Charidimou, A., Pantoni, L., & Love, S. (2016). The concept of sporadic cerebral small vessel disease: A road map on key definitions and current concepts. *International Journal of Stroke*, 11(1), 6-18.
<https://doi.org/10.1177/1747493015607485>

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The concept of sporadic cerebral small vessel disease: a road map on key definitions and current concepts

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Keywords: cerebral microbleeds, cerebral small vessel disease, cerebral amyloid angiopathy, intracerebral haemorrhage, antithrombotics, leukoaraiosis

Word count: 3303

Conflicts of interest: None declared

Abstract

Sporadic cerebral small vessel disease is considered to be among the most common known neuropathological processes and has an important role in stroke, cognitive impairment and functional loss in elderly persons. The term is now commonly used to describe a range of neuroimaging, neuropathological, and associated clinical features, the pathogenesis of which is largely unclear but that are thought to arise from disease affecting the perforating cerebral arterioles, capillaries, and venules. Modern neuroimaging has revolutionized our understanding of the consequences of small vessels disease on the brain parenchyma, even though small arteries, arterioles, capillaries and venules are difficult to directly visualize with current techniques used in clinical practise. In this short review we focus on histopathological and neuroimaging perspectives, basic definitions and recent advances in the field.

Introduction

Most of the modern advances and effective interventions in cerebrovascular disorders target disease of large arteries only. Until recently, small cerebral arteries have received little attention and clinicians have much less to offer for the prevention and treatment of small vessel disease (1). This is partly because small vessels are technically inaccessible to image and hard to study directly *in vivo*; hence the underlying mechanisms of small vessel disease remain relatively poorly understood (2). Yet, sporadic small vessel diseases are considered to be among the most prevalent known neurologic processes and contribute substantially to stroke, cognitive impairment, dementia and other disabilities commonly seen in the elderly (including depression, motor and gait disturbances, urinary symptoms and functional impairment) (2-4). In addition, small vessel disease can increase mortality (5, 6) and pose significant clinical dilemmas in routine practice, including antithrombotic drug use.

The current review is not intended to provide a comprehensive overview of the all manifestations of small vessel disease nor is it intended to review all the aspects related to pathology, pathophysiology, and pathogenesis. For background information the reader is directed to excellent recent comprehensive reviews on each of these topics (2, 3, 7-9), as well as reviews of each of the MRI manifestations of small vessels disease (10-13). Instead, in this short review we aim to discuss key neuropathological and neuroimaging definitions, focusing on the concept and classification of small vessel disease in the brain, and briefly to consider possible future directions for research. Throughout the paper we focus on key aspects of the two main types of sporadic small vessel disease, namely cerebral amyloid angiopathy and 'hypertensive arteriopathy'.

Small vessels in the brain

The term sporadic cerebral small vessel disease is used with various meanings in different contexts, to describe a range of neuroimaging and pathological findings, as well as associated clinical and cognitive features or syndromes. However, in its most basic form, the term encompasses a group of age-related neuropathological processes affecting the small perforating arteries, arterioles, capillaries, and rarely venules in the brain (though venules have received little attention in the literature) (1-3). Before considering these pathological processes, it is important to define what a small vessel is and specifically, 'how small a small vessel is'. Interestingly, a survey performed among leading neuropathological centres

revealed that the definition of a small vessel is not consistent: fewer than 50% of the participants agreed on a size limit of less than 500 μm in transverse diameter or all vessels located deeper than the cerebral cortex (14). The same survey also reported that the laboratory tools used and criteria for small vascular lesions were heterogeneous and could significantly influence the obtained results. However, a follow-up survey of the BrainNet Europe consortium concluded that a certain level of harmonisation had been reached (15). Others have arbitrarily suggested a transverse diameter of $\leq 300 \mu\text{m}$, predominantly referring to arterioles – reflecting that pathological processes of the arteriolar tree are better characterized than those of other types of small vessel (e.g. capillaries) (2). The current definition of small vessels is more inclusive, referring to all vascular structures (ranging from around 5 μm to 2 mm in diameter) in the brain parenchyma (i.e. intraparenchymal) or the subarachnoid space (i.e. leptomeningeal) and encompassing small arteries, arterioles, capillaries, venules and small veins (2). The small arteries and arterioles either: (a) penetrate the brain cortex superficially, supplying the grey matter with short branches ('cortical' arteries) of three lengths (reaching cortical layer III, V and the grey–white matter junction), and the subcortical white matter with longer branches ('medullary' arteries) (Fig. 1); or (b) stem from deep arterial perforators at the base of the brain and supplying the basal ganglia, thalami and brainstem structures (2, 16). Perforating arterioles show a branching pattern that resembles that of poplars rather than oak trees (3, 16, 17). Both superficial and deep perforators are end-arterioles and have very limited collateral connections with adjacent small vessels until they branch into capillaries. Although capillary beds do interconnect to a certain extent, the collateral flow is rather local and limited. This has important implications for small infarcts after perforating arteries occlusion (18). Finally, the two systems of cerebral perforators do not connect but only meet in a junctional zone around the lateral ventricles (16), where leukoaraiosis commonly occurs. Specific small vessel pathologies can differentially affect these two systems as well as different ranges of vessels within each system (see later).

The rationale for making a clear distinction between small vessels and large vessels is twofold. First, this separation highlights the fact that pathological processes affecting small vessels in the brain are to a large extent different from those that affect larger vessels. Small and large vessel disease processes can overlap and often co-exist, particularly in the elderly (e.g. hypertension-related atherosclerosis and arteriolosclerosis). This is not surprising, as the two subtypes of cerebrovascular disease tend to be driven by very similar risk factors,

not the least of which is simply aging. However, 'aging,' per se, should not be considered a cause of cerebrovascular injury, but rather a variable which probably captures multiple accumulating biological changes over time that together affect brain vessels and parenchyma. It is also important to keep in mind that large and small vessel systems form a continuum and therefore there is a dynamic interaction between large arterial changes and microvascular brain injury. For example, progressive age-associated increase in large artery stiffness exposes small vessels to higher pulse pressure which can, in turn, lead to arteriolosclerosis, progressive white matter damage and cognitive impairment (19). Yet, although subdividing cerebrovascular disease into micro-vascular (i.e. small vessel) and macro-vascular (i.e. large vessel) components represents an oversimplification, this distinction highlights the differences in the putative pathophysiology and clinical and pathological consequences of diseases affecting small and large vessels. Approximately one third of symptomatic strokes are caused by diseases of small perforating arteries and arterioles of the brain; the consequences include lacunar stroke syndromes (20) and most cases of spontaneous parenchymal brain haemorrhage (PBH)¹ - the most severe and lethal type of stroke (1). However, beyond its role in clinically overt acute stroke syndromes, small vessel disease causes widespread microvascular damage (seen on neuroimaging or at autopsy) which is not symptomatic itself but has important cumulative effects on cognition. Cerebral small vessel disease is one of the most important contributors to cognitive impairment in the elderly, contributing to up to 45% of dementias (21, 22). The substantial cognitive components of microvascular damage in the brain have been often ignored, probably overshadowed by the attention given to Alzheimer's disease, and also due to the fact that individual features of small vessel disease have not been traditionally viewed as combined components of a group of disorders. As people live longer, the burden of small vessel disease is likely to grow, becoming an increasing global healthcare challenge (23).

Neuroimaging markers of small vessel disease

Since small vessels (and hence the structural alterations of small vessel disease) cannot be visualised easily *in vivo* with the current neuroimaging techniques used in clinical practice, the brain parenchymal magnetic resonance imaging (MRI) lesions which they are thought to cause have been adopted as markers of disease involving small vessels (2). As a result, the

¹ We use this term instead of 'intracerebral haemorrhage', as it encompasses cerebellar and brain stem haemorrhages as well.

term cerebral small vessel disease is frequently used indiscriminately to describe both the underlying small vessel pathologies and the neuroimaging correlates of their effects on the brain parenchyma (2). The latter are heterogeneous, including both ischaemic and haemorrhagic manifestations - now recognised to be inter-related (2, 8, 24). Historically, the term small vessel disease has been often (and still is) used misleadingly to describe only the ischaemic consequences on imaging (3). However, sporadic small vessel disease is the leading cause of PBH, the distribution of which parallels the topography of the underlying microvascular pathology, so that spontaneous deep PBH (in the basal ganglia, internal capsule and thalami) is predominantly caused by sporadic non-amyloid microangiopathy, whereas lobar (cortical-subcortical) PBH is frequently caused by CAA. Lacunes and white matter hyperintensities (leukoaraiosis) are well known imaging markers of cerebral small vessel disease that have been extensively studied by MRI since the early 1990s (25, 26). Advances in neuroimaging now provide an unprecedented ability to investigate more complex dynamics (both haemorrhagic and non-haemorrhagic) of small vessel disease *in vivo*: new (or re-discovered) manifestations of small vessel disease visible on conventional structural MRI include cerebral microbleeds (27), cortical superficial siderosis (cSS) and convexity subarachnoid haemorrhage (7), cerebral microinfarcts at the large end of the size spectrum (28) and MRI-visible enlarged perivascular spaces (29) (Fig. 2). Accumulating evidence shows that there are also pathological changes associated with small vessel disease which are detectable by advanced (e.g., diffusion tensor imaging, magnetisation transfer ratio etc.) or high-field MRI. These include tissue changes in white matter areas appearing normal on post-mortem MRI (including altered white matter integrity, altered myelination, disrupted axonal connections, increased brain water content), secondary focal thinning of the cortical grey matter (30) and cortical microinfarcts (Fig. 3) (31). Although 'invisible' on conventional clinical MRI these small vessel disease-associated changes may contribute substantially to abnormalities of clinical function (24).

Exactly how intrinsic small vessel disease processes result in brain parenchymal injury (including the manifestations visible on MRI) and how small vessel disease lesions contribute to neurological or cognitive symptoms, are largely unknown. A useful concept to bear in mind when approaching neuroimaging markers of small vessel disease (and hence markers of pathologic consequences on the brain parenchyma), is that their pathogenic mechanisms are probably not uniform, and any given marker may be found in different types of small vessel disease (24). For example, in view of different topographical distribution of sporadic non-

amyloid microangiopathy and CAA, it is hypothesized that cerebral microbleeds have a preferential location depending on the underlying small vessel pathology: sporadic non-amyloid microangiopathy is commonly associated with cerebral microbleeds in deep brain regions (e.g. basal ganglia, thalamus and brainstem), whereas CAA is characterised by cerebral microbleeds in a lobar distribution (cortical-subcortical).(27) Hence, each marker or lesion on neuroimaging has to be interpreted in the context of other information, including the specific clinical scenario.

Neuroimaging standards for research into small vessel disease

Advances in neuroimaging were recently illustrated in an international working group position paper from the Centres of Excellence in Neurodegeneration under the acronym STAndards for ReportIng Vascular changes on nEuroimaging (STRIVE v1) (10). This consensus paper presents a unified approach (including common language and minimum standards for imaging acquisition and analysis) to small vessel disease as a neuroimaging-defined concept, which is changing rapidly paralleling the continued advances in neuroimaging techniques. Table 1 provides an overview of the six small vessel disease lesions included in the STRIVE paper (10). The inclusion of brain atrophy “not related to a specific macroscopic focal injury such as trauma or infarction” as another imaging manifestation of small vessel disease represents a significant change in thinking in the field and highlights the cross-talk between small vessel disease, neurodegeneration and cognitive impairment (32, 33). A second advance in the field is the expansion of the spectrum of neuroimaging manifestations to include enlarged perivascular spaces; although they have been known pathologically for many years, enlarged perivascular spaces visible on MRI have received little attention and indeed have been considered normal or unimportant. Only recently has evidence begun to emerge that enlarged perivascular spaces are a potential neuroimaging marker of small vessel disease. This is particularly interesting in view of the growing published work on perivascular fluid drainage impairment and the development of cerebral amyloid angiopathy.

Neuropathological aspects of the two main types of sporadic small vessel disease

Sporadic of small vessel disease is typically – and somewhat arbitrary – categorised in two main forms. The first is sporadic CAA, a chronic degenerative disease characterised by

progressive deposition of amyloid- β (A β) in the media and adventitia of small arteries, arterioles and sometimes capillaries in the cerebral cortex, and small arteries, arterioles and sometimes venules in the overlying leptomeninges (Fig. 4); the cerebellum may also be involved, although usually to a much lesser extent (7, 34-36). The vessels affected by amyloid- β can show secondary vasculopathic changes, such as fibrinoid necrosis, loss of smooth muscle cells, wall thickening, microaneurysm formation, and perivascular blood breakdown products deposition (37). CAA-related vasculopathy is thought to predispose to the vascular occlusion or rupture that cause ischaemic or haemorrhagic parenchymal brain injury – for a comprehensive summary of the topic, see (8). However, some of the ischaemic brain lesions caused by CAA are not currently visible on conventional MRI (e.g. microinfarcts, or microstructural alterations) and hence their prevalence and significance in CAA have long been underestimated (8). The extent of direct contribution of CAA to ischaemic stroke syndromes is currently uncertain, but the presence of multiple lobar microbleeds (a marker of the disease) can affect treatment decisions in ischaemic stroke, e.g. regarding antithrombotic drug use (38, 39). Similar to the modern concept of cerebral small vessel disease, the term CAA now encompasses not only a specific cerebrovascular pathological trait and disorder, but also a clinical syndrome and brain parenchymal lesions seen on neuroimaging (including a set of diagnostic imaging criteria – the Boston criteria (Table 2) (40, 41).

Some of these ischemic lesions are not visible magnetic resonance imaging (MRI), and their prevalence in CAA has therefore long been underestimated.¹⁰

In contrast to CAA which is specific and relatively easy to define, the more common form of sporadic small vessel disease is less specific and more difficult to define. The term ‘hypertensive arteriopathy’ is widely used to describe non-amyloid, degenerative alterations in the vessel wall, often related to advanced age (but not clearly age-driven), hypertension, diabetes mellitus, cigarette smoking and other common vascular risk factors, and typically affecting the small perforating end-arteries of the deep grey nuclei and deep white matter (2). It is characterised pathologically by collagenous thickening of the vessel wall with narrowing of the lumen and progressive loss of smooth muscle, and sometimes by exudation of fibrin and other serum proteins or by scanty mural deposition of lipid (Fig. 5); pathological descriptors/subtypes include arteriolosclerosis, fibrinoid necrosis and lipohyalinosis. These alterations to the vessel wall are often associated with enlargement of

the surrounding perivascular spaces (Fig. 5A-C), and sometimes with microinfarction (Fig. 5D), thrombosis (Fig. 6A) or microhaemorrhage (Fig. 6B). This very common sporadic form of small vessel disease has been variously termed arteriolosclerosis, age-related or vascular risk-factor-related small vessel disease, or degenerative microangiopathy in the literature (2, 42, 43).

The term 'hypertensive arteriopathy' is misleading as it groups together a variety of sporadic small vessel disease pathologies not accounted by sporadic CAA but not necessarily (or even often) related specifically to hypertension (44), although hypertension can influence their evolution. The focus on hypertension perhaps diverts attention from the study of other possible factors involved in the initiation and progression of sporadic non-amyloid small vessel disease. Furthermore, there is not a consensus on the microscopic characterisation of small vessel changes of 'hypertensive arteriopathy', so that its severity is difficult to evaluate in any given case. From a histopathologic perspective, the cerebral microvascular changes associated with hypertension are largely identical to those of other sporadic non-amyloid, degenerative alterations in the vessel wall (i.e. fibrocollagenous thickening and hyalinization, narrowing of the lumen and loss of smooth muscle cells from the tunica media). Other possible pathological features can include distal manifestations of atherosclerosis (microatheroma, see Fig. 6C) and 'microaneurysms' (i.e. elongated and tortuous or dilated vessels) (2). Some researchers have subdivided 'hypertensive arteriopathy' according to the most pronounced structural histopathological abnormalities, e.g. distal atherosclerosis, arteriolosclerosis, lipohyalinosis ('mural disease'), fibrinoid necrosis, microaneurysms. (2). These subtypes have a predilection for microvessels of slightly different size and distribution and can exist separately or in various combinations (Fig. 7). Of these histopathological features, the one most specifically associated with hypertension is fibrinoid necrosis, which is more common in hypertensive patients' brains than in those without hypertension (45-47), and is often found in arterioles adjacent to deep PBH (46-50). It is worth noting that the more effective treatments for hypertension in recent years are likely to have modified the specific pathological features, natural history and disease spectrum of hypertensive arteriopathy (44).

Despite the limitations in definitions and given the lack of an alternative widely accepted term, for simplicity and consistency, the term 'hypertensive arteriopathy' is usually adopted in recent literature as one of convenience to avoid unnecessarily long and complex terms

being repeated. We suggest the alternative umbrella term 'sporadic non-amyloid microangiopathy' as being more accurate. Whatever term one prefers for this small vessel disease type, the pathological changes associated with sporadic non-amyloid microangiopathy presumably impair functional autoregulation (the adjustment of vascular calibre to match blood flow to local metabolic demand) and maximal perfusion; the drainage of interstitial fluid along the vessel wall and the transport of solutes across it (51); and the compliance and tensile strength of the vessels. Not surprisingly, sporadic non-amyloid microangiopathy has historically been associated with leukoencephalopathy (52), enlarged perivascular spaces (53, 54), lacunar infarcts (55) and intracerebral haemorrhage (56). Table 3 summarises and compares the most salient pathological and neuroimaging characteristics of the two major sporadic small vessel disease processes, which might manifest separately or in various combinations.

Future perspectives

Although cerebral small vessel disease is emerging as a neuroimaging-defined concept, future studies should aim to provide stronger support and further insights on putative MRI biomarkers from histopathological-imaging correlations. For example, from the perspective of a neuropathologist, evidence from autopsy studies to indicate that signal changes seen on imaging and defined as enlarged perivascular spaces actually represent pathological expansion of these spaces is still very limited (57, 58). Also, the literature on histopathological-neuroimaging correlations of cerebral microbleeds is currently limited to fewer than 20 cases (59). More direct correlation studies between neuroimaging manifestations of small vessel disease and underlying pathology-morphology are needed if these are to be assessed as reliable biomarkers.

A natural next step is to try to combine these different manifestations of small vessel disease on structural imaging, to gauge total brain small vessel disease severity. Recently, the approach of assessing total MRI small vessel disease burden into a score has been developed and validated in patients at high risk for ischaemic small vessel damage, including lacunar or non-disabling cortical stroke (60-62). This comprehensive framework should also be evaluated in other types of small vessel disease (60) and in different clinical cohorts, as it has potential advantages over individual markers. A total MRI small vessel disease score may better stratify the impact of microangiopathy-related damage on clinical outcomes (such as

disability and cognition) and ultimately be used as a composite endpoint in clinical trials (63). In parallel, studies have suggested neuropathology-based staging schemes to assess the spectrum of cerebral small vessel disease (including CAA) in aging brains (64-66), and the use of adjunctive biochemical techniques that can be applied to post-mortem brain tissue to quantify ante-mortem perfusion, microvessel density, blood-brain barrier function and tissue damage (67-71).

Another key area of need is the identification of neuroimaging biomarker dynamic progression over time and determination as to whether this captures clinically relevant changes. Further progress in molecular imaging of small vessel disease may allow the direct quantification of the vessel pathology in vivo: the detection of vascular amyloid by PET scanning with the amyloid radioligand CII-labelled Pittsburgh Compound B (PiB-PET) has revolutionised the field (72-74), but no similar methods have yet emerged to measure sporadic non-amyloid microangiopathy pathology. Finally, a combined neuroimaging, molecular imaging and histopathological approach can provide insights into potential (endo-)phenotypes of small vessel disease (75), with implications for treatment. Despite recent advances in sporadic cerebral small vessel disease processes, many pathophysiological and clinical aspects remain unknown, prevention and treatment is still mostly empirical (2) – and probably suboptimum or even dangerous (76) – while specific disease-modification is not currently available.

Acknowledgement:

Dr Andreas Charidimou thanks Dr David Werring and Prof Rolf Jager for their comments on an early/preliminary version of the manuscript. The illustrations of pathology are from brains submitted to the South West Dementia Brain Bank, supported by BRACE (Bristol Research into Alzheimer's and Care of the Elderly), Brains for Dementia Research and the Medical Research Council. Special thanks to Susanne van Veluw and Dr. Geert Jan Biessels for kindly providing the microinfarcts images on behalf of the Utrecht Vascular Cognitive Impairment Study group, Utrecht, the Netherlands.

Box: 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”, “cerebral amyloid angioapthy” and “cerebral microbleeds” from 1990 to 2015. Articles were also identified through searches of the authors’ own files. The final list of references was decided based on their relevance to the themes covered in this review.

Tables

Table 1. Neuroimaging manifestations of small vessel disease included in STRIVE v1 and a consensus paper on cortical superficial siderosis(12), along with their proposed terms and definitions (10).

- **Recent small subcortical infarct:** Neuroimaging evidence of recent infarction in the territory of one perforating arteriole, with imaging features or clinical symptoms consistent with a lesion occurring in the previous few weeks.
 - **Lacune of presumed vascular origin:** A round or ovoid, subcortical, fluid-filled cavity (signal similar to CSF) of between 3 mm and about 15 mm in diameter, consistent with a previous acute small subcortical infarct or haemorrhage in the territory of one perforating arteriole.
 - **White matter hyperintensity of presumed vascular origin:** Signal abnormality of variable size in the white matter that shows the following characteristics: hyperintensity on T2-weighted images such as fluid-attenuated inversion recovery, without cavitation (signal different from CSF). Lesions in the subcortical grey matter or brainstem are not included in this category unless explicitly stated. If deep grey matter and brainstem hyperintensities are also included, the collective term should be subcortical hyperintensities.
 - **Perivascular spaces:** Fluid-filled spaces that follow the typical course of a vessel as it goes through grey or white matter. The spaces have signal intensity similar to CSF on all sequences. Because they follow the course of penetrating vessels, they appear linear when imaged parallel to the course of the vessel, and round or ovoid, with a diameter generally smaller than 3 mm, when imaged perpendicular to the course of the vessel.
 - **Cerebral microbleed:** Small (generally 2–5 mm in diameter, but sometimes up to 10 mm) areas of signal void with associated blooming seen on T2*-weighted MRI or other sequences that are sensitive to susceptibility effects.
 - **Brain atrophy:** Reduced brain volume that is not related to a specific macroscopic focal injury such as trauma or infarction. Thus, infarction is not included in this measure unless explicitly stated.
-
- **Cortical superficial siderosis (cSS) and acute convexity subarachnoid haemorrhage:** Well-defined, homogeneous hypointense curvilinear signal intensity (black) on T2*-GRE or SWI MRI in the superficial layers of the cerebral cortex, within the subarachnoid space, or both. If there is corresponding signal hyperintensity in the subarachnoid space on proton density-weighted or FLAIR sequences (or hyperdense on CT if available) the term 'acute cSAH' is recommended.

Table 2. Boston diagnostic criteria for sporadic cerebral amyloid angiopathy.
(*Modifications compared to the classic Boston criteria based on Linn et al(41))

<p>1. Definite CAA</p> <p>Full post-mortem examination demonstrating:</p> <ul style="list-style-type: none"> • Lobar, cortical, or cortical-subcortical haemorrhage • Severe CAA with vasculopathy • Absence of other diagnostic lesion
<p>2. Probable CAA with supporting pathology</p> <p>Clinical data and pathologic tissue (evacuated haematoma or cortical biopsy) demonstrating:</p> <ul style="list-style-type: none"> • Lobar, cortical, or cortical-subcortical haemorrhage • Some degree of CAA in specimen • Absence of other diagnostic lesion
<p>3. Probable CAA</p> <p>Clinical data and MRI or CT demonstrating:</p> <ul style="list-style-type: none"> • Multiple haemorrhages restricted to lobar, cortical, or cortical-subcortical regions (cerebellar haemorrhage allowed) <p><i>*[OR single lobar, cortical, or cortical-subcortical haemorrhage and focal^b or disseminated^c superficial siderosis]</i></p> <ul style="list-style-type: none"> • Age ≥55 years • Absence of other cause of haemorrhage^a
<p>4. Possible CAA</p> <p>Clinical data and MRI or CT demonstrating:</p> <ul style="list-style-type: none"> • Single lobar, cortical, or cortical-subcortical haemorrhage <p><i>*[OR focal^b or disseminated^c superficial siderosis]</i></p> <ul style="list-style-type: none"> • Age ≥55 years • Absence of other cause of haemorrhage^l

^a **Other causes of haemorrhage (differential diagnosis of lobar haemorrhages):** antecedent head trauma, haemorrhagic transformation of an ischemic stroke, arteriovenous malformation, haemorrhagic tumour, warfarin therapy with international normalisation ratio > 3, vasculitis

^b **Focal siderosis: siderosis restricted to 3 or fewer sulci.**

^c **Disseminated siderosis: siderosis affecting at least 4 sulci**

Table 3. Predominant neuropathological, clinical and neuroimaging characteristics of the two major sporadic cerebral small vessel disease subtypes: cerebral amyloid angiopathy and ‘hypertensive arteriopathy’

Characteristics	Cerebral amyloid angiopathy	Sporadic non-amyloid microangiopathy ('hypertensive arteriopathy')
Small vessel pathology	Amyloid- β deposition and associated vasculopathy in cortical and leptomeningeal vessels	A range of different features, e.g. arteriosclerosis, fibrinoid necrosis, mural damage etc.
Intracerebral haemorrhage	Lobar (cortical-subcortical), cerebellar?	Typically deep: basal ganglia, thalamus, pons cerebellum; sometimes lobar
Ischaemic stroke	Not typically associated with lacunes Uncertain role other than affecting treatment decisions, e.g. antithrombotic drugs, thrombolysis etc.	Lacunar syndromes
Other clinical syndromes	Transient focal neurological episodes ('amyloid spells'), cognitive impairment and dementia, inflammatory CAA	Vascular cognitive impairment and dementia
Cerebral microbleeds	Lobar	Deep
Cortical superficial siderosis	Very common: ~40% in symptomatic CAA	Rare: <5%
MRI-visible perivascular spaces	Centrum semiovale (i.e. cerebral white matter)	Basal ganglia
White matter hyperintensities	Posterior predominance	No predilection for brain region

Figures

Fig. 1. Schematic representation of penetrating vessel patterns in the cortex. A. Short (S) penetrating arterioles ('cortical') reaching three different depths in the cortex (i.e. cortical layer III, V and the grey–white matter junction, S1-3 respectively), while long penetrators ('medullary') continue into the subcortical white matter.

Fig. 2. Key ischaemic (or non-haemorrhagic) and haemorrhagic imaging features of sporadic small vessel disease visible on conventional structural MRI at 1.5T or 3T. (A) Diffusion-weighted image of an acute small subcortical infarct. (B) A lacune on coronal FLAIR imaging, i.e. a CSF-containing cavity, between 3mm to 1.5cm diameter, in deep grey matter. Note the marked associated cortical atrophy (including the temporal lobe) in this patient. (C) Confluent white matter hyperintensities on FLAIR imaging. (D) MRI-visible perivascular spaces in cerebral white matter (i.e. centrum semiovale) on axial T2-weighted imaging, an associated neuroimaging feature of cerebral amyloid angiopathy in the appropriate clinical context. They are small (generally less than 3mm in diameter) hyperintense lesions containing CSF-like fluid, round or linear in shape, depending on their direction and the section plane. (E) Multiple strictly lobar microbleeds in a patient with probable cerebral amyloid angiopathy. Axial susceptibility-weighted imaging. (F) Axial FLAIR depicting cortical brain atrophy not related to specific macroscopic focal injury (e.g. trauma, infarction etc.), but only with white matter hyperintensities in an old patient. (G) Cortical superficial siderosis on susceptibility-weighted imaging in a patient with a lobar intracerebral haemorrhage fulfilling the criteria for probable cerebral amyloid angiopathy.

Fig. 3. Cerebral microinfarcts. Top panel: ex vivo images of a brain slice showing a lesion with the signal characteristics of a cortical microinfarct on 7T T1 (A) and T2 (B) MRI sequences, verified on histopathological examination (right panel, haematoxylin-eosin staining and immunostaining for glial fibrillary acidic protein-GFAP). Lower panel: *in vivo* images on 7T FLAIR (C1), 7T T1 (C2), and a 3T T1 (C3) scan showing a probable cortical microinfarct, in the same subject. Compared to microinfarcts seen pathologically these MRI-defined lesions probably are at the large end of the size spectrum. (Images are courtesy of Susanne van Veluw and Dr. Geert Jan Biessels on behalf of the Utrecht Vascular Cognitive Impairment Study group, Utrecht, the Netherlands)

Fig. 4. Microvascular alterations in cerebral amyloid angiopathy (CAA). **(A)** Concentric splitting (arrows) of the walls of arterioles in the leptomeninges. Also note the deeply eosinophilic staining of the walls, typical of CAA. **(B)** A section from the same region of temporal lobe immunolabelled for $A\beta$. Amyloid in the vessel walls is strongly immunopositive (brown), as are plaques in the adjacent cortex. The arrow indicates a leptomeningeal arteriole with splitting of the vessel wall. **(C)** Immunohistochemical demonstration of $A\beta$ in the walls of several capillaries (arrowheads) in the deep frontal cortex.

Fig. 5. Pathological findings in 'hypertensive arteriopathy' (sporadic non-amyloid microangiopathy). **(A)** Section through the putamen, showing moderate enlargement of perivascular spaces (asterisks) and a deeply eosinophilic fibrinoid exudate within the wall of an arteriole (arrow). **(B)** Perivascular spaces (asterisks) are also enlarged in the subcortical white matter, and there is collagenous thickening of the walls of arterioles (arrow). **(C)** This arteriole in the putamen shows a combination of changes: collagenous thickening, exudation of fibrinoid material and accumulation of lipid droplets within cells (arrowheads) in the vessel wall. **(D)** Focus of putaminal infarction (arrow) within which are sheets of macrophages, a few containing haemosiderin. Lipid-laden macrophages (arrowheads) are also present in the wall of an adjacent arteriole, which has a markedly thickened wall and narrowed lumen.

Fig. 6. Microvascular alterations in 'hypertensive arteriopathy'. **(A)** Fibrin thrombus within an arteriole in the base of the pons. **(B)** Focal microhaemorrhage, with central accumulation of orange-yellow haematoidin and surrounding haemosiderin-laden macrophages. **(C)** Microatheroma within an arteriole in the putamen.

Fig. 7. Suggested schematic illustration of the hypothetical relationship between vessel diameter, distribution and predilection to different types of pathological process affecting cerebral small vessels. The size bar in the upper plot represents a logarithmic scale of the vessel diameter range of arteries, arterioles and capillaries.* The schematic representation of a perforating arteriole on the top of the scale, again shows a typical branching pattern (3, 16, 17). Note that 1mm (dotted line in the scale bar) is also the limit of vessels visualization in conventional angiography. The range of vessels involved in sporadic cerebral amyloid

angiopathy is indicated by the dark green bar, and the different types and vascular involvement in light yellow bars. The range of vessels and the main characteristics of the four predominant subtypes under the umbrella term sporadic non-amyloid microangiopathy (dark red bar) is shown in light red bars.

(* As suggested by Brandner S. Histopathology of cerebral microbleeds. In: Werring DJ, ed. Cerebral Microbleeds: Pathophysiology to Clinical Practice. Cambridge, England: Cambridge University Press, 2011: 49-64, Modified and revised with permission)

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