clinically recognised form, focusing on causes and implications of white matter hyperintensities, lacunes, recent small subcortical infarcts, and subvisible findings. Microinfarcts and haemorrhagic small vessel diseases (cerebral amyloid angiopathy, microbleeds, and superficial siderosis) have been reviewed elsewhere.[3,12,13] We review the evidence that sporadic small vessel disease starts in the endothelium, and discuss how it causes focal lesions that are more dynamic than traditionally thought, and how it affects the whole brain. We consider potential explanations for the different clinical effects of small vessel disease and highlight potential therapeutic targets and interventions.

Small vessel disease as a dynamic, whole-brain disorder

Pathology studies of small vessel disease mechanisms describe abnormalities in arterioles, such as arteriolosclerosis, lipohyalinosis, or fibrinoid necrosis,[1,12,14] and risk factors, particularly hypertension.[1] In arteriolosclerosis and fibrinoid necrosis, the arteriolar wall is thickened and the lumen can be narrowed, occluded, or dilated. Capillaries and venules can also be abnormal and arteriolar abnormalities and small vessel disease lesions can occur in individuals without hypertension.[12] These findings suggest that the pathogenesis of small vessel disease is more complex than simply that arteriolar occlusion leads to infarcts. Although the presence of arteriolosclerosis and fibrinoid necrosis are signs of vessel dysfunction that probably accelerate tissue damage, there is some debate on what initiates microvascular abnormalities and on how dysfunction of the arteriolar or capillary wall causes brain damage. The arteriolar endothelium continues into the

capillary and the brain injury seen in small vessel disease is not just periarteriolar.[12,13] Hence, to better understand the pathogenesis of small vessel disease at the earliest stages, it is important also to consider how capillary endothelial cells and pericytes interact with astrocytes, oligodendrocytes, and microglia, which together form the neuro-glio-vascular unit. Improved understanding of small vessel disease mechanisms is essential to find ways to prevent damage to the brain, to delay worsening or even reverse the damage, or enhance repair to prevent or delay the damaging clinical consequences of the disease.

Blood–brain barrier

Starting at the cellular level, the vascular endothelium, together with a specialised basement membrane, pericytes, and astrocyte end-feet, forms the blood–brain barrier (figure 1). The vascular endothelium also affects brain oxygenation, metabolite transport, and interstitial fluid balance through effects on cerebral blood flow, active and passive transporters, and fluid clearance, most of which depend on interactions between endothelial cells, pericytes, astrocytes, and oligodendroglial cells.[15]

Oligodendrocytes form myelin, which accelerates axonal signal conduction, are highly interconnected, and support axons by supplying energy. Oligodendrocytes arise from oligodendrocyte precursor cells, and are replaced through maturation of these precursors when injured. In a rodent model of sporadic small vessel disease and on histopathology of human white matter hyperintensities, dysfunctional endothelial cells were shown to block oligodendrocyte precursor cell maturation, thereby impairing myelination and myelin repair.[16] In cathepsin A-related arteriopathy with strokes and leukoencephalopathy, a rare familial small vessel disease, endothelial dysfunction also blocked oligodendrocyte precursor cell maturation.[17] Thus, evidence from both sporadic and monogenic small vessel disease suggests that dysfunctional endothelial cells can hamper myelin formation and repair in addition to causing direct damage to myelin from microvessel dysfunction.

Astrocytes connect neurons with capillaries, with astrocyte end-feet wrapping around the outside of the endothelial cells at one end and their processes abutting dendrites at the other end. Upon neuronal activity, astrocytes signal to the endothelial cells to increase local blood flow and secure energy supply (figure 1).[15,18] Astrocyte end-feet have special water channel proteins called aquaporin-4 that normally face the capillary. Aquaporin-4 molecules are thought to be important in regulating fluid flow through the interstitial space, thereby helping to maintain the interstitial milieu required for proper neuronal function. In areas of damage, aquaporin-4 molecules might relocate to the outer side of the astrocyte end-foot, as seen in human white matter hyperintensities.[18]

At the tissue level, dysfunction of the blood–brain barrier might have several adverse effects: the leakage of fluids, proteins, and other plasma constituents into the perivascular tissues might increase interstitial fluid (oedema) and thicken and stiffen arteriole walls, impairing further vasodilatation, oxygen, and nutrient transport. Blood constituents might be harmful in multiple ways—eg, after crossing the blood–brain barrier, fibrinogen is cleaved to fibrin, which activates microglia and recruits peripheral macrophages, promoting inflammation.[19] Fibrinogen blocks oligodendrocyte precursor cell maturation (inhibiting myelin maintenance and repair). It further binds amyloid-β, blocking its clearance and promoting formation of amyloid-β plaques and pericyte loss.[19] Perivascular fibrin deposits are increased in patients with Alzheimer's disease, providing a potential mechanistic link between small vessel disease and Alzheimer's disease pathology.[19]

Subtle blood–brain barrier dysfunction occurs with normal ageing,[1] but might be accelerated by genetic predisposition. For example, genes expressed in brain vascular endothelial cells and pericytes, such as *Foxf2*, have been linked to sporadic small vessel stroke and

***Panel:* Definitions of terminology used in small vessel diseases**

Small vessel disease

Neuroimaging and neuropathological abnormalities in the cerebral white and deep grey matter that are thought to arise from abnormalities in the microscopic perforating cerebral arterioles, capillaries, and venules. Many affected individuals do not have symptoms, but the brain damage can lead to stroke (25% of ischaemic and most haemorrhagic strokes), cognitive decline or dementia (the commonest cause of vascular dementia and common in mixed dementias), gait and balance problems, and mood disorders in older people. Most small vessel disease is sporadic, perhaps related to hypertension or other vascular risk factors, but a small proportion is due to rare genetic variants, of which the commonest is cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

White matter hyperintensities, lacunes, microbleeds, perivascular spaces, and recent small subcortical infarcts

Common types of small vessel lesions seen on neuroimaging or neuropathology where the brain is most damaged. Many lesions gradually worsen, although some lesions might improve for unknown reasons. Normal appearing brain is often identified as abnormal if assessed with sensitive imaging methods, especially as the number of lesions increases and in the tissue around the visible lesions.

Endothelial dysfunction

When the layer of cells that line the blood vessels in the brain are not functioning properly, which manifests in several ways. The cells lining the capillaries should regulate transport of fluid, nutrients, and waste in and out of the brain, but they become leaky, leading to perivascular tissue and arteriolar wall damage. The arterioles lose the ability to contract and dilate to match blood supply to demand in the brain. The vessels stiffen so that the pulsatility of the pulse wave increases, diminishing the flow of fluid in the perivascular spaces, which is thought to affect interstitial fluid flushing.

Neurogliovascular unit

The way in which the common types of vascular and brain cells (endothelial cells, pericytes, astrocytes, oligodendrocytes, and neurons) are organised and linked together into millions of functional units in the brain. In these groupings, the cells interact to regulate entry of fluid and nutrients into the interstitium, manage blood supply, maintain and repair myelin, clear fluid and waste, and maintain the interstitial milieu for proper cell function.

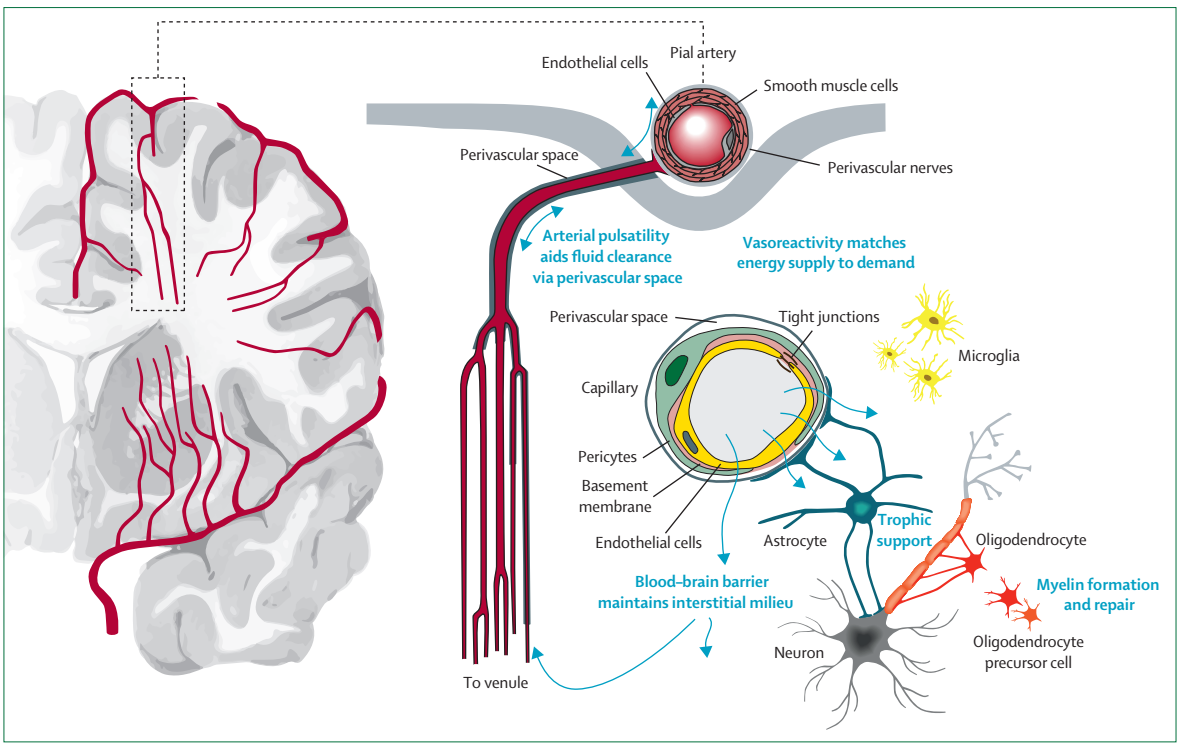

Figure 1: **Key constituents of the vascular-glio-neuronal unit and possible entry points for disease mechanisms in cerebral small vessel disease**
Arterioles penetrate the brain and branch into capillaries. They are each surrounded by a perivascular space that is connected to the CSF. Capillary endothelial cells, including their connecting tight junctions, a specialised basement membrane, pericytes, and astrocyte end-feet collectively form the blood–brain barrier. The blood–brain barrier is essential for maintaining the interstitial milieu. Astrocytes maintain the interstitial fluid balance, provide energy to neurons, and relay signals between neurons and other cells to the vasculature to adapt blood flow to energy demand. Oligodendrocytes form and repair myelin around axons to which they also provide metabolic and trophic support. At the cellular level, endothelial cell dysfunction and blood–brain barrier dysfunction increase interstitial fluid and proteins, disrupt astrocyte end-feet, which impairs interstitial fluid exchange, block oligodendrocyte precursor cell maturation, which impairs myelination and repair and energy support to axons, and impede normal astrocyte function, decreasing neuronal energy supply. The order of these events is not yet determined. Several of the cellular and functional constituents of the vasculo-glio-neuronal unit (ie, endothelial cells, pericytes, astrocytes, oligodendrocytes, neurons, and the extracellular matrix) represent possible entry points for disease mechanisms in small vessel disease.

white matter hyperintensities.[20] *Notch3X*^{R169C} transgenic mice modelling of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), the commonest type of familial small vessel disease, show changes in key blood–brain barrier constituents (pericytes, astrocytic end-feet, and extracellular matrix).[21] Blood–brain barrier dysfunction is worse in patients with vascular dementia and Alzheimer's disease.[22] Many clinical studies show blood–brain barrier dysfunction in small vessel disease in patients with stroke,[23,24] cognitive disorders,[25–27] or small vessel disease features on imaging[26,28] using biochemical (CSF or blood),[22] neuroimaging, or neuropathology methods.[12] Blood–brain barrier dysfunction increases with increasing white matter hyperintensity burden.[8,27–29] Blood–brain barrier leakage is apparent in normal appearing white matter of patients with small vessel disease,[8,25] and worsens with proximity to the white matter hyperintensity,[28] a predilection site for future white matter hyperintensity expansion[30,31] and incident lacunes.[32] In one MRI study,[25] blood–brain barrier dysfunction was worse in the perilesional normal appearing white matter than in white matter hyperintensity, although other studies have found the opposite.[28] Blood–brain barrier dysfunction was not found in some neuropathology studies,[33] which might reflect the fluctuating or focal nature of defects or difficulty identifying subtle changes. Consistent with blood–brain barrier dysfunction, interstitial fluid content increases in white matter hyperintensities and in normal appearing white matter as white matter hyperintensity burden increases,[11,28] and is highest in white matter hyperintensities, followed by perilesional normal appearing white matter, then more distant tissue.[8,11] Further indirect evidence for a causative role of blood–brain barrier dysfunction in small vessel disease comes from studies in patients presenting with acute lacunar stroke symptoms,[28] or in CADASIL,[34] in whom interstitial fluid and brain volume were higher at presentation with stroke symptoms compared with when these had declined several months later, changes that were paralleled by reductions in white matter hyperintensity,[35] suggesting that the decrease in white matter hyperintensity and brain volume was not atrophy from cell loss but clearance of excess interstitial fluid. Three studies[23,25,28] found that long-term outcomes were

associated with blood–brain barrier disruption at initial assessment. For example, blood–brain barrier dysfunction in normal appearing white matter predicted poor functional outcome 3 years later,[23] blood–brain barrier dysfunction in normal appearing white matter predicted cognitive decline 1 year after lacunar stroke,[28] and some areas of normal appearing white matter with abnormal blood–brain barrier permeability at baseline developed new white matter hyperintensities on follow-up scans 1 year later.[25]

Cerebral blood flow

Compromised cerebral blood flow is another manifestation of endothelial dysfunction, but the relationship between cerebral blood flow and the formation of small vessel disease lesions is complex. For example, in a meta-analysis of 38 studies (n=4006),[36] patients who had white matter hyperintensities had lower resting cerebral blood flow than patients who did not in cross-sectional studies, but this association disappears with age-matching and exclusion of patients with dementia, reflecting that impaired cerebral blood flow occurs early in patients with Alzheimer's disease.[37] However, three of five large (n>400) longitudinal studies showed that high white matter hyperintensity burden predicts falling cerebral blood flow, not vice versa,[36,38] although cerebral blood flow was reduced in normal-appearing tissue that became abnormal at follow-up in one study.[30] Whole-brain or tissue-resting cerebral blood flow is not very informative in determining lesion-relevant perfusion, because resting cerebral blood flow varies widely from minute to minute and between brain regions and is lower in white than in grey matter.[30] Furthermore, reduced resting cerebral blood flow might reflect loss of viable tissue, rather than reduced cerebral blood flow causing tissue damage. A mismatch between capillary flow and oxygen delivery, referred to as capillary transit time heterogeneity, has been observed in rodent models of small vessel disease and might occur in and around white matter hyperintensities.[39] The mechanism for increased cerebral blood flow heterogeneity might reflect a dysfunction to direct blood flow to exactly where it is needed or, as suggested by the authors, to shunting, but the mechanism remains to be determined.

Resting cerebral blood flow is not a good indicator of oxygen extraction or of the ability to match tissue supply to demand.[39] A better indication of the adequacy of tissue-level cerebral blood flow in patients with small vessel disease might be cerebrovascular reactivity, which is the ability of arterioles and capillaries to dilate in response to increased neuronal activity or a metabolic or vasodilatory challenge, such as breathing 6% carbon dioxide in inspired air.[40] For example, patients with CADASIL had relatively normal resting cerebral blood flow but impaired local increase in cortical cerebral blood flow in response to neuronal activity.[41] However, assessment of subcortical tissue-based cerebrovascular reactivity in patients is challenging and, hence, data are scarce.[42] Cross-sectional studies of community-dwelling older (≥65 years of age) participants, people with white matter hyperintensities, and people with minor stroke[41–44] show that cerebrovascular reactivity declines with increasing age, hypertension, in lacunar versus non-lacunar stroke, and with increasing white matter hyperintensity burden. Longitudinally, reduced cerebrovascular reactivity might predict progression from normal appearing white matter to white matter hyperintensities.[43] Cerebrovascular reactivity declined in deep grey and white matter with increased systolic blood pressure, pulse pressure, and intracranial vascular pulsatility,[45] but reduced cerebrovascular reactivity was not associated with resting cerebral blood flow,[44] similar to the dissociation of cerebrovascular reactivity from cerebral blood flow seen in patients with CADASIL.[41] Patients with minor stroke with more white matter hyperintensities had lower cerebrovascular reactivity in white matter and higher intracranial vascular pulsatility,[45] independent of age or blood pressure, suggesting that impaired cerebrovascular reactivity and high intracranial vascular pulsatility might be more strongly linked to formation of white matter hyperintensities than reduced resting cerebral blood flow. However, the relationship between the different components of endothelial dysfunction (blood–brain barrier dysfunction, cerebrovascular reactivity, intracranial pulsatility, and cerebral blood flow), and the order in which they occur, is unknown. Studies measuring all these parameters simultaneously are ongoing (eg, ISRCTN10514229) and should provide answers soon.

Perivascular spaces

Fluid and compounds that enter the brain, and the waste generated, must be removed to maintain normal brain function. The main drainage conduits are the perivascular, or paravascular, spaces which surround brain microvessels (figure 1)[46] and form part of the glymphatic system.[18] In rodents, glymphatic dynamic function shown with optical imaging through cranial windows or MRI with intrathecal gadolinium showed that CSF from the basal cisterns and cerebral convexities enters the periarteriolar perivascular spaces to flush the interstitial space.[18] In humans, perivascular spaces are visible on T2-weighted and T1-weighted MRI as thin linear or round CSF-intensity structures that run parallel with perforating vessels[2] shown to be arterioles on 7T MRI.[47] Because of the limitations of past MRI technology, fewer studies of perivascular spaces than of the other small vessel disease features have been done; consequently perivascular spaces are not yet universally accepted as a small vessel disease marker.[4] However, perivascular spaces as seen on MRI are associated with several small vessel disease-related factors—hypertension,[48] circulating inflammatory markers, and cognitive decline (reviewed elsewhere[46])—that (like several other small vessel disease lesions) are highly heritable.[49] Furthermore, perivascular space visibility increased with increasing white matter hyperintensities,

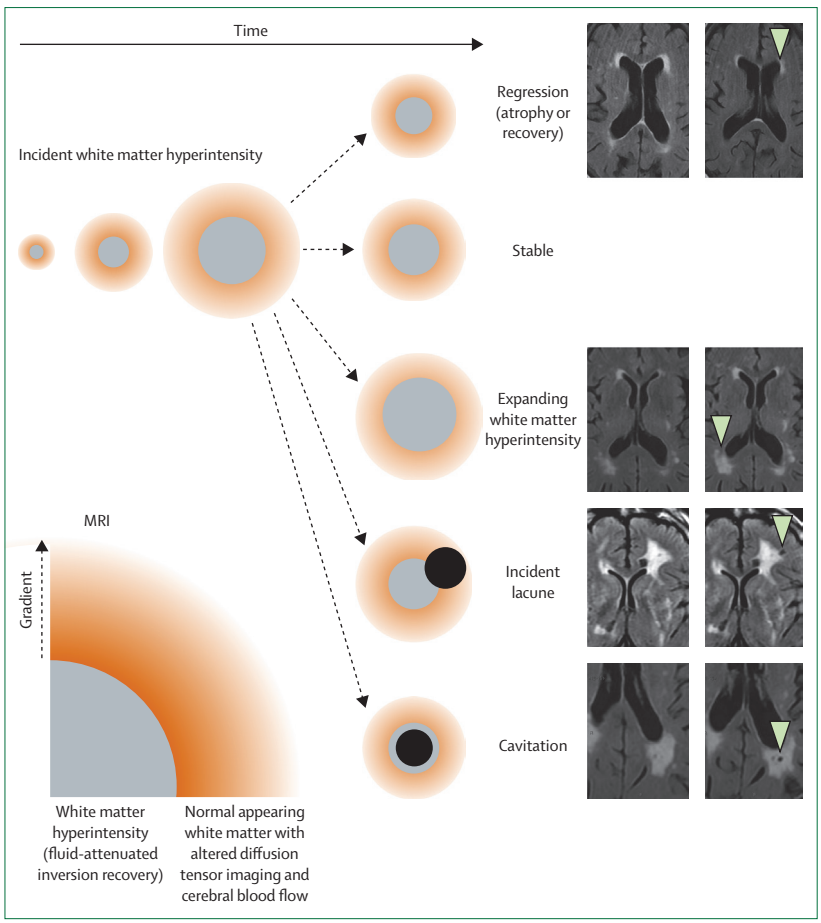

Figure 2: **White matter hyperintensities, their long-term fate, and the perilesional zone**
White matter hyperintensities (detectable on fluid-attenuated inversion recovery or T2-weighted MRI sequences at conventional field strengths; grey circles) might regress, remain stable, expand, develop incident lacunes at the edge of the white matter hyperintensity, or cavitate (ie, turn into a lacune). Representativie examples of serial MR images (co-registered) are shown on the right (left panel: initial scan; right panel: follow-up scan). White matter hyperintensities and other small vessel disease lesions are typically surrounded by a zone of increasingly abnormal tissue (depicted in orange) that appears normal on conventional fluid-attenuated inversion recovery or T2-weighed MRI or pathology (normal appearing white matter) but shows altered signal characteristics on several MRI methods, including diffusion tensor imaging and at pathology. Green arrows indicate key findings.

microbleeds, and cerebral amyloid angiopathy and in lacunar versus non-lacunar stroke,[46] mediated the association between plasma inflammatory markers and white matter hyperintensities,[50] might predict progression of white matter hyperintensities,[51] and was associated with blood–brain barrier dysfunction[1] and increased intracranial and extracranial vascular pulsatility (stiffness).[45,48,52,53] These findings indicate that perivascular spaces are important markers of several pathological processes associated with vascular dysfunction that leads to brain damage and, therefore, should not be ignored in future research.

In rodents, perivascular CSF flow depends on normal elastic arteriolar pulsation and becomes slower and irregular if arteriolar pulsatility increases, such as with raised blood pressure, leading to fluid stagnation in perivascular spaces and impaired interstitial flushing.[18,54] Therefore, the association between intracranial vascular pulsatility and perivascular space visibility in humans[45] suggests that perivascular space visibility on MRI could be a marker of dysfunctional perivascular flow and, consequently, of impaired interstitial flushing. Dysfunctional perivascular flow might impair interstitial fluid drainage (in addition to any excess fluid from blood–brain barrier dysfunction) and impede clearance of metabolites (including β-amyloid and other proteins[12]) from tissues. Alzheimer's disease, cerebral amyloid angiopathy, and several monogenic small vessel diseases have been described as protein elimination failure angiopathies.[12] The increased interstitial fluid would also increase the distance over which oxygen and nutrients have to diffuse to reach neurons, thus propagating a worsening cycle of tissue injury.

Although the precise sequence of endothelial dysfunctions in humans is unknown, we suggest that blood–brain barrier dysfunction might increase interstitial fluid and arteriolar wall and tissue damage. Arteriolar wall thickening and stiffening, including when secondary to vascular risk factors, increases pulsatility, restricts vasodilation, and impairs normal perivascular fluid flushing and removal of waste. Together these effects reduce oxygen and nutrient supply (figure 1). Although speculative, drawing these elements together provides a unifying explanation for the common microscopic and in-vivo vascular and brain lesions reported in humans, while retaining consistency with information emerging from relevant rodent models.[18,54] However, further research is needed to confirm this hypothesis.

Progression of white matter hyperintensities

The snapshots used to visualise the human brain in vivo and post mortem might obscure the brain's dynamic rhythms from cardiovascular, respiratory,[18] circadian, and physical activity and might have hampered understanding of small vessel disease.[10,55,56] Small vessel disease lesions are considered to be permanent, with white matter hyperintensities representing demyelination, axon loss, and gliosis, lacunes being cavities replacing destroyed tissue, and microbleeds being fixed haemorrhages. Several longitudinal studies report white matter hyperintensity progression,[57] although some changes in white matter hyperintensity volume included small decreases.

Two longitudinal clinical studies[35,58] show that small vessel disease lesions can shrink or disappear as well as grow. The Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Imaging Cohort (RUN DMC) study[58] assessed older community-dwelling participants (mean age 62·5 years [SD 7·7] at baseline) three times over 9 years. White matter hyperintensity volume decreased in 26 (9·4%) participants between two assessments 5·4 years apart, and lacunes disappeared in 10 (2·6%) participants and microbleeds in 15 (5·7%) over three assessments 9 years apart. In the Mild Stroke Study-2 (MSS-2) of 190 patients with lacunar or mild cortical ischaemic

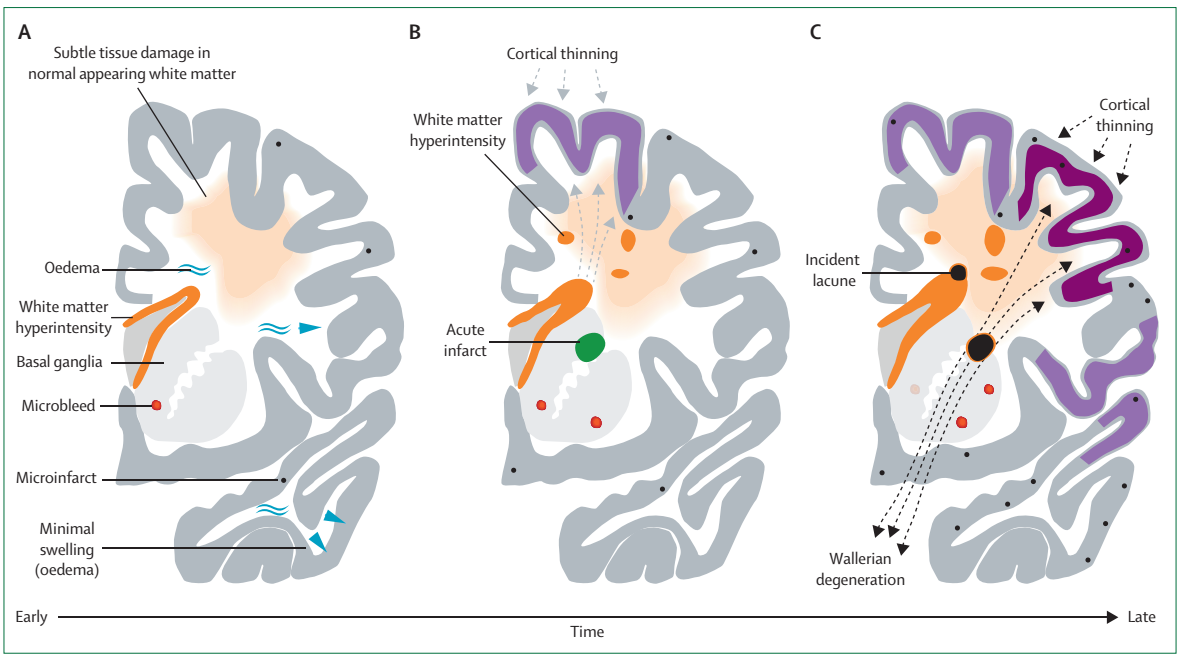

Figure 3: **Small vessel disease effects on the whole brain**
Shown left to right is the progression of small vessel disease-related lesions detectable on MRI. Note that incident lesions, such as infarcts and microbleeds, might occur at variable timepoints during disease progression or be absent. Acute infarcts and white matter hyperintensities (visible on fluid-attenuated inversion recovery and T2-weighted MRI sequences) cause secondary loss of grey and white matter in connected brain regions, and regions with less direct connections, resulting in cortical thinning, brain atrophy, and neurodegeneration. (A) Interstitial fluid increases produce subtle changes in normal white matter, leading to white matter hyperintensity formation. (B) White matter hyperintensities progress, leading to secondary cortical thinning. Acute small subcortical infarcts might appear. (C) White matter hyperintensities, lacunes, microbleeds, secondary cortical thinning, and long tract degeneration worsen.

stroke,[35] 71 (37%) had some degree of white matter hyperintensity decline over 1 year. Both studies[35,58] also found white matter hyperintensity progression was associated with increased age and increased baseline white matter hyperintensity volume. MSS-2 found that white matter hyperintensity decrease was associated with better blood pressure control between baseline and 1 year,[35] whereas the RUN DMC study found no factors associated with lesion reduction.[58] In MSS-2,[35] patients with white matter hyperintensity reduction had slight reduction in brain volume and fluid content compared with those who had increased or unchanged white matter hyperintensities, which is consistent with white matter hyperintensities being areas of increased tissue water, and with reduction in recurrent strokes.

Small vessel disease lesions progress partly by expansion into adjacent tissue. Longitudinal spatial mapping with MRI shows new white matter hyperintensities forming superficial to small subcortical infarcts (caps)[55] and new lacunes forming at the proximal margin of white matter hyperintensities (with regard to the perforating arterioles).[32] Additionally, quantitative MRI methods such as diffusion tensor imaging, T1 mapping, or dynamic contrast-enhanced MRI, reveal increasingly abnormal tissue (increased mean diffusivity, reduced fractional anisotropy, and increased absolute T1 values) in a perilesional zone of normal appearing white matter around white matter hyperintensities[8,28,31] and lacunes,[59] and reduced cerebral blood flow[30] (figure 2), thus identifying the perilesional zone as vulnerable tissue with microstructural tissue changes liable to recruitment into lesions. This perilesional zone extends outwards with a corresponding gradient of diffusor tensor imaging and absolute T1 values (and blood–brain barrier dysfunction) that becomes more normal with distance from the edge of the white matter hyperintensity.[8,28] Longitudinal diffusion tensor imaging studies[30,43] show progressive loss of tissue integrity in perilesional tissue over time and conversion of normal appearing white matter to white matter hyperintensities. Lower cerebrovascular reactivity,[43] and fractional anisotropy and higher mean diffusivity[30] in perilesional tissue independently predicted conversion of normal appearing white matter to white matter hyperintensities.[30] Although technical issues (partial volume effects and tissue misclassification) might account for some perilesional tissue findings on MRI, autopsy studies also reported molecular disorganisation of axons adjacent to lacunes and microinfarcts in the perilesional zone.[13,59]

The focus of small vessel disease research on MRI visible lesions might have distracted attention from the whole-brain effects of small vessel disease. These effects include the diffuse changes in normal appearing white matter and grey matter detailed above,[8,9] and secondary loss of connected overlying cortex and in long descending fibre tracts (figure 3).[10,55] Worse small vessel disease

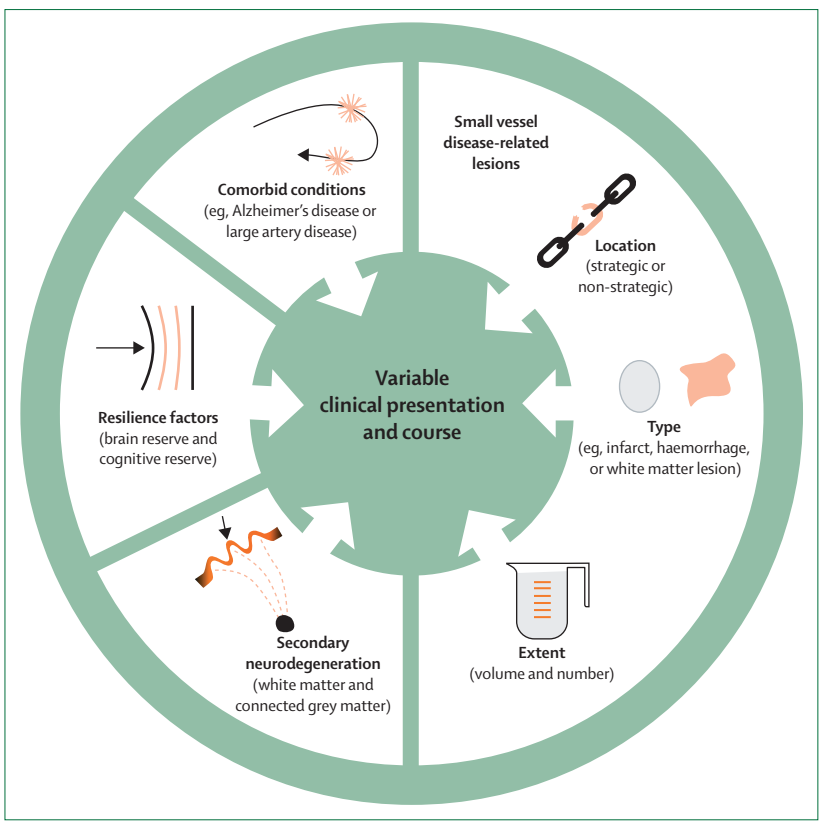

Figure 4: **Factors influencing the clinical presentation of small vessel disease**
The clinical presentation and course of small vessel disease is highly variable. Shown are factors that contribute to this variability, including affected brain location[70,71] and lesion type and extent.[60] Age, environmental, and genetic factors also have a determining role—eg, by influencing vascular risk (exposure) or premorbid risk.[72,73]

lesions (ie, more white matter hyperintensities, lacunes, or perivascular spaces) are associated with diffuse loss of white matter and cortex in connected and in unrelated brain areas.[8,9,56,60] Diffusion tensor imaging and functional MRI also show loss of global network connectivity and reduced network efficiency with increasing white matter hyperintensity burden.[60,61] Considering the global visible and subvisible lesions together, rather than separately, might better predict conversion to dementia,[60] relationships with vascular risk,[62] concurrent cognition,[61] and mobility,[63] although optimal combination and weighting of these features remains unclear.[64]

Clinical implications

Many of the clinical manifestations of small vessel disease, including stroke, cognitive decline,[65] gait problems,[66] apathy,[67] depression,[68] and extrapyramidal symptoms,[69] relate to functions with structural and functional underpinnings in widely distributed neuronal networks, consistent with diffuse effects of small vessel disease on the brain, and are important when considering mechanisms and interventions. The presenting symptoms and clinical course of small vessel disease are highly variable. We suggest that this variability relates to several factors, including variations in the vascular injury (location, type, and extent), variable degrees of secondary neurodegeneration, resilience factors such as brain reserve, and comorbid conditions (figure 4).

Associations between typical acute lacunar motor and sensory syndromes (eg, pure motor hemiparesis, pure sensory hemiparesis, ataxic hemiparesis, sensorimotor stroke, and dysarthria-clumsy hand syndrome) and recent small subcortical infarcts in specific anatomical locations (eg, posterior limb of the internal capsule, thalamus, lentiform nucleus, white matter lateral to the body of the lateral ventricle, or pons), and between sudden cognitive deficits and strategic infarcts in the thalamus, are well established.[70] Lesion–symptom associations might reflect the total burden of lesions, preponderance in specific brain subregions, or subvisible changes.[11] The total lesion burden, whether of individual types of lesions (such as white matter hyperintensities) or in aggregate as reflected by total small vessel disease burden scores, is associated with declines in cognition,[61,74–76] gait and balance,[63] and mood.[4,68] Voxel-based lesion–symptom mapping suggests that lesions in distinct subcortical grey and white matter structures are associated with cognitive deficits[71] or apathy.[67] Although lesion type (eg, cavitating infarct *vs* white matter lesion *vs* haemorrhage) and extent (volume and number) affect symptoms, subvisible tissue changes might also account for clinical effects; the decline in white matter structure as detected with diffusion tensor imaging in normal appearing white matter correlates with cognitive impairments.[11] Similarly, subcortical microinfarcts, which are by definition invisible to the naked eye, correlate with arteriolar pathology[13] and worsening cognition.[3] However, more studies with detailed sequential assessment of the brain (using detailed structural and diffusion tensor imaging MRI techniques), clinical findings, and cognitive and physical function are needed to determine the effects of comorbidities and whether this also applies to unselected patients attending cognition or mobility clinics.[77]

Several studies[10,56,60,78–80] have further emphasised a role for secondary neurodegeneration in determining clinical status. Discrete subcortical infarcts induce loss of connected cortex remote from the infarct through degeneration of white matter tracts.[10] Increasing white matter hyperintensity burden associates with worse whole-brain atrophy, cortex thinning overlying areas of high white matter hyperintensity density,[60] and altered sulcal morphology,[78] although the precise relationship between white matter hyperintensity progression and brain volume loss remains controversial.[56] Brain atrophy is a strong independent predictor of clinical status and progression in patients with small vessel disease,[79] and path analyses show that the effects of small vessel disease-related vascular lesions on clinical status are in part mediated by changes in brain atrophy and cortex morphology.[60,80] Prevention of secondary atrophy might help delay the clinical effects of small vessel disease.

	Design	Population	N	Age, years†	Comments
Standard pharmacological treatment					
Antiplatelet	Meta-analysis; 17 trials[85]	Patients with lacunar stroke	42 234	64	Includes SPS3; follow-up 4 weeks to 3·5 years; single *vs* no antiplatelet therapy reduced recurrent stroke; no difference between several antiplatelet drugs; long-term dual antiplatelet therapy in SPS3 increased risk of intracerebral haemorrhage
Anti-hypertensive	Randomised controlled trial; SPS3[86]	Patients with lacunar stroke	3020	63 (11)	Follow-up 3 years; different blood pressure lowering agents at the discretion of the treating clinician. No reduction in stroke or cognitive decline with intensive compared with guideline blood pressure reduction
Anti-hypertensive	Meta-analysis of four trials; ACCORD-MIND, PRoFESS, PROGRESS, SCOPE[87]	Patients with any type of stroke	1369	62 (5), 66 (8), 61 (12), 77 (4)	Follow-up 28–47 months; less white matter hyperintensity progression with intensive compared with guideline blood pressure reduction
Anti-hypertensive	Randomised controlled trial substudy; PRESERVE[88]	Hypertension, lacunar stroke, severe white matter hyperintensity	62	69	Follow up 3 months; cerebral blood flow did not fall with intensive blood pressure reduction
Statins	Randomised controlled trial substudy; VITATOPS[89]	Patients that took statins before stroke	81	..	Follow up 24 months; less white matter hyperintensity progression with statin before stroke than no statin use
Statins	Randomised controlled trial substudy[90]	Rosuvastatin	668	>60	Follow-up 61·8 (SD 2·2) months; less white matter hyperintensity progression in patients who took rosuvastatin than in control and in non-*APOE4* carriers than *APOE4* carriers
Novel pharmacological intervention*					
Nitric oxide	Randomised controlled trial; ENOS[91]	Patients with stroke, including lacunar stroke	4011	70 (12)	Effect of short-term (7 days) glyceryl trinitrate on neurological, functional, and cognitive outcomes will be investigated; 1397 patients with with lacunar stroke analysed, of whom 41% had white matter hyperintensities
Nitric oxide	Randomised controlled trial; RIGHT-2 (ISRCTN26986053)	Patients with stroke, including lacunar stroke	1149	..	Effect of short-term glyceryl trinitrate on neurological, functional, and cognitive outcomes will be investigated
Nitric oxide	Randomised controlled trial; LACI trials (LACI-1 [EudraCT 2015-001953-33][92] and LACI-2 [EudraCT 2016-002277-35])	Patients with lacunar stroke	57 (LAC-1), 400 (LAC-2)	..	Effect of isosorbide mononitrate on recurrent stroke, cognitive decline, and small vessel disease lesion burden will be investigated
Phosphodiesterase 3′ inhibitor (cilostazol)	Meta-analysis of five trials; trials of stroke prevention[93]	Patients with ischaemic stroke	6000	67	Patients receiving cilostazol experienced fewer recurrent strokes during follow-up *vs* control (odds ratio 0·64, 95%CI 0·51-0·79)
Phosphodiesterase 3′ inhibitor (cilostazol)	Randomised controlled trial; LACI trials (LACI-1 [EudraCT 2015-001953-33][92] and LACI-2 [EudraCT 2016-002277-35])	Patients with lacunar stroke	57 (LAC-1), 400 (LAC-2)	..	Effect of cilostazol on recurrent stroke, cognitive decline, and small vessel disease lesion burden will be investigated
Phosphodiesterase 3′ inhibitor (cilostazol)	Observational study; National Registry Taiwan[94]	Patients in central hospital registry	9148	>40	Cilostazol use was associated with a significant reduction in incident dementia
Xanthine oxidase inhibitor (allopurinol)	Randomised controlled trial; XYLO-FIST (NCT02122718)	Patients with ischaemic stroke	..	..	Effect of allopurinol on white matter hyperintensity progression and recurrent stroke will be investigated
Phosphodiesterase 5′ inhibitor (tadalafil)	Randomised controlled trial; PASTIS (EudraCT 2015-001235-20)	Patients with white matter hyperintensities	..	..	Effect of tadalafil single dose on resting cerebral blood flow will be investigated
Folic acid and vitamin B12	Randomised controlled trial substudy; VITATOPS[95]	Patients with stroke	359	64	Vitamin supplements for 2 years reduced white matter hyperintensity progression in patients with the worst hyperintensities at baseline
Lifestyle interventions and factors					
Smoking	Observational study; MSS-2[62]	Patients with stroke	264	67	Smoking increases small vessel disease score and risk of stroke and dementia and accelerates rate of cortical thinning
Smoking	Observational study; Paris-Munich CADASIL[79]	Patients with CADASIL	290	50·6 (11·4)	Smoking increases small vessel disease score and risk of stroke and dementia and accelerates rate of cortical thinning

(Table continues on next page)

	Design	Population	N	Age, years†	Comments
(Continued from previous page)					
Smoking	Observational study; Lothian Birth Cohort[96]	Older subjects in community	504	73 (8·9 months)	Smoking increases small vessel disease score and risk of stroke and dementia and accelerates rate of cortical thinning
Exercise	Randomised controlled trial; FINGER trial[97]	Older subjects at risk of dementia	1260	69·5 (4·6)	Diet, exercise, cognitive training, and vascular risk monitoring (administered by a nurse), compared with general health advice alone, improved executive function and delayed cognitive decline
Diet: sodium chloride	Observational study; MSS-2[95]	Patients with stroke	264	67	High dietary sodium increased risk of stroke, lacunar compared with cortical stroke, white matter hyperintensity, and total small vessel disease burden

SPS3=Secondary Prevention of Small Subcortical Stroke trial. ACCORD-MIND=Action to Control Cardiovascular Risk in Diabetes: Memory in Diabetes substudy. PRoFESS=Prevention Regimen for Effectively Avoiding Second Strokes. PROGRESS=Peridopril protection against recurrent stroke study. SCOPE=Study on Cognition and Prognosis in the Elderly. VITATOPS=Vitamins to Prevent Stroke trial. ENOS=Efficacy of Nitric Oxide in Stroke. RIGHT-2=Rapid Intervention with Glyceryl Trinitrate in Hypertensive Stroke Trial. LACI=Lacunar Intervention Trial. XYLO-FIST=Xanthine Oxidase Inhibition for Improvement of Long-Term Outcomes Following Ischaemic Stroke and Transient Ischaemic Attack. PASTIS=Perfusion by Arterial Spin Labelling Following Single Dose Tadalafil in Small Vessel Disease Trial. MSS-2=Mild Stroke Study-2. CADASIL=cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. FINGER=Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability. *All studies are ongoing unless otherwise stated. †Mean (SD) if given.

Table: **Clinical studies assessing pharmacological and lifestyle interventions and factors in patients with small vessel disease**

Another factor contributing to the clinical symptoms of small vessel disease is resilience, which refers to the capacity to cope with brain pathology. Brain reserve refers to inter-individual differences in brain structure, whereas cognitive reserve refers to differences in the way the brain processes specific tasks. Both reserves are influenced by experiences, including those early in life,[72] and are likely to be inter-related. Although both concepts are still under development, both seem relevant to all clinical manifestations of small vessel disease. High cognitive reserve, commonly operationalised as educational attainment and IQ, attenuates the effects of small vessel disease burden on cognition,[73,81,82] affects motor functions,[83] and age at stroke.[81] Brain resilience might depend on white matter structural integrity and network connectivity, because global white matter network efficiency mediated the effects of small vessel disease lesions on cognition and progression to dementia.[60] Premorbid cognitive ability (ie, peak intelligence, a measure of cognitive reserve) can be estimated using tests such as the National Adult Reading Test, influences risk of small vessel disease lesions in later life,[72] and could explain some of the variation between small vessel disease and cognitive function.[81]

Comorbid conditions are common in older patients (>65 years of age), particularly in patients diagnosed with dementia. The most frequent comorbid disorder in patients with dementia is mixed vascular and Alzheimer's disease-type pathology, with patients with multiple pathologies more likely to have dementia than those with one.[6] As such, comorbid neurodegenerative disease or other vascular lesions (eg, large artery stroke) might also modify symptoms of small vessel disease. The mechanisms and clinical effects of vascular and dementia comorbidities are subject to intensive research to understand relationships between cognitive, focal neurological, and physical dysfunctions.

Pharmacological and lifestyle interventions

Evidence on prevention and treatment of small vessel disease comes from randomised controlled trials of vascular risk modifying agents, drugs used in other fields with relevant modes of action,[84] and modifiable lifestyle factors (table).

In the Secondary Prevention of Small Subcortical Stroke (SPS3) trial of 3020 patients with lacunar ischaemic stroke (mean age 63 years, trial duration 3 years),[85] long-term dual versus single antiplatelet therapy increased bleeding and death without reducing recurrent stroke.

Guideline (systolic 130–140 mm Hg) versus intensive (systolic <120 mm Hg) blood pressure reduction has mixed results. For example, in SPS3,[86] intensive blood pressure reduction did not reduce recurrent stroke or cognitive decline but did reduce intracerebral haemorrhage. A meta-analysis[87] of four trials of blood pressure lowering for secondary prevention in patients with ischaemic stroke (1369 patients, mean age 65 years, mean trial duration 3 years) found less white matter hyperintensity progression with blood pressure reduction. The PRESERVE trial[88] of 62 patients with hypertension and MRI-confirmed symptomatic lacunar ischaemic stroke and confluent white matter hyperintensities (mean age 69 years, trial duration 3 months) found no difference in cerebral blood flow with blood pressure reduction. This finding suggests that blood pressure reduction might not worsen cerebral blood flow (a worry for many physicians), but the full trial results have yet to be published. The results of the SPRINT MIND study (NCT01206062; mean age 67·9 years), which is investigating whether systolic blood presure reduction is associated with reductions in cardiovascular risk in 8563 patients, are awaited.

Although the aforementioned studies broadly support control in patients with lacunar stroke or white matter hyperintensities, white matter hyperintensities are

commonest in patients older than 80 years.[4] However, too rapid or large blood pressure reductions in individuals older than 80 years, in whom brain perfusion might depend on elevated blood pressure,[98] or with severe small vessel disease as in CADASIL,[99] could lead to hypoperfusion. Although the PRESERVE cerebral blood flow substudy[88] provides reassurance that intensive blood pressure reduction did not affect cerebral blood flow, the mean age was only 69 years. Hence, although blood pressure control is important, data are scarce on optimal individual blood pressure targets in older (>79 years of age) patients with severe white matter hyperintensities.

Statins are now guideline therapy for secondary stroke or cardiovascular disease prevention, with no evidence of different effects in lacunar ischaemic stroke.[84] Low dose rosuvastatin might delay white matter hyperintensity progression, particularly in patients with the *APOE4* allele,[100] statins before stroke might reduce post-stroke white matter hyperintensity progression,[89] and intensive lipid-lowering therapy after stroke might reduce cognitive impairment.[101]

Emerging targets for new therapies include blood–brain barrier integrity, vasoreactivity, vascular compliance, perivascular inflammation, or myelin repair.[16,84] Several drugs approved for other indications have relevant modes of action for small vessel disease (table). For example, cilostazol, a phosphodiesterase 3´ inhibitor used for stroke prevention in Asia-Pacific countries, might reduce cognitive decline,[94] endothelial dysfunction, and inflammation and enhance myelin repair,[16] with supporting genetic data.[20] Trials testing cilostazol for cognitive decline or recurrent stroke are ongoing. Nitric oxide donors (eg, isosorbide mononitrate, glyceryl trinitrate, or diet sources) might benefit patients with small vessel disease (improved blood–brain barrier integrity, vasodilation, and anti-inflammatory effects) with trials ongoing.

Among lifestyle modifications, smoking cessation is a priority for patients with small vessel disease; smoking accelerates lesion progression in CADASIL,[79] predicts total small vessel disease lesion burden in patients with sporadic small vessel diseases,[62] and accelerates cortical thinning.[96] Regular exercise, healthy diet, and guideline-based vascular risk reduction slowed cognitive decline in participants at risk of dementia compared with vascular risk factor reduction alone.[97] High dietary sodium increases stroke risk and worsens white matter hyperintensities and total small vessel disease burden.[95] A Mediterranean diet and folic acid and vitamin B12 might reduce white matter hyperintensities.[95] Furthermore, good sleep hygiene is important, because brain interstitial fluid and waste clearance through perivascular spaces might accelerate during sleep.[18,46]

Search strategy and selection criteria

We searched PubMed, Google Scholar, ClinicalTrials.gov, Cochrane Library, from Dec 1, 2012, to Dec 31, 2018, using search terms "lacunar", "stroke", "dementia", "small vessel disease" and its terminologies ("white matter hyperintensities", "white matter lesions", "leukoaraiosis", "lacune", "microbleed", "perivascular space", "Virchow-Robin space"), "meta-analysis", "systematic review", and "randomised controlled trial", restricting to human studies published in English, German, Spanish, French, or Mandarin. We checked reference lists of reviews.

Conclusions and future directions

Small vessel disease causes a fifth to a quarter of all strokes, age-related cognitive, physical, and mood decline, and about half of all dementias.[3–7] Despite this high burden of disease, understanding of the pathophysiology is incomplete. Much understanding of pathophysiological mechanisms in humans derives from advanced neuroimaging methods, such as diffusion tensor imaging and imaging of the blood–brain barrier, cerebrovascular reactivity, and cerebral blood flow, which demonstrate dysfunctions of the cerebrovascular endothelium, including subtle but diffuse blood–brain barrier dysfunction,[28] impaired vasoreactivity,[43] increased intracranial vascular pulsatility,[45] white matter oedema,[34] lesion regression and progression,[58] and diffuse structural effects throughout normal appearing white matter[29] and secondary remote tissue atrophy.[78] These brain vascular and tissue changes are supported by other data (eg, rodent models and human pathology studies) pointing to common pathophysiological pathways offering targets for prevention and therapy of small vessel disease.[16,20]

Improved awareness of the dynamic, whole-brain effects, balance of primary versus secondary injury, balance of risk factor exposure versus resilience and complex disease patterns should inform future clinical trials, observational human studies, experimental models, and clinical practice. Future studies should address the order of, and interactions between, blood–brain barrier dysfunction, impaired vasoreactivity, increased pulsatility, vessel wall damage, impaired interstitial fluid drainage, and function of perivascular spaces in patients with sporadic small vessel diseases. Trials of agents that maintain endothelial function and improve risk factors and of lifestyle improvements are needed.[84] An approach that integrates research from cells to tissues to systems, and across clinical specialties, would facilitate progress in understanding small vessel disease. Because humans are their own best model, improved pathology-imaging correlations[12] and brain banking with data linkage are needed.[102]

Research is also needed to determine the relative contributions of different manifestations of endothelial dysfunctions and timescales to brain damage in patients with small vessel diseases. Longitudinal studies with detailed risk factor assessment and lesion monitoring are needed to determine reasons for the wide variation in rates of progression of small vessel disease lesions, why

some lesions regress, and why some lesions lead to secondary damage in remote brain regions. Elucidation of the role of genetic susceptibilities versus environment and risk factor exposures, from birth to later life, is also important to understand variation in small vessel disease lesion development and clinical symptoms. This knowledge would help predict the effects of disease on clinical, physical, and cognitive outcomes. Understanding the reasons for the variable symptomologies, and the role of brain reserve and cognitive reserve, would improve detection, diagnosis and, in future, help tailor the clinical management of individual patients.

Contributors

JMW, CS, and MD each drafted sections of text. JMW combined the text. All three authors edited the text, helped to prepare the figures, provided insight, context and balanced interpretation of evidence through discussion, and approved the final version for submission.

Declaration of interests

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