Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges

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The term cerebral small vessel disease refers to a group of pathological processes with various aetiologies that affect the small arteries, arterioles, venules, and capillaries of the brain. Age-related and hypertension-related small vessel diseases and cerebral amyloid angiopathy are the most common forms. The consequences of small vessel disease on the brain parenchyma are mainly lesions located in the subcortical structures such as lacunar infarcts, white matter lesions, large haemorrhages, and microbleeds. Because lacunar infarcts and white matter lesions are easily detected by neuroimaging, whereas small vessels are not, the term small vessel disease is frequently used to describe the parenchyma lesions rather than the underlying small vessel alterations. This classification, however, restricts the definition of small vessel disease to ischaemic lesions and might be misleading. Small vessel disease has an important role in cerebrovascular disease and is a leading cause of cognitive decline and functional loss in the elderly. Small vessel disease should be a main target for preventive and treatment strategies, but all types of presentation and complications should be taken into account.

Lancet Neurol 2010; 9: 689–701

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Introduction

Small vessel disease is a term used with various meanings and in different contexts (ie, pathological, clinical, and neuroimaging aspects). These diseases are thought to be the most frequent pathological neurological processes[1] and have a crucial role in at least three fields: stroke, dementia, and ageing. In this Review, the definition of small vessel disease is critically reassessed and an overview of recently described clinical consequences of cerebral forms of the disease is provided. Clarification of some of these concepts is needed because the term small vessel disease is likely to be used (or otherwise misused) more frequently in the near future as risk of developing these diseases increases with the ageing population and as increased use of MRI will identify more people with these diseases. Developing lines of research into the treatment of small vessel disease are outlined, and suggestions on the role of neuroimaging as a possible surrogate marker in therapeutic trials are provided. The aim of this Review is to provide clinicians and researchers with some basic concepts with a modern overview of small vessel disease to enable understanding of recent progress and future directions in the field.

Nosology

Definitions

The term small vessel disease encompasses all the pathological processes that affect the small vessels of the brain, including small arteries and arterioles but also capillaries and small veins. However, the definition of a small vessel is not uniform: the results from a survey showed that there was less than 50% agreement among leading neuropathological centres on its definition.[2] Most often, small vessel disease is used to refer only to the arterial vessels and little attention has been paid to the venous compartment. This possible exclusive reference to the arterial part of the vascular tree must be kept in mind when dealing with small vessel disease: in such cases, the term arterial small vessel disease is proposed. In this Review, the focus will be on diseases of the leptomeningeal and intraparenchymal arterial vessels (including small arteries and arterioles). The difference between small arteries and arterioles is the absence of a continuous lamina elastica. There is another pathological process of the deep small cerebral vessels that affects the veins, which is known as venous collagenosis.[3] This process, which has received scarce attention, is associated with one of the parenchyma changes (namely, white matter lesions) that will be discussed in this Review.

Cerebral arterial small vessels have two origins: superficially, they stem from the subarachnoid circulation as the terminal vessels of medium-sized arteries, which originate from larger arteries; and, deeper at the base of the brain, they stem directly from the large vessels as arterial perforators. These two systems converge towards each other and, after having passed the cortical layers and the deep grey structures, respectively, they tend to merge in the deepest areas of the subcortical white matter where there is a watershed area.[4–7]

Unlike large vessels, small vessels cannot be currently visualised in vivo; therefore, the parenchyma lesions that are thought to be caused by these vessel changes have been adopted as the marker of small vessel disease, and small vessel disease has become a synonym of brain parenchyma lesions. However, misleadingly, the term small vessel disease is used to describe only the ischaemic component of the pathological process (ie, lacunar infarcts and white matter lesions). Instead, a broader view of small vessel disease should be kept in mind, particularly for therapeutic aspects, because patients with small vessel disease also have a risk of haemorrhage.

Classification

Small vessel diseases are mainly systemic disorders that affect various organs and areas of the body. In some cases, the brain can be a main target of these diseases, and the lesions and effects of these diseases might even be confined to the brain; in other cases, cerebral areas might not be affected at all.

Panel: **Aetiopathogenic classification of cerebral small vessel diseases**

Type 1: arteriolosclerosis (or age-related and vascular risk-factor-related small vessel diseases)
Fibrinoid necrosis
Lipohyalinosis
Microatheroma
Microaneurysms (saccular, lipohyalinotic, asymmetric fusiform, bleeding globe)
Segmental arterial disorganisation

Type 2: sporadic and hereditary cerebral amyloid angiopathy

Type 3: inherited or genetic small vessel diseases distinct from cerebral amyloid angiopathy
For example, CADASIL, CARASIL, hereditary multi-infarct dementia of the Swedish type, MELAS, Fabry's disease, hereditary cerebroretinal vasculopathy, hereditary endotheliopathy with retinopathy, nephropathy and stroke, small vessel diseases caused by *COL4A1* mutations

Type 4: inflammatory and immunologically mediated small vessel diseases
For example, Wegener's granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis, Henoch-Schönlein purpura, cryoglobulinaemic vasculitis, cutaneous leukocytoclastic angiitis, primary angiitis of the CNS, Sneddon's syndrome, nervous system vasculitis secondary to infections, nervous system vasculitis associated with connective tissue disorders such as systemic lupus erythematosus, Sjögren's syndrome, rheumatoid vasculitis, scleroderma, and dermatomyositis

Type 5: venous collagenosis

Type 6: other small vessel diseases
For example, post-radiation angiopathy and non-amyloid microvessel degeneration in Alzheimer's disease

CADASIL=cerebral autosomal dominant arteriopathy with subcortical ischaemic strokes and leukoencephalopathy. CARASIL=cerebral autosomal recessive arteriopathy with subcortical ischaemic strokes and leukoencephalopathy. MELAS=mitochondrial encephalopathy with lactic acidosis and stroke-like episodes.

There are different types of small vessel diseases and a simplified aetiopathogenic classification is proposed in the panel. The frequency of these types is very different, and type 1, arteriolosclerosis, and type 2, sporadic and hereditary cerebral amyloid angiopathy, are the most prevalent forms.

A group of inherited cerebral small vessel diseases has been reported recently and the number of these forms is increasing.[8] Of these diseases, CADASIL (cerebral autosomal dominant arteriopathy with subcortical ischaemic strokes and leukoencephalopathy) and Fabry's disease are among the most prominent.[9–11] These diseases are important because they could be used as models for the understanding of the pathogenesis of sporadic small vessel diseases.

Inflammatory and immunologically mediated small vessel diseases are a heterogeneous group of rare diseases characterised by the presence of inflammatory cells in the vessel walls (vasculitis) and are usually part of a systemic disease (panel).[12] Venous collagenosis is a pathological appearance of veins and venules closely located to the lateral ventricles.[3] These vessels have an increased thickness of the walls that results in narrowed lumen and, sometimes, occlusion. The material in the thickened walls is mainly collagen.

Post-radiation angiopathy, a delayed side-effect of cerebral irradiation therapy (after months or years), is classified within a miscellaneous group of small vessel diseases.[13] This angiopathy mainly affects the small vessels of the white matter that show fibrinoid necrosis, thickening of the wall caused by deposition of hyaline material, narrowing of the lumen, and thrombotic occlusion. The consequence is a diffuse leukoencephalopathy with degeneration of the myelin sheaths that can be so severe in some cases that a state of frank coagulative necrosis is reached.[13] These parenchyma changes are thought to be ischaemic in origin. Also included in the same group are the non-amyloid changes seen in the capillaries and basal membrane in patients with Alzheimer's disease.[14]

Pathology and pathogenesis

Pathological features

Most of the topics dealt with in this Review are linked to the first two types of small vessel diseases and, therefore, only the pathological characteristics of these diseases are described.

Type 1: arteriolosclerosis

Arteriolosclerosis is also known as age-related and vascular risk-factor-related small vessel disease. From a pathological point of view, type 1 small vessel diseases are mainly characterised by loss of smooth muscle cells from the tunica media, deposits of fibro-hyaline material, narrowing of the lumen, and thickening of the vessel wall (figure 1). This form of the disease is a common and systemic type that also affects the kidneys and retinas and is strongly associated with ageing, diabetes, and, in particular, hypertension.[15] For this reason, type 1 diseases are also named hypertensive small vessel diseases. Other possible pathological features of this form of micro-angiopathy are distal manifestations of atherosclerosis (microatheroma) and the presence of elongated and dilated vessels (microaneurysms).

Some authors subdivide this type 1 disease according to the most pronounced histological changes; however, these subtype features can coexist. Moreover, efficacious and diffuse treatment of hypertension is likely to have modified the pathological features of the disease.[16] The different pathological features of arteriolosclerosis have been reviewed in detail elsewhere.[17–19]

Type 2: cerebral amyloid angiopathy

Cerebral amyloid angiopathy is characterised by the progressive accumulation of congophilic, βA4 immuno-reactive, amyloid protein in the walls of small-to-medium-sized arteries and arterioles predominantly located in the leptomeningeal space, the cortex, and, to a lesser extent, also in the capillaries and veins. In the most severe form of cerebral amyloid angiopathy, the vessels become dilated and disrupted, with focal wall fragmentation

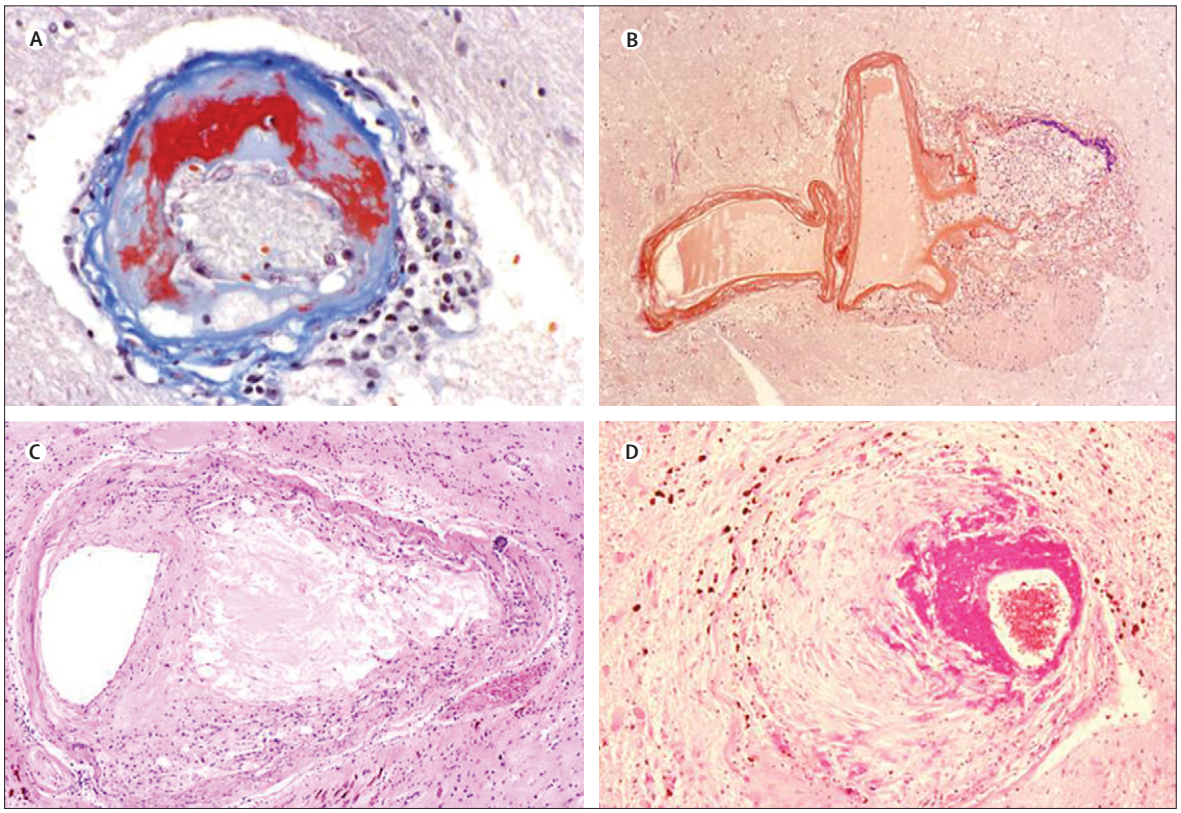

Figure 1: **Pathological features of small vessel disease**
(A) Lipoyalinosis (basal ganglia ×100). (B) Microaneurysm in the right thalamus in a 70-year-old hypertensive patient who died 42 days after developing a massive intracerebral haemorrhage in the left thalamus. Fibrinoid necrosis of the aneurysmal wall is almost ready to rupture. Phosphotungstic acid haematoxylin stain. Original magnification ×25. (C) Microatheroma (basal ganglia ×20). (D) Fibrinoid necrosis (pons ×20).

and blood extravasation, with or without micro-aneurysmal dilatation, and sometimes show luminal occlusion.[20,21] A green birefringent appearance under polarised light when stained with Congo red and the fluorescent appearance under ultraviolet light when stained with thioflavin S are quite specific histological features of cerebral amyloid angiopathy. Another typical feature on light microscopy is the "double barrel" appearance given by the splitting of the internal elastic lamina caused by the deposition of hyaline material in the vessel wall.

Cerebral amyloid angiopathy is a pathological hallmark of Alzheimer's disease, in which it is almost invariably seen.[22,23] As well as occurring in Alzheimer's disease, this type 2 small vessel disease also occurs in rare genetically transmitted diseases[24] and in other disorders such as Down's syndrome. This angiopathy is also very frequent in the general elderly population, as noted on autopsy, and its frequency increases with age, becoming as frequent as 50% of individuals in the ninth decade.[25] In some patients, cerebral amyloid angiopathy is particularly associated with large lobar haemorrhages, which are frequently recurrent.[26] There is also an association of cerebral amyloid angiopathy with microbleeds on MRI.[27,28] This type of small vessel disease has also been associated with the presence of cerebral ischaemic changes such as white matter lesions[29,30] and microinfarcts.[31]

Pathogenesis of cerebral damage

The mechanisms that link small vessel disease with parenchyma damage are heterogeneous and not completely known. There is little knowledge because animal models that convincingly reflect the pathological changes in human small vessel disease are scarce.[32] The hypothesised cascade of pathophysiological events leading from small vessel disease to brain damage is summarised in figure 2. Pathological changes in the small vessels can lead to both ischaemic and haemorrhagic consequences. The reason why some vessel ruptures lead to major haemorrhage while others lead to microhaemorrhage is unknown. In cerebral amyloid angiopathy, differences in thickness of vessel walls are thought to explain the differences in haemorrhage, with thicker walls associated with more microhaemorrhages.[33]

Although the mechanisms underlying haemorrhagic forms of small vessel disease are more clear if the pathological changes described earlier are taken into account and if the vessel wall damage reaches the point of rupture, the pathogenesis (and even the aetiology) of

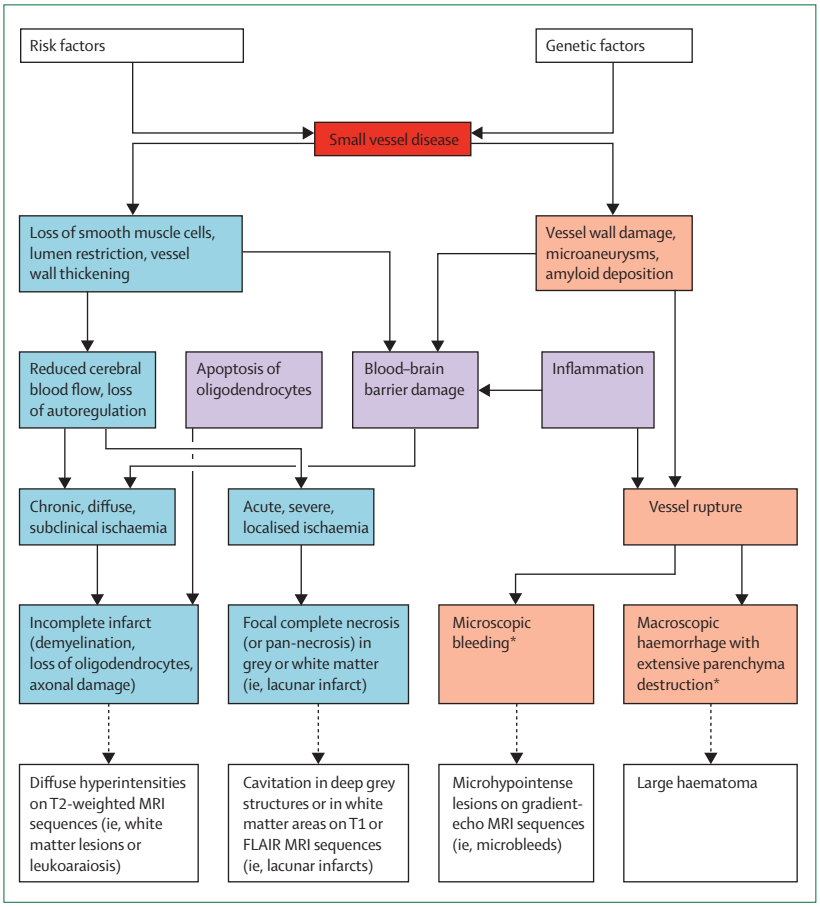

Figure 2: **Pathogenesis of brain damage as a result of small vessel disease**
FLAIR=fluid-attenuated inversion recovery. *Based on the hypothesis by Greenberg and colleagues.[33]

some ischaemic lesions such as white matter lesions is more hypothetical.[7,34] In ischaemic lesions caused by small vessel disease, the vessel lumen restriction is thought to lead to a state of chronic hypoperfusion of the white matter, eventually resulting in degeneration of myelinated fibres as a consequence of repeated selective oligodendrocyte death. This ischaemic mechanism has been demonstrated in animals.[35,36] This kind of white matter damage is thought to be a form of incomplete infarct or selective necrosis[37] similar to what has been described for neurons.[38] Alternatively, acute occlusion of a small vessel is hypothesised to occur, leading to focal and acute ischaemia and complete tissue necrosis (pan-necrosis): this is the putative mechanism of lacunar infarcts. Although this theory was proposed many years ago in the seminal papers by Fisher,[39,40] the so-called lacunar hypothesis remains unproven[41,42] and there is scarce pathological documentation for this hypothesis.

Other mechanisms such as blood–brain barrier damage,[43] local subclinical inflammation,[44–46] and oligodendrocytes apoptosis[47] could be involved in the so-called ischaemic forms of small vessel disease and contribute to the final pathological picture.

Neuroimaging

Neuroimaging correlates of small vessel disease

As mentioned earlier, the consequences of small vessel disease on the brain parenchyma are heterogeneous, encompassing ischaemic and haemorrhagic manifestations (figures 1 and 2). However, in neuroimaging, the term small vessel disease is often used misleadingly to describe the ischaemic consequences (ie, white matter lesions and lacunar lesions). Haemorrhagic lesions can be further distinguished as macrolesions and microlesions. Although major haemorrhages are easily recognised by conventional neuroimaging, including CT, the detection of microbleeds requires the use of appropriate magnetic resonance sequences such as gradient-echo sequences (figure 3A and figure 3B). For more on microbleeds, readers are referred to Greenberg and colleagues.[48]

White matter lesions on MRI are seen as more or less confluent areas that are bilaterally and symmetrically sited in the hemispheric white matter and that appear hyperintense on T2-weighted and fluid-attenuated inversion recovery images (figure 3C). The CT correlates are hypodense periventricular or subcortical areas. By definition, these lesions should not be adjacent to focal areas of cortical damage or ventricular enlargement to distinguish them from the effects of focal large infarcts on white matter.[49] The term leukoaraiosis, meaning rarefaction of the white matter, was introduced more than 20 years ago[49] to describe these lesions in an attempt to prevent confusion with a specific pathological process that had vague borders (ie, with no criteria or consensus about the definition of the disease; so-called Binswanger's disease) and to avoid attributing an explicit clinical significance to these white matter lesions. At the time of the introduction of this neologism, most studies were CT based and, therefore, some authors still believe that the term should be used only for describing the CT lesions. Despite the fact that white matter lesions are typically supratentorial, they do frequently occur in one infratentorial location (ie, the pons) and this has been called pontine ischaemic rarefaction or pontine leukoaraiosis.[50] Taking the location and risk factor profile of patients into account, this lesion is likely to be another expression of small vessel disease.[51] 20 years after the introduction of the term leukoaraiosis, the amount of data on the clinical and pathological correlates of white matter lesions has enormously increased and white matter lesions are currently generally thought to be a consequence of small vessel disease. New magnetic resonance techniques such as diffusion tension imaging and functional MRI are expected to contribute to the understanding of the pathophysiology of white matter lesions (and of small vessel diseases in general) and their clinical correlates.[52]

Frequently associated with white matter lesions, lacunar infarcts are typically seen on MRI in locations such as the basal ganglia, internal capsule, thalamus, and

pons (figure 3D). Lacunar infarcts are defined as hypointense foci on MRI T1-weighted sequences. There is no full consensus on the size of lacunar infarcts; the maximum accepted diameter for the definition of a lacunar infarct is usually 15 mm because this is the size derived from the original pathological studies.[39] A consensus on the minimum diameter is more difficult to establish; an ongoing multinational study has chosen a cut-off size of 3 mm.[53]

Some lacunar infarcts are located within areas of diffuse white matter lesions. In these cases, it is difficult to determine whether these lesions should be classified as pure lacunar infarcts or the extreme consequences of chronic white matter rarefaction. In fact, the most severe forms of white matter rarefaction are visualised on neuroimaging as holes when focal and, therefore, might be interpreted as lacunar infarcts.

Lacunar infarcts are a widely accepted sign of small vessel disease. However, this classification might not apply to all the cavitated small infarcts. For example, isolated lacunar infarcts, such as striatal infarcts, might be caused by non-small vessel disease mechanisms such as emboli from atherosclerotic plaques in the carotid arteries or aortic arch.[54,55] Some authors find it more appropriate to classify patients with lacunar infarcts as having small vessel disease only when the lacunar infarcts are multiple or associated with moderate-to-severe white matter lesions.[56]

Another problem in the assessment of lacunar infarcts on MRI is the need to distinguish these from dilated perivascular spaces. These are enlargements of the spaces around the penetrating vessels in the brain parenchyma (also called Virchow-Robin spaces) and are typically located in some areas (eg, anterior commissure, vertex) that are different from those of lacunar infarcts. Other MRI characteristics that can help to distinguish dilated perivascular spaces from lacunar infarcts are that dilated perivascular spaces are usually smaller than 1×2 mm[57] and have an isointense appearance with the CSF on proton density sequences.[58,59] Lacunar infarcts and dilated perivascular spaces share the same risk factor profile and, in fact, some investigators believe that dilated perivascular spaces are another expression of small vessel disease in the brain.[60]

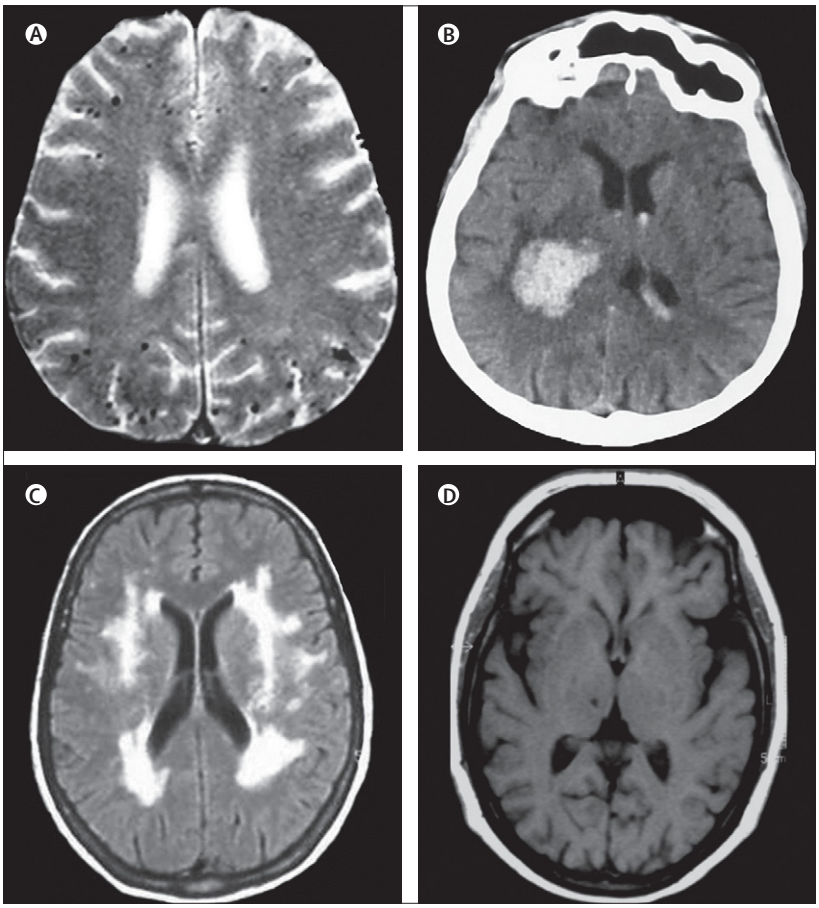

Figure 3: **Neuroimaging features of small vessel disease**
(A) Multiple microbleeds (small foci of hypointensity) in the cortex of a patient with possible cerebral amyloid angiopathy as shown on a gradient-echo MRI sequence. (B) Acute haematoma on a CT scan. (C) White matter lesions or hyperintensities on MRI (FLAIR image). (D) A lacunar infarct in the right thalamus on a T1-weighted MRI. FLAIR=fluid-attenuated inversion recovery.

Neuroimaging correlates of cognitive and age-related disability

Effects of small vessel disease on cognition

Recently, there has been an increasing interest in the clinical significance of lacunar infarcts and white matter lesions, particularly in relation to cognitive function. Typically, the onset of cognitive impairment has been considered an exclusion criterion for the diagnosis of a lacunar stroke.[61] However, there has been an increasing number of reported cases with so-called strategically located single lacunar lesions associated with cognitive disturbances since the acute phase of the lesion and stroke.[62] More importantly, lacunar infarcts are associated with cognitive decline and dementia onset during follow-up.[63–65] Factors that are associated with cognitive decline in lacunar infarcts are presence of multiple lacunes[66] and location; for example, in one study, the presence of lacunes in the thalamus was associated with low scores on the mini-mental state examination and poor compound scores for speed and motor control and executive functions;[67] there was also a significant negative association between the presence of lacunes in the putamen or pallidum and memory performance.[67]

Cognitive decline is also associated with so-called silent lacunar infarcts[68]—infarcts not related to clinically obvious stroke and found incidentally on neuroimaging.[69] Therefore, the term silent is misleading as these infarcts are associated with long-term poorer outcome.[70,71] Silent infarcts are frequently detected by both CT[72] and MRI[73,74] and are, by far, more frequent than those associated with stroke.[75] In the Framingham study,[74] one in ten individuals who were stroke-free and living in the community had silent infarcts. An association between cognition and

	Initial stage	Intermediate stage	Terminal stage
Cognitive performance	Mild deficits (eg, in executive functions, attention, set-shifting abilities) appreciable only with appropriate cognitive tests	Clinically obvious cognitive deterioration not reaching the severity of dementia (corresponds to vascular subcortical mild cognitive impairment)	Dementia with associated memory deficits (ie, subcortical vascular dementia)
Mood	Depressive symptoms	Depression	Not assessable
Sphincteric functions	From normal to urgency	Urinary incontinence episodes	Complete urinary incontinence, sometimes also faecal incontinence
Gait	From normal to mild slowing, subjective postural instability	Apraxic gait*	Bedridden
Pseudo-bulbar signs	Absent (primitive reflexes† on neurological examination can be present)	Dysphagia, dysarthria, pathological laughing, and crying	Severe dysphagia (PEG might be required), unintelligible speech
Daily living functions	Independence, small difficulties in some IADL might be present	Functional impairment; notable alterations in IADL and some alterations in BADL	Complete loss of autonomy

PEG=percutaneous endoscopic gastrostomy. IADL=instrumental activities of daily living. BADL=basic activity of daily living. *Notably slowed, short-stepped, wide-based, shuffling gait (lower body parkinsonism clinical picture). †Sucking reflex, palmar grasp reflex, palmomental reflex, snout reflex, glabellar reflex, or "tap".

Table: **Types and severity of symptoms associated with cerebral small vessel disease**

white matter lesions in patients with lacunar infarcts has been reported, suggesting that these two aspects of small vessel disease should be investigated together.[63,76]

Although white matter lesions were once thought to be a neuroimaging finding of unclear and even doubtful clinical significance, these lesions have been repeatedly associated with cognitive, mood, gait, and urinary problems in cross-sectional studies[77] and with cognitive decline and dementia in longitudinal studies.[52] An extensive appraisal of the clinical correlates of white matter lesions is beyond the scope of this Review. Two aspects are briefly reviewed here: the cognitive correlates of white matter lesions and the role of white matter lesions as a predictor of disability.

Data from early cross-sectional studies have indicated a possible association between white matter lesions (or leukoaraiosis) and cognitive impairment.[78,79] Recent studies have expanded these initial observations. An appraisal of 16 studies published in 2005–06 in which the association between cognition and white matter lesions was assessed in different settings, from hospital-based to population settings, showed that a positive association was found in all studies.[52] This finding is so consistently reported that there should now be little doubt about the role of white matter lesions in cognition. However, white matter lesions are not associated with global cognitive decline unless other lesions are also present, and they should not be considered as an indicator of dementia.[80] These lesions are associated with specific cognitive deficits such as psychomotor retardation, deficits of attention, planning, and set-shifting, and dysexecutive syndrome.[81,82] White matter lesions are a predictor of cognitive decline[83] and dementia,[84,85] and there is a correlation between progression of white matter lesion load and decline in cognitive performance.[86]

Therefore, lacunar infarcts and white matter lesions are an important substrate for cognitive impairment. This conclusion, based on neuroimaging data, has recently received confirmation from data from a large pathological study in which the presence of small vessel disease was associated with a more than two-times increased risk of dementia at the age of 75 years (456 patients were evaluated post mortem).[87] Microbleeds might be an additional factor in risk of dementia.[88] By contrast with dementia that occurs acutely after a major stroke, the process leading from these parenchyma lesions to cognitive decline should be seen as one with various stages and a progressive course (table).

Small vessel disease is today thought to be among the main causes of vascular cognitive impairment. Vascular cognitive impairment itself is a broad term under which all forms of vascular disease that possibly lead to cognitive consequences are grouped.[89] Despite repeated efforts,[89,90] we are far from having definite classification and criteria for this type of cognitive impairment. This is due to several reasons, of which the heterogeneity of the pathological and clinical aspects of vascular cognitive impairment and the different underlying pathogenic mechanisms and neuroimaging correlates are among the most important. One possible solution that clinicians and researchers are working towards is to improve the definition of some vascular cognitive impairment subcategories. Vascular cognitive impairment associated with small vessel disease has recently received particular attention because of the following five factors. First, small vessel disease is reputed to be a common, and possibly the most frequent, cause of vascular cognitive impairment. Second, this type of cognitive impairment is thought to be reasonably homogeneous in clinical and neuroimaging terms[91,92] and, therefore, suitable as a target for implementing studies and therapeutic trials.[93] Third, the neuroimaging correlates of small vessel disease have been the object of many studies and, thus, this type of cognitive impairment could be appropriately studied in vivo. Fourth, vascular cognitive impairment associated with small vessel disease is thought to be a progressive condition from normal cognitive status to frank dementia[94] (table); therefore, it is a category that might benefit from prevention. Finally, because this type

of cognitive impairment has homogeneous clinical and neuroimaging features and a progressive course, it is thought to be a disease rather than a condition, by contrast with post-stroke dementia.

As well as cognitive disorders, the clinical characteristics of vascular cognitive impairment associated with small vessel disease are gait, mood and behavioural, and urinary disturbances. In the early phases, these disturbances can be mild and loosely associated. The final stage is one in which the patient fits the criteria for dementia (ie, cognitive deficits have a clear and relevant effect on the functional status), gait is very impaired with many patients almost unable to walk and having frequent falls, mood is altered with prominent depressive symptoms or apathy, and urinary incontinence is present (table). A detailed treatment of each of these aspects is beyond the scope of this Review, but it is important to emphasise that the non-cognitive disturbances are often overlooked and patients are mainly assessed for their cognitive deficits, similar to patients with Alzheimer's disease. This focus on cognition results in a limited view of patients with cerebrovascular pathology, by contrast with patients with Alzheimer's disease in whom the cognitive problems are by far the most prevalent symptoms.

Effects of small vessel disease on age-related disability

Because white matter lesions are not only associated with cognitive disorders but also with gait[95–97] and mood disturbances,[98,99] and urinary problems,[100] it has been hypothesised that they are a neuroimaging correlate of age-associated disability. The multicentre study Leukoaraiosis and Disability (LADIS) was specifically started to investigate this proposal.[101] More than 600 patients, aged 65–84 years, who were independent in daily living at baseline and had different degrees of white matter lesion severity on MRI were enrolled. Patients were followed up for up to 3 years with repeated and composite clinical assessments and a final MRI. The first analysis of follow-up data after 1 year showed that the rate of transition to disability was different across the three groups of patients with different levels of severity of white matter lesions (9% in the mild group, 15% in the moderate group, and 26% in the severe group). Patients with severe white matter lesions had more than twice the risk of transition than patients with mild lesions, independently of many other predictors of disability.[102] The final results confirmed those of the interim analysis. The yearly rate of transition or death was 10·5%, 15·1%, and 29·5% for patients with mild, moderate, or severe age-related white matter lesions, respectively (Kaplan-Meier log-rank test p<0·001).[103] A comparison of the groups with severe versus mild age-related white matter lesions, with adjustment for clinical factors of functional decline, revealed a two-times higher risk of transition to disability or death in the severe group (hazard ratio 2·36; 95% CI 1·65–3·81). The effect of severe white matter lesions remained significant after correction for baseline degree of brain atrophy and infarct number.[103]

Therapeutic aspects

Small vessel disease and acute ischaemic stroke

Small vessel disease is the cause of about a quarter of all acute ischaemic strokes.[104,105] Overall, strokes caused by small vessel disease are less severe than other types of stroke in terms of the clinical picture during the acute phase and short-term prognosis.[106,107] However, the long-term outcome of these patients cannot be thought of as benign in terms of mortality and functional impairment.[108] No specific treatment for strokes caused by small vessel disease in the acute phase has yet been proposed and there are no data to support the suggestion that any of the three approaches with recognised evidence-based efficacy in the acute setting (aspirin, thrombolysis, admission to a stroke unit) are not efficacious in strokes caused by small vessel disease.[109] The presence of small vessel disease is instead a marker of a poor outcome in some specific therapeutic settings, including acute phase thrombolysis.

Small vessel disease and prognosis in specific treatment settings

Thrombolysis

Intravenous thrombolysis with recombinant tissue plasminogen activator is an effective treatment for acute ischaemic stroke within the first 3 h after onset.[110] Intracranial bleeding is the most serious side-effect of this treatment, and efforts have been made to identify predictors of this occurrence. In addition to advanced age, hyperglycaemia, and increased blood pressure levels,[111] neuroimaging evidence in small vessel disease indicates a risk of haemorrhagic transformation of brain infarcts.[112,113] In both these studies,[112,113] the rate of symptomatic cerebral haemorrhages was about 10% in the presence of moderate-to-severe leukoaraiosis. In the Canadian Alteplase for Stroke Effectiveness Study (CASES),[113] the multivariable analysis showed that the increased risk of bleeding determined by the presence of leukoaraiosis or multiple lacunes was independent of age and other factors reported to increase this risk.

Recent data suggest that the time window of thrombolysis could be extended up to 4·5 h with potential benefits.[114] At present, there are no data on whether the presence of small vessel disease on neuroimaging confers an additional risk of bleeding in this extended time window.

Carotid endarterectomy and major vascular surgery

In the North American Symptomatic Carotid Endarterectomy Trial (NASCET),[115] the presence of leukoaraiosis on baseline CT scans conferred an increased risk of stroke and death during the peri-operative period (30 days), with a three-times increased risk in patients with widespread leukoaraiosis in comparison to those without leukoaraiosis. These results suggest that the presence of leukoaraiosis predicts a

reduced benefit from the treatment, but should not be taken as a contraindication to surgical treatment.

The role of concomitant small vessel disease has also been investigated in other major vascular surgery settings, such as thoracic aorta replacement,[116] and is also a predictor of neurological injury. These data emphasise the role of small vessel disease as a marker of adjunctive risk and raise the question of whether preventive measures could be specifically targeted in these patients. To the best of my knowledge, the risk given by concomitant small vessel disease has not been studied in cardiac surgery, another setting burdened by a high frequency of neurological injury.

Anticoagulation

As discussed earlier, one of the manifestations of small vessel disease is cerebral haemorrhage. For this reason, the presence of small vessel disease has been assessed as an additional risk for bleeding in specific treatment conditions. In the Stroke Prevention in Reversible Ischemia Trial (SPIRIT),[117] leukoaraiosis was, together with an age older than 65 years, the only independent predictor of major bleeding during anticoagulation started after cerebral ischaemia (OR 2·7, 95% CI 1·4–5·3). These data were confirmed by another group that reported leukoaraiosis to be present on CT in 24 of 26 patients who were treated with warfarin for secondary prevention of stroke and who developed intracranial haemorrhage versus 27 of 56 controls without intracranial haemorrhage;[118] this difference resulted in an odds ratio of 8·4 (95% CI 1·4–51·5) for leukoaraiosis as an independent risk factor for warfarin-related intracranial haemorrhage in the multivariate analysis.[118]

Summary

Taken together, these data suggest that small vessel disease on neuroimaging is a marker of worse prognosis in some specific therapeutic settings such as thrombolysis for acute stroke and cardiovascular surgery. The presence of small vessel disease, however, cannot be taken as a contraindication to treatment with the procedures discussed above. Similarly, care should be taken when proposing anticoagulation in patients with clear manifestation of small vessel disease and, when possible, lower doses of anticoagulant drugs should be used in patients with manifest small vessel disease.

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Apart from the intrinsic risk of bleeding given by the presence of small vessel disease, the reasons why patients with manifest small vessel disease have increased frequency of poor outcome are not entirely clear. In one study of patients with acute cerebellar infarcts, the functional outcome was strongly affected by the presence of supratentorial white matter lesions, which might have been caused by the loss of compensatory network integrity.[119] This is similar to the hypothesis that white matter lesions might reduce brain plasticity and cognitive reserve.[120]

Small vessel disease as a target in therapeutic trials

Prevention trials for stroke caused by small vessel disease

Given the different pathogenetic mechanisms of strokes caused by small vessel disease, one would ideally expect a distinct therapeutic and preventive approach from that used for atherosclerotic or cardioembolic strokes. However, stroke caused by small vessel disease has rarely been the specific object of trials and recent progress in treatment and prevention of stroke mainly apply to large vessel pathology.[121] Some data on antiplatelet drugs in secondary stroke prevention after stroke caused by small vessel disease can be derived from a few trials: the Accidents, Ischemiques Cerebraux Lies a l'Atherosclerose (AICLA) trial of aspirin plus dipyridamole versus placebo,[122] the Canadian American Ticlopidine Study (CATS) trial of ticlopidine versus placebo,[123] and the Chinese Acute Stroke Trial (CAST) study of aspirin versus placebo for early prevention after 30 days;[124] results from all these studies suggested efficacy of the study drug in the subgroup of patients with stroke caused by small vessel disease but there was no evidence that one drug, or combination, was better than another. Moreover, there are no data about a possible increased risk of haemorrhage. In the Cilostazol Stroke Prevention Study,[125] a placebo-controlled, double blind, multicentre study, 1095 patients were enrolled and about 75% had a lacunar stroke. Treatment with cilostazol (100 mg per day) was associated with a relative risk reduction of recurrence of lacunar stroke of 43·4% (3·0–67·0), which was on the border of statistical significance (p=0·04).[125]

With regard to other pharmacological preventive measures, results from the Stroke Prevention by Aggressive Reduction of Cholesterol Levels (SPARCL) study[126] have shown that patients with small vessel disease and increased low-density lipoprotein cholesterol have a similar risk of stroke recurrence as do patients with large vessel strokes, and that treatment with atorvastatin 80 mg daily is equally effective in reducing this risk, implying that patients with small vessel disease also benefit from statin therapy.

The ongoing Secondary Prevention of Small Subcortical Strokes (SPS3) trial[127] has been designed to specifically focus on cerebral small vessel disease. This trial is an interventional phase 3 study for which 2500 patients are hoped to be enrolled (1500 have already been randomly assigned). The study includes two trials: in the first double-blind trial, treatment with aspirin will be compared with treatment with aspirin plus clopidogrel; in the second (open-arm) trial, the standard (130–149 mm Hg) control of systolic blood pressure will be compared with intensive control of blood pressure (target <130 mm Hg). The primary outcomes of the study are the prevention of recurrent stroke and a reduction in cognitive decline. Patients with small vessel disease are defined on the basis of criteria from the Trial of ORG 10172 in Acute Stroke Treatment (TOAST)[128] supplemented by MRI data. The study is of particular

interest because it is specifically targeted at small vessel disease, compares two antiplatelet regimens, assesses the control of the major risk factor for small vessel disease, and also takes into account a cognitive outcome measure.[127]

Trials in dementia and small vessel disease

Some indirect evidence about the cognitive effect of anti-dementia drugs on patients with small vessel disease can be extrapolated from trials done in unselected samples of patients with vascular dementia. Memantine, an NMDA antagonist used in Alzheimer's disease, slightly improved cognition in a group of more than 500 patients with vascular dementia.[129] The authors reported that the largest clinical effect was seen in patients without cerebrovascular macrolesions, who made up about four-fifths of the group.[129] In another double-blind trial, the acetylcholin-esterase inhibitor galantamine was superior to placebo in the general population with vascular dementia in terms of cognition and function but was also superior to placebo in the vascular dementia subgroups; two of these subgroups could possibly be defined as small vessel disease groups (patients with multiple lacunar infarcts and extensive white matter changes).[130] However, these secondary and limited analyses have shortcomings because they were based only on neuroimaging grouping of patients.

There have been many other negative trials in which the populations affected by vascular dementia have not been specified or well described.[93] Small vessel disease dementia (also named subcortical vascular dementia) has been proposed as an appropriate target for therapeutic studies because it has been deemed more homogeneous in clinical, neuroimaging, and pathological terms.[91,92] After some preliminary experiences with this target population,[131,132] the first placebo-controlled study specifically focused on small vessel disease dementia was done.[133] In this trial, which tested oral nimodipine for up to 12 months, positive findings were reported only for secondary outcome measures (lexical production and a deterioration of three or more points on the mini-mental state examination), whereas negative results were reported for the main outcome (a measure of global cognitive status).[133]

A second trial was done exploratively in patients with CADASIL and cognitive impairment.[134] The study enrolled 168 patients who were followed up after randomisation to the cholinesterase inhibitor donepezil or placebo for 18 weeks. Significance on the primary outcome measure (a change in the score on the vascular Alzheimer's disease assessment scale cognitive subscale) was again not met, but in the group treated with the active drug, the investigators reported a reduced decline on two secondary cognitive measures that were more specifically affected in patients with small vessel disease dementia.[134]

These two studies[133,134] confirm that patients with the small vessel disease subtype of vascular cognitive dementia can be selected as a target group for a trial. They also lend support to the view that the cognitive measures to be implemented in this sort of study should be different from the general cognitive measures used in trials of other dementia types and should be focused on the specific cognitive deficits seen in subcortical vascular dementia.[135,136]

Another cholinesterase inhibitor, rivastigmine, has been tested in two preliminary open studies in small vessel disease dementia, with some encouraging results that need to be tested in larger double-blind studies.[137,138] The Vascular Dementia trial studying Exelon (VANTAGE)[139] was a large international trial in which more than 700 patients with pure vascular dementia were randomly assigned to receive rivastigmine (3–12 mg per day) or placebo and were followed up for 24 weeks and then for an open phase of a further 12 months.[139] The study had a pre-specified inclusion subgroup of patients with small vessel disease defined on the basis of a combination of clinical and neuroimaging criteria.[91] These criteria were used because the commonly used measures for vascular dementia are not sensitive in detecting cognitive impairment caused by small vessel disease. At the end of the study, the population with small vessel disease proved to make up three-quarters of the entire population, whereas only 18% had large vessel vascular dementia and another 8% had a combination of the two forms.[139] Unfortunately, only the main results relating to the entire group have been published and no analysis about the group with small vessel disease has been released.[139]

Neuroimaging as a surrogate marker in small vessel disease trials

As mentioned earlier, neuroimaging has a central role in defining small vessel disease. Additionally, the use of neuroimaging as a surrogate marker to assess treatment effects in small vessel disease, a model already in use for other white matter diseases such as multiple sclerosis, has been suggested.[140] This proposal has already been adopted in some studies. In one trial, MRI was used to assess whether a regimen of active blood pressure control was able to reduce progression of white matter lesions;[141] positive results were reported, particularly in patients with severe white matter lesions. Two other trials have investigated the effect of statins on white matter lesion progression. In one study, pravastatin treatment (40 mg daily) proved inefficacious in preventing worsening of white matter lesions.[142] In a second study, treatment with simvastatin (20 mg daily) over a period of 2 years was associated with a significant reduction in the increase of white matter lesion volumes in stroke-free individuals (total n=208) with baseline severe (but not with mild) white matter lesions in comparison with placebo.[143] Preliminary experience suggests that more sophisticated magnetic resonance techniques, such as diffusion imaging and spectroscopy, could also be implemented in future studies.[144] Although preliminary, these studies show that it is possible to use

Search strategy and selection criteria

References for this Review were identified through searches of PubMed with the search terms "small vessel disease(s)", "white matter lesions", "white matter changes", "lacunar infarcts", "subcortical vascular dementia", "vascular cognitive impairment", "neuroimaging", "pathology", and "therapy" from 1966 to January, 2010. Articles were also identified through searches of the author's own files. Only papers published in English were reviewed.

neuroimaging as a surrogate marker in clinical trials. Moreover, the data imply possible therapeutic effects of some drugs in reducing the burden of small vessel disease. The use of MRI as a surrogate marker for small vessel disease is supported by natural history data that show progression of these lesions.[145–148] Whether a reduction in white matter lesion burden is associated with a decrease in the incidence of cognitive and functional decline needs to be further tested. Given the strong association between vascular risk factors and small vessel disease, all the drugs with beneficial effects on the control of these risk factors (eg, anti-hypertensive drugs, cholesterol-lowering drugs, and anti-diabetic drugs) seem of potential interest. In one recent study, an association between low concentrations of serum vitamin B12 and white matter lesion volume was found, which suggests a potential future preventive approach.[149]

CSF biomarkers as in-vivo markers of small vessel disease

Results from preliminary studies have indicated an association between levels of structural biomarkers in the CSF and white matter lesion load in patients with small vessel disease. In a small group of 53 patients who did not have dementia, neurofilament light protein, a constituent of large myelinated axons, significantly correlated with the volume of white matter lesions, although there was no association between white matter lesions and biomarkers of Alzheimer's disease (tau and amyloid).[150] These results corroborate previous results from the same group.[151] On the basis of these data, it has been proposed that, as for Alzheimer's disease, CSF biomarkers could be used as surrogate markers for small vessel disease pathology and could be used to evaluate the course and effects of possible interventions. However, further confirmation and validation are needed.

Conclusions and future directions

Small vessel disease is an important cause of stroke, cognitive decline, and age-related disability. More attention and targeted efforts are needed to better understand the pathogenesis of vascular injury to the brain caused by small vessel disease and to thoroughly define the clinical consequences of these diseases. Given the frequent coexistence of different forms of small vessel disease (ie, white matter lesions, lacunar infarcts, and microbleeds), all relevant lesion types need to be taken into account. Furthermore, specific preventive and therapeutic measures to reduce the burden of functional loss caused by small vessel disease need to be designed. Neuroimaging could be a major tool to assess efficacy of these measures.

Conflicts of interest

I have no conflicts of interest.

Acknowledgments

I thank Jun Ogata for providing the pathological pictures in figure 1 and for useful teaching in small vessel disease pathology. I thank Julia Waldman for kind revision of the language. This paper is dedicated to the memory of Julio H Garcia (1933–1998).

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