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Heterogeneity of small vessel disease: a systematic review of MRI and histopathology correlations

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Abstract

Background: White matter hyperintensities (WMH), lacunes and microbleeds are regarded as typical MRI expressions of cerebral small vessel disease (SVD) and they are highly prevalent in the elderly. However, clinical expression of MRI-defined SVD is generally moderate and heterogeneous. By reviewing studies that directly correlated postmortem MRI and histopathology, this paper aimed to characterize the pathological substrates of SVD in order to create more understanding as to its heterogeneous clinical manifestation.

Summary: Postmortem studies showed that WMH is also heterogeneous in terms of histopathology. Damage to the tissue ranges from slight disentanglement of the matrix to varying degrees of myelin and axonal loss. Glial cell responses include astrocytic reactions, e.g. astrogliosis and clasmatodendrosis, as well as loss of oligodendrocytes and distinct microglial responses. Lipohyalinosis, arteriosclerosis, vessel wall leakage and collagen deposition in venular walls are recognized microvascular changes. Suggested pathogenetic mechanisms are ischemia/hypoxia, hypoperfusion due to altered cerebrovascular autoregulation, blood-brain barrier leakage, inflammation, degeneration and amyloid angiopathy. Only a few postmortem MRI studies have addressed lacunes and microbleeds so far. Cortical microinfarcts and changes in the normal appearing white matter are ‘invisible’ on conventional MRI, but are nevertheless expected to contribute substantially to clinical symptoms.

Conclusion: Pathological substrates of WMH are heterogeneous in nature and severity, which may partly explain the weak clinoradiological associations found in SVD. Lacunes and microbleeds have been relatively understudied and need to be further investigated. Future studies should also take into account ‘MRI-invisible’ SVD features and consider the use of e.g. quantitative MRI techniques, to increase the sensitivity of MRI for these abnormalities and study their effect on clinical functioning.

Background

MRI and clinical expression of small vessel disease

White matter hyperintensities (WMH), lacunes, and microbleeds are regarded as MRI expressions of small vessel disease (SVD) and are commonly found on brain MRI of elderly subjects. WMH are visible as hyperintense areas on T2-weighted MRI scans (including FLAIR), while lacunes are identified on MRI as small cavities with a diameter of 3mm to 10-15mm, and signal intensities comparable to cerebrospinal fluid. Lacunes are located in the white matter (WM) or subcortical gray matter and often have a surrounding hyperintense halo. Microbleeds are small, round, hypointense foci on gradient-echo T2*-weighted MRI, and are mostly located in the basal ganglia or cortical-subcortical areas.^{1,2} Examples of these abnormalities are given in Figure 1. Unfortunately, definition and quantification of these MRI expressions of SVD vary between studies. This warrants a standardization of SVD rating on MRI, as the extrapolation of results from different studies to more general conclusions may be severely hampered otherwise.

In non-demented elderly subjects, WMH, lacunes and microbleeds have been associated with cognitive decline, including reduced mental speed and impaired executive functions.³⁻⁷ WMH have also been related to other potentially disabling symptoms, such as gait disturbances, depression and urinary incontinence.⁸⁻¹¹ SVD is even more common in subjects with AD, and it might interact with the neurodegenerative changes in AD and with their effect on cognitive decline.^{12,13}

Thus, SVD probably contributes significantly to clinical disability in the elderly. As it can potentially be treated or prevented, increased insight in underlying pathological mechanisms of SVD is of paramount importance.

The value of postmortem MRI studies

The association between SVD features on MRI and clinical symptoms is modest. An explanation for this may be heterogeneity of the neuropathological substrates underlying SVD. T2-weighted MRI dichotomizes the white matter as 'hyperintense' (WMH) or 'normal', whereas the hyperintense areas may reflect pathological tissue changes that vary in type and severity. It further reveals the presence of lacunes and microbleeds, but it has been suggested that expressions of SVD that are not readily

detectable on conventional MRI, i.e., cortical microinfarcts and tissue changes in the normal appearing white matter (NAWM), may play an even more important clinical role in terms of clinical symptomatology (Figure 2). These abnormalities can now only be revealed post mortem.¹⁴

To better understand the pathological changes involved in SVD, postmortem MRI scanning and direct correlation with pathology is a valuable tool, as it bridges the gap between MRI findings and clinical studies.^{15;16} As it has been shown for other neurological diseases, such as multiple sclerosis,^{15;17} postmortem MRI-histopathology correlation studies may help to solve the weak clinical-radiological associations in SVD.

Aim

This paper aimed to investigate the published pathological substrates of WMH and other features of SVD, by comprehensively reviewing studies that have directly compared postmortem MRI and histopathology. Another aim was to pinpoint the gaps in our knowledge and provide the readership with suggestions for further studies, which will hopefully contribute to the development of future treatment options for demented and non-demented elderly suffering from SVD.

A small proportion of patients with SVD features on their MRI suffer from genetic disorders such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) or hereditary cerebral amyloid angiopathy (CAA). These diseases have a distinct etiology, and we will only focus on SVD that is observed in 'normal' aging and AD here.

Method (search strategy)

We have systematically searched PubMed for scientific reports correlating postmortem MRI and histopathological assessment of WMH, lacunes and microbleeds until December 2009. The following search terms were used: postmortem, MRI, magnetic resonance, white matter (hyperintensities/lesion[s]), lacune(s), lacunar infarct(ion), microbleed(s).

White matter hyperintensities (WMH)

Studies having correlated postmortem MRI to histopathology of WMH are summarized in Table 1. These studies confirmed in-vivo studies, stating that WMH are highly prevalent (94%) in elderly populations¹⁸. The first studies are small and descriptive. However, subsequent studies have specified WMH by distinguishing PVL versus DWMH and the extent of DWMH.

Box: Sensitivity and specificity of postmortem MRI

All studies identified by the abovementioned search criteria have used formalin-fixed brain specimens. Fixation duration and time to autopsy influence the reliability of postmortem MRI measurements. It has been shown that tissue fixation decreases both T1- and T2-relaxation times in both gray and white matter.^{19;20}

Early descriptive studies have claimed that postmortem MRI of 0.25T to 1.5T can already visualize WMH with sufficient image quality.^{16;21;22} However, the sensitivity of postmortem MRI does appear to be dependent on the size of WMH. Smaller punctate WMH, thought to have little clinical impact, can be less clearly visible on postmortem MRI.²³⁻²⁵ A sensitivity of 95% (range: 87-99%) and specificity of 71% (range: 44-90%) was found for PVL on postmortem T2-weighted post mortem MRI, which could be directly compared to myelin loss in Luxol Fast-Blue stainings. For DWMH, the sensitivity was 86% (range: 79-93%) and specificity was 80% (range: 72-88%).^{24;26} Overall, postmortem MRI was considered a valuable technique for translating pathological findings to the clinical setting.

Descriptive MRI and histopathology studies

Using direct post mortem MRI and histopathology correlations, a plethora of histopathological alterations in WMH was described in several studies, including studies with AD patients, patients with cortical infarctions and with Binswanger's disease. WMH was shown to reflect partial loss of myelin, axons and oligodendroglial cells, astrogliosis, dilatation of perivascular spaces, activated macrophages and fibrohyalinotic vessel changes.^{16;21;22;27} This range of tissue changes was suggested to be

collectively suggestive of incomplete infarcts. Also, complete deep white matter infarcts were found, mostly in WMH with arteriolosclerotic vessel changes.^{16;27;28}

Distinct types of WMH

In clinical studies using in vivo MRI, an attempt to improve specificity for WMH was made by distinguishing between periventricular WMH (thin hyperintense line, smooth halo or irregular bands / caps) and WMH in the deep WM (punctate, early confluent and confluent WMH).²⁹ Postmortem MRI and histopathology correlation studies have described that each type of WMH reflects distinct pathological changes.^{23;30-33}

Mild periventricular WMH presents with discontinuity of the ependyma, mild-moderate gliosis in the subependymal layer, loosening of the fibre network and myelin loss around so-called 'tortuous venules' and dilated perivascular spaces. No arteriolosclerotic vessel changes were found in these regions.^{23;34} Irregular PVL was shown to correspond to more severe, partly confluent, areas with varying fibre and myelin loss and reactive gliosis. Some complete infarcts were seen in irregular PVL regions, in combination with fibrohyalinotic and arteriosclerotic vessels.

Punctate, early confluent and confluent WMH in the deep WM were found to be associated with increasing severity of tissue changes. In punctate DWMH, tissue changes were generally mild and confined to the area around dilated perivascular spaces with myelin loss and atrophic neuropil around fibrohyalinotic arterioles. In early confluent DWMH, perivascular rarefaction of myelin was accompanied by varying degrees of axonal loss and astrogliosis. In confluent DWMH, diffuse areas of incomplete parenchymal destruction were observed, together with loss of myelin, axons and oligodendrocytes, astrogliosis, spongiosis and focal transitions to complete infarcts.^{23;26;30-32;35} Examples of pathological samples with periventricular and deep WMH, defined on postmortem MRI, are shown in Figure 3.

The above described studies imply that smooth periventricular WMH and punctate WMH are mild forms of WMH and may therefore not be clinically relevant or even detectable.³⁵ Irregular periventricular WMH and confluent DWMH, however, correspond to more severe tissue changes, probably of ischemic origin, and are more likely to produce clinical symptoms.^{28;30;31;35} Of note is the

dependence on subject selection: in the relatively healthy NUN-study cohort, evidence of ischemia was not found in extensive DWMH.³⁴

Pathogenetic mechanisms underlying WMH

Recently, several studies further assessed possible pathogenetic mechanisms of WMH by quantitative assessment of immunohistochemical stainings. These studies include important work on the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS) cohort that prospectively collects unselected brain specimens from a large community-based cohort.³⁶

First, the role of hypoxia in the pathogenesis of WMH was investigated using specific markers for vascular morphology and tissue hypoxia.³⁷ Thicker vessel walls and larger perivascular spaces were found in WMH. In DWMH specifically, capillary endothelial cells were found to be activated and an increased expression of several hypoxia markers was observed. Other studies on characterization of afferent vessels showed arteriolar tortuosity and decreased vessel densities in WMH.^{38;39} These findings support an ischemic pathogenesis of WMH, especially in DWMH.

Second, blood-brain barrier dysfunction was demonstrated in a proportion of WMH.^{28;40} This was shown by the presence of swollen, eosinophilic, GFAP-positive astrocytes in both DWMH and PVL.⁴¹ These clasmatodendritic astrocytes stained positively for serum fibrinogen implying leakage of the blood-brain barrier.⁴² Furthermore, vascular integrity (as determined by CD31 staining) and P-glycoprotein, an important constituent of the blood-brain barrier, were decreased in WMH.⁴³ Concentric collagen deposition in venular walls may cause intramural thickening, stenosis and eventually venous insufficiency. Venous collagenosis then induces ischemic stress and may cause dysfunction of the blood-brain barrier.^{39;41}

Third, the role of microglial cells in the pathogenesis of WMH was investigated.⁴⁴ Microglial cells in PVL showed a greater tendency to be immunologically activated than DWMH, as shown by the expression of MHC class II. DWMH contained microglial cells with an amoeboid morphology, which were less immune-activated but were likely involved in the phagocytosis of myelin breakdown products. Alternative pathogenetic mechanisms of WMH included altered cerebral blood flow

autoregulation, axonal depletion from Wallerian degeneration or toxic effects of amyloid on vascular permeability in AD patients.⁴⁵

These findings have illustrated that MRI-visible WMH are associated with various underlying pathological features and (patho)biological responses in the MRC CFAS cohort.⁴⁶ This cohort, however, consists of a heterogeneous community-based group of subjects, including healthy elderly, AD patients and subjects with other neurological disorders. The large heterogeneity encountered in this group may therefore be partly artificial and WMH may be pathologically distinct for patient (and control) groups.⁴⁰

WMH in AD patients

MRI expressions of SVD are more prevalent in patients with Alzheimer's disease than in non-demented elderly.¹² In addition to the prototypical neuropathological characteristics of AD, i.e. amyloid plaques and neurofibrillary tangles, cerebrovascular pathology is also more frequently observed in AD compared to the general elderly population.^{36;47} The impact of cerebrovascular pathology on cognitive decline in AD patients remains to be established. For WMH, some studies have suggested a synergistic effect with common AD pathology on cognitive decline,^{13;48} whereas others have not found a distinct role for WMH in AD.⁴⁹

Although WMH was found to be more extensive in AD patients than in controls, the nature of pathological correlates, including vascular morphological changes and specific markers for hypoxia were comparable between these groups.^{37;50;51} An exception is microglial activation, which was specific for WMH in AD patients.⁵² The severity of tissue changes, however, differed with more severe loss of myelinated axons, ependyma denudation, gliosis and thicker adventitia of the deep white matter arteries in AD patients.^{50;51} In vascular dementia (VaD) patients, the histopathological profile of WMH was comparable to that of AD patients.⁵³ This generally comparable pathology suggests that WMH associated with aging, AD and VaD does not have a distinct pathogenesis, but instead may be part of a pathological continuum.³⁷

A specific pathology possibly linking SVD and AD is CAA.^{54;55} CAA is characterized by amyloid deposition in the smooth muscle cells of cortical, subcortical, and leptomeningeal small

arteries and arterioles.^{32;56} Patients with CAA can present with intracerebral hemorrhage, transient neurologic events and cognitive decline.⁵⁶ In CAA patients, the severity of CAA was found to be associated with WMH severity,⁵⁴ possibly due to global vascular dysfunction, which includes the vasculature in the white matter.⁵⁴ In AD, some studies have found weak correlations between WMH and CAA in AD,^{37;57;58} whereas other studies failed to find any correlations.^{27;28;47;50}

Other expressions of SVD

Lacunes

In pathological terms a 'lacune' corresponds to small (lacunar) infarcts, dilated perivascular spaces or old, small hemorrhages.^{59;60} However, the term 'lacune' in MRI studies is generally used for a lacunar infarct. These are focal cerebrospinal fluid-filled cavities, often surrounded by a hyperintense rim on FLAIR images. Lacunes are typically located in the areas supplied by the deep thalamoperforant, lenticulostriate, or pontine paramedian arterioles, i.e. basal ganglia, thalamus, internal capsule, pons and centrum semiovale.^{61;62}

The few postmortem MRI studies that have focused on lacunes are summarized in Table 2. On histological examination, MRI-defined lacunes were found to correspond to irregular cavitations with scattered fat-laden macrophages, which can be accompanied by surrounding reactive gliosis and myelin and axonal loss.^{22;60;63;64} With increasing age of the lacune, the density of macrophages diminishes and gliosis becomes more fibrillary.⁶⁴ A subtype of lacunes may be seen that is not yet cavitated, but shows selective neuronal loss with relative preservation of glial elements.⁶⁵

Several postmortem MRI studies have compared lacunes to dilated perivascular (Virchow-Robin) spaces, as these structures appear similar on MRI, which generally hinders a clear distinction.^{21;30;32} The clinical relevance of enlarged perivascular spaces, if any, is not yet fully elucidated. In general, enlarged perivascular spaces are considered to be asymptomatic, but a relation with SVD may exist. A discriminating feature between lacunes and enlarged perivascular spaces may be that lacunes are commonly larger (>3 mm), and can be accompanied by perifocal signal changes.^{66;67} Focal cavities in the anterior perforated substance and the lower part of the basal ganglia / putamen have been reported to generally refer to perivascular spaces rather than to lacunes.⁶⁸⁻⁷⁰

The most frequently reported cause of lacunes is acute arteriolar occlusion by arteriosclerosis/thrombosis, but the existence of non-cavitated lacunes and the relationship with WMH suggest that there may be other pathogenetic mechanisms with a more gradual development.^{59;65;71-75} Possible alternatives include thrombo-embolism, general, ongoing hypoxia or tissue damage by extravasated toxic serum proteins due to blood-brain barrier leakage.^{71;76} Future postmortem MRI studies with histopathological confirmation is warranted to further investigate these mechanisms.

Microbleeds

Clinical MRI studies have generally regarded small foci of signal loss on gradient-echo T2*-MRI sequences as microbleeds.^{1;77} They are not only a predictor of future lobar intracerebral hemorrhage, but are also independently associated with cognitive decline.^{6;7;78}

Only few studies have used direct postmortem MRI-pathological correlations to establish the pathological changes responsible for these MRI-hypointensities (see Table 3).⁷⁹⁻⁸¹ A recent study that systematically correlated susceptibility weighted imaging, an advanced T2*-MRI sequence, to tissue pathology of hypointensities in AD patients,⁸² found that most lesions indeed seem to be microscopic bleedings. A minority of these lesions, however, corresponded to small lacunes, dissections of a vessel wall or to microaneurysms. Microbleeds may also correspond to focal accumulations of hemosiderin-containing macrophages in the perivascular space, and there is evidence of heme degradation activity with a surrounding inflammatory reaction with activated microglial cells, late complement activation and apoptosis.⁸² Microbleeds were found to be occasionally surrounded by gliosis and incomplete ischemic changes. The walls of ruptured arterioles may show CAA related vascular damage, with thickened, acellular morphology, lack of the muscularis layer, and β amyloid deposition. CAA-related microbleeds tended to be localized at the grey-white matter junction and in superficial cortical layers of the parietal and occipital lobes. Microbleeds in hypertensive subjects, however, were more often seen in the basal ganglia, brain stem and cerebellum.⁸³ Arteriosclerosis of the vessel walls was often present in these subjects.^{79;84}

MRI-‘invisible’ expressions of SVD

As noted above, there is accumulating evidence that there are also pathological changes associated with SVD which are ‘invisible’ to conventional MRI, such as tissue changes in white matter areas appearing normal on postmortem MRI (NAWM) and cortical microinfarcts. Pathologically, NAWM may correspond to mild tissue changes with a slightly lower myelin density, activated endothelium, a looser but still largely intact axonal network and a normal glial density^{18;26}. Furthermore, it has been shown that the density of small afferent vessels is not only decreased in WMH, but extends into NAWM and cortex.³⁸

Cortical microinfarcts are microscopically small lesions. They are attributed to ischemia, consisting of complete or incomplete cavitation with myelin pallor and neuronal loss, surrounded by glial cells and/or macrophages.⁸⁵ Cystic microinfarcts tend to be larger (up to 5 mm) than non-cystic microinfarcts (0.05-0.4 mm).^{85;86} Several population-based prospective autopsy studies suggested that cortical microinfarcts are major determinants of dementia.⁸⁵⁻⁸⁷ Microinfarcts also have an independent influence on cognitive decline in the non-demented elderly, with only little or moderate AD changes on histology.^{14;88} Moreover, microinfarcts were associated with CAA in patients with VaD.⁸⁵

All these findings suggest that SVD is a widespread disease and has various expressions throughout the brain of which only some aspects can be visualized with conventional MRI. As illustrated by Figure 2, MRI-‘invisible’ pathologies, including cortical microinfarcts and tissue changes in the NAWM, hence contribute to the clinical-radiological association that is found in SVD.

Postmortem quantitative MRI: more specific for SVD-related pathology than T2-weighted MRI?

To be able to draw conclusions on the clinical relevance of SVD, additional pathology-specific tools are needed in vivo. Recently, quantitative MRI techniques (QMRI) have been suggested to be more specific for underlying pathology.^{24;26;53} It has been shown that Magnetization Transfer Imaging (MTI) and Diffusion Tensor Imaging (DTI) distinguish between WMH and NAWM in elderly subjects.^{45;89} When correlating postmortem QMRI and pathology, it needs to be taken into account that both the time to autopsy and fixation duration have an effect on T1- and T2-relaxation times and diffusivity measures.^{90;91}

Although several postmortem studies using QMRI have been performed in patients with multiple sclerosis and other neurological diseases,⁹²⁻⁹⁴ postmortem QMRI studies in elderly with SVD are still scarce. Two small studies showed that DTI measures in WMH seem to correspond to the degree of myelin loss. Also, the area of diffusivity and pathological changes was found to be more spatially extensive than indicated by the hyperintense areas on conventional T2-weighted MRI.^{95;96} Pathological correlates of fractional anisotropy (FA) in DTI and T1-relaxation time were established in a recent study on WMH in AD patients and controls. FA reflected axonal loss, whereas T1-relaxation time corresponded with axonal loss, myelin loss and microglial activation.⁵²

These few studies reveal that QMRI techniques may be promising in assessing tissue damage in vivo, because they sensitively and specifically reflect the severity of pathological substrates and reveal tissue changes in areas that appear normal on conventional MRI (NAWM).

Conclusions and considerations for future research

This review has considered the pathological correlates of SVD, as reflected on MRI. The available literature suggests that several explanations may exist for the weak clinical-pathological associations.

First, pathological substrates of SVD expressions on MRI, such as WMH, lacunes and microbleeds, are heterogeneous in nature and differ in severity. Relative to WMH, postmortem MRI-pathology correlation studies of lacunes and microbleeds are still scarce. For lacunes, pathological correlation studies are certainly warranted to be able to further investigate their hypothesized multiple etiologies including acute thromboembolism, continuing moderate ischemia with eventual focal tissue loss and inflammation. For microbleeds, the pathogenetic mechanisms and their relationship with WMH and lacunes also needs to be further unraveled. It should be noted that in this review, we have only focused on normal aging and dementia. In specific brain diseases, such as CADASIL and hereditary CAA, SVD features are also present, but may differ with regard to their MRI and histopathology profiles.

Second, until recently, clinical MRI studies have often focused on separate aspects of SVD, such as WMH, and found only weak associations with clinical symptoms. However, not only WMH, but also lacunes and microbleeds are bound to contribute to clinical symptoms such as cognitive

decline.^{3;6} Furthermore, the previously discussed MRI-‘invisible’ lesions, i.e. microinfarcts and tissue changes in the NAWM, may be clinically relevant, independently of MRI-‘visible’ characteristics of SVD.⁸⁸ The combination of SVD features is therefore a better predictor of cognitive decline than separate SVD expressions.⁹⁷ Moreover, SVD should be assessed together with frequently co-existing large vessel infarcts, which may improve insight in the mechanisms of vascular cognitive impairment. In addition to vascular disease, other (degenerative) brain changes, e.g. AD pathology, CAA or cortical Lewy bodies, may interact and modulate their specific contributions to cognitive decline.^{87;98-101} Future studies should therefore consider the full spectrum of SVD expressions, together with vascular and degenerative pathologies co-existing in the aging brain.

Unfortunately, MRI sequences that are commonly used in radiological practice, are insufficiently sensitive and specific to detect all the tissue changes related to SVD. Novel QMRI techniques, such as DTI, MTI, T1- and T2 relaxation time measurements have two advantages over conventional MRI. First, QMRI better reflects the severity of underlying pathological substrates. Second, it may better reveal clinically relevant tissue changes in the WM that appears normal on conventional MRI.^{95;96} QMRI techniques are therefore more adequate at reflecting the full range of SVD expressions. Several QMRI abnormalities were confirmed histopathologically, and these techniques are promising, pathology-specific tools for future in vivo studies. It should be noted that, even though study logistics will become more complex, the use of fresh brain tissue in exploratory post mortem MRI studies is preferred above the use of fixed specimens, as formalin fixation has been shown to influence tissue proton relaxation characteristics. Unlike tissue changes in the NAWM, QMRI techniques have not yet been investigated to visualize cortical microinfarcts. The future use of high resolution MRI, using 7 Tesla MRI scanners, may achieve in vivo assessment of these lesions, which are probably beyond the resolution of 1.5 or 3 Tesla MRI.

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Table 1. Postmortem studies on characterization of WMH using postmortem MRI – pathology correlation

Reference	Subjects	Histochemistry	Immunohisto-chemistry	MRI	Main findings
Awad 1986 ²¹	7 neur (-) controls	HE, LFB	GFAP	1.5T	WMH correspond to a spectrum of histological alterations. Mild tissue changes = enlarged perivascular spaces, vascular ectasia. Severe tissue changes = degeneration axons, gliosis.
Englund 1987 ¹⁶	21 AD 19 neur (+) controls	HE, LFB		0.25T	T1 and T2 relaxation times increased with severity of tissue changes in WMH.
Marshall 1988 ²⁸	16 neur (-) controls	HE, Congo Red, Alcian Blue, LFB	GFAP, IgG, Albumin	0.35T	WMH correspond to intermediate and old infarctions: - intermediate infarctions = necrosis, minimal cavitation, gliosis. - old infarction = cavitation, surrounded by demyelination, fibrohyalinoses and isomorphic gliosis (swollen reactive astrocytes, positive for IgG and albumin). Findings imply blood-brain barrier leakage. No correlation with CAA.
Braffmann 1988 ⁶⁶ Mascalchi 1989 ¹⁰²	23 neur (+/-) controls 1 VaD	HE, Weil, LFB, Bodian HE, Woelke, Congo Red		1.5T 0.5T	WMH vary from subtle gliosis and demyelination to frank infarction. Case report: WMH reflect demyelination, axonal loss, moderate astrogliosis, oligodendroglial swelling, a few macrophages and slight edema. Arterial/ arteriolar wall changes: severe thickening with stenosis, hyperplasia and hyalinoses. Scarce vascular amyloid deposition.
Revesz 1989 ²²	4 VaD	HE, KB, Nissl, Holzer axons, cresyl violet, EvG, Heidenhain's myelin, Bielschowsky, PTAH		0.5T	Good correlation of extent of WMH on MRI and pathological changes. Vascular wall changes = arteriosclerotic changes with thickening, fibrosis and splitting of the internal elastic lamina, dilated perivascular spaces.
Van Swieten 1991 ²⁷	11 neur (-) controls 8 demented pts	HE, LFB, Weil, EvG, PTAH, PAS, Congo Red, Bodian		1.5T	WMH = demyelination, gliosis and arteriolosclerotic changes. Arteriolar wall thickening in moderate/severe WMH.
Fazekas 1991 ²³	2 controls - neur 4 neur (+) controls	HE, Masson's trichrome, KB		1.5T	Punctate WMH = spectrum of perivascular damage with fibrohyalinoses, atrophic neuropil and rarefaction myelinated fibres.
Grafton 1991 ¹⁰³	3 AD 4 neur (+/-) controls	LFB-PAS, Holzer astrocytes, Holmes, galloyanin	GFAP		PVL = myelin pallor, gliosis and widened perivascular spaces. DWMH did not correlate with any neuropathological measure.
Chimowitz 1992 ³⁰	7 neur (-) controls	KB, Congo red, desmin	GFAP	1.5T	Each type of WMH correlated with distinct PA: Periventricular rims = ependymal loss and subependymal gliosis. Periventricular caps/patches = myelin pallor. Punctate DWMH = widened perivascular spaces.
Fazekas 1993 ³¹	11 neur (+) controls	HE, Masson's trichrome, KB		1.5T	PVL: <i>Smooth PVL</i> = myelin pallor, loose fibres, tortuous venules, no arteriolosclerosis, discontinuity ependym, mild-moderate gliosis. <i>Irregular PVL</i> = varying fibre loss, gliosis and cavitation, fibrohyalinoses. DWMH: <i>Punctate DWMH</i> = no ischemic changes; demyelination, atrophic neuropil around fibrohyalinoses arterioles and perivenous damage. <i>Early confluent DWMH</i> = perivascular rarefaction of myelin, mild-moderate fibre loss, varying gliosis. <i>Confluent DWMH</i> = irregular areas of incomplete parenchymal destruction with focal transitions to true infarcts.

Munoz 1993 ³²	2 AD 13 neur (-) controls	HE, chromoxane cyanin, Bielschowsky, Congo red		1.5T	Extensive DWMH = broad areas of loss of myelin, axons and glial cells (oligodendrocytes) and spongiosis. No infarction or vascular wall changes. Punctate WMH = dilated perivascular spaces.
Scarpelli 1994 ³⁵	16 neur (-) controls 5 neur (+) controls	HE LFB	GFAP	1.0T	PVL = atherosclerotic changes, vacuolisation of the myelin, neuropil and fibrous gliosis with proliferation of ependymal cells. DWMH = vacuolated myelin around atherosclerotic arteries/arterioles, widened perivascular spaces with degenerated myelin and recent infarction PVL/ focal DWMH no clinical consequences, whereas confluent DWMH are potentially pathological.
Scheltens 1995 ¹²	6 AD 9 neur (-) controls	HE, PTAH, KB, Bodian, EvG, Congo Red		0.6T	AD vs controls: some AD pts show more extensive WMH than controls. WMH = loss of myelinated axons, gliosis, no atherosclerosis. In AD, the nature of pathological changes is comparable with but more severe than in controls.
Smith 2000 ³⁴	12 pts not specified	LFB		-	Extent of WMH on MRI correlates well with extent of WM pathology. No ischemic changes (microinfarcts or lacunes) in a sample with few cardiovascular risk factors.
Bronge 2002 ²⁶	6 AD	HE, KB		1.5T	More extensive WMH on PA than on MRI. +PA/-MRI lesions: mild changes = lower myelin density, loose but intact fibre network, normal glial density. +PA/+MRI lesions = variable myelin/ axonal loss, irregular and fragmented axons, vacuolation, decreased cell density, dilated perivascular spaces, smooth muscle degeneration. no gliosis/infarction.
Moody 2004 ³⁸	21 neur (-) controls	alkaline phosphatase, Congo red, Masson trichrome, Kultchitsky hematoxylin/LFB, Cresyl violet acetate plus light green and Gill hematoxylin.		1.5T	WMH correlates with decreased vascular density (arteries/arterioles/capillaries). Subjects with WMH have a decreased vascular density in WMH, NAWM and cortex, but especially apparent in youngest subjects.
Fernando 2004 ¹⁸	16 neur (-) controls 17 AD + VaD	HE, LFB/Loyez method	CD68, collagen- IV, ICAM-1	1.0T	PVL-MRI: sensitivity = 95% (87-99%), specificity = 71% (44-90%), DWMH-MRI: sensitivity = 86% (79-93%), specificity = 80% (72-88%). weighted Kappa MRI-PA: PVL= 0.4, DWMH= 0.3; underestimation small lesions. MRI+ versus MRI- lesions: difference in myelin loss and endothelial upregulation. no difference in microglial activation.
Fernando 2006 ³⁷	99 demented 108 neur (+/-) controls		CD68, Col IV, ICAM1, HIF1 α / 2 α , MMP7, Ngb, NMBR, VEGFR2, β A4	1.0T	Vascular changes in WMH: wall thickening, dilated perivascular spaces. In PVL: ependym denudation. In DWMH specifically: higher capillary network density, microglial activation (CD68), upregulation hypoxia factors (HIF1/2 α , VEGFR2, Ngb) and correlation CAA~ HIF1 α . Both DWMH and PVL: upregulation MMP7. C/ hypoxia plays a role in a part of WMH. differences DWMH vs PVL. no differences demented and non-demented subjects.
Simpson 2007 ⁴⁰	Unselected tissue blocks; 12 PVL, 12 DWMH, 15 NAWM	HE, LFB	MBP, GFAP, CD68, PDGF α R, MAP-2(+13), fibrinogen	1.0T	DWMH and PVL differ with regard to pathological profiles and biological responses: More microglial activation (CD68) in DWMH > PVL. Clasmatodendritic astrocytosis, positive for serum proteins (42% DWMH, 67% PVL), suggesting blood-brain barrier dysfunction. Attempts at regeneration/ remyelination in PVL (MAP-2+13, PDGF α R/OPC)

Simpson 2007 ⁴⁴	Unselected tissue blocks: 12 PVL, 12 DWMH, 15 NAWM		HLA-DR, B7-2, CD40, MCM2, PCNA, Ki67	1.0T	Microglial responses: PVL: more MHCII-positive microglia and costimulatory B7-2 and CD40, suggesting a more proliferative/ immune reactive environment.
Young 2008 ⁴³	17 demented (various) 3 neur (+/-) controls.	HE, PAS, Weil	dMBP, CD31, GFAP, hGLUT-5, APP, HLA-DR, P-gp, IgG	3.0T	In DWMH: amoeboid microglia for phagocytosis of myelin breakdown products. WMH extent scored using Scheltens Scale ¹⁰⁴ . PVL extent ~ reactive microglia, DWMH extent ~ vascular integrity. WMH not associated with myelin pallor. Model for prediction of WMH extent (correctly classifies WMH/NAWM in 80%): only independent predictor = decreased vascular integrity (CD31). P-gp: WMH > NAWM, but no difference with IgG → Blood-brain barrier dysfunction.
QMRI					
Englund 2003 ⁹⁵	2 AD	KB		3.0T	Postmortem DTI is feasible in fixated brain specimens. DTI measures in WMH correlates with severity of myelin loss.
Larsson 2004 ⁹⁶	1 FTD	HE, LFB		3.0T	The area of DTI changes was more extensive than WMH areas on conventional MRI. WMH correlates with gliosis and demyelination.
Gouw 2008 ⁵²	11 AD 7 neur (-) controls	HE, LFB-CV, Bodian	GFAP, HLA-DR	1.5T	Quantitative MRI distinguishes WMH from AD and controls. More microglial activation in WMH than NAWM in AD patients specifically. QMRI ~ severity of pathological changes. Independent predictor of fractional anisotropy in DTI = axonal loss Independent predictors of T1-relaxation time = axonal loss, myelin loss, microglial activation.

AD = Alzheimer's disease, neur (-) controls = non-demented subjects without neurological disease, neur (+) controls = non demented patients with neurological disease. FTD = frontotemporal dementia, VaD = vascular dementia. HE = Haematoxylin-Eosin, LFB = Luxol Fast Blue, LFB-PAS = Luxol Fast Blue/periodic acid-Schiff, KB = Klüver-Barrera, EvG = Elastic van Gieson, MBP = myelin basic protein, GFAP = glial fibrillary acidic protein, HIF = hypoxia inducible factor, IgG = immunoglobulin, PTAH = Phosphotungstic Acid Hematoxylin, MMP7 = matrix metalloproteinase 7, ICAM1 = intercellular adhesion molecule, Ngb = neuroglobin, NMBR = neuromedin B receptor, VEGFR2 = vascular endothelial growth factor receptor 2, MCM2, PCNA and Ki67 = cell proliferation-related molecules, B7-2, CD40 and CD40-Ligand = immune costimulatory molecules, PDGFR = platelet-derived growth factor receptor, OPC = oligodendrocyte precursor cells, MAP-2 +13 = microtubule-associated protein-2 expressing exon 13, CD31 = vascular integrity, hGLUT-5 = human glucose transporter-5, APP = amyloid precursor protein, HLA-DR = human leukocyte antigen-DR, P-gp = P-glycoprotein, (D)WMH = (deep) white matter hyperintensities, PVL = periventricular white matter hyperintensities, DTI = diffusion tensor imaging, (Q)MRI = (quantitative) magnetic resonance imaging, CAA = cerebral amyloid angiopathy, PA = pathology.

Table 2. Postmortem studies on characterization of lacunes using postmortem MRI – pathology correlation

Reference	Subjects	Histochemistry	Immuno-histochemistry	MRI	Main findings
Braffman 1988 ⁶⁶	36 neur (+/-) controls	HE, Weil, LFB, Bodian		1.5T	- lacunes in 6 subjects: 4 subjects with 6 lacunes in basal ganglia, 2 subjects with 3 lacunes in posterior fossa and 2 subjects with 5 supratentorial white matter lacunes. Usual morphology: slitlike or ovoid, size 3 - 14mm, varying degrees of cavitation. - état criblé in 4 subjects. Usual morphology was round or linear, 1mm – 5mm.
Revesz 1989 ²²	4 VaD	HE, KB, Nissl, Holzer axons, cresyl violet, EvG, Heidenhain's myelin, Bielschowsky, PTAH		0.5T	All subjects: lacunes in the white matter, basal ganglia and pons. 1 subject: a lacune in internal capsule. In 2 cases old cystic cavities were densely lined by haemosiderin-containing macrophages (possibly reflect microbleeds)
Pullicino 1995 ⁷⁰	2 subjects postmortem MRI, 1 in vivo MRI. not specified	HE, LFB-PAS, Gomori's trichrome, Verhoeff's elastic	actin	-	Infraputaminar cavities or 'lacunes' are single or grouped enlarged perivascular spaces. Histology: regular and clearly demarcated walls, some arteries within cavity were tortuous (not occluded), thickened adventitia. Surrounding white matter showed corpora amylacea, vacuolation, myelin loss and minimal gliosis, but no infarction.
Bokura 1998 ⁶⁷	9 neur (+) controls (cerebrovascular disease) 3 neur (-) controls	HE, KB		1.5T	114 asymptomatic lesions detected on PA. Basal ganglia n= 87 (76%): 29 lacunes, 58 VRS. WM: 11 lacunes, 8 VRS. Thalamus: 2 lacunes, 3 VRS. Brainstem: 3 lacunes, no VRS. In basal ganglia more VRS, in WM more lacunes. Morphology: VRS more round/ linear, lacunes more wedge shaped, but both could be ovoid. VRS are smaller than lacunes (72% of VRS < 2x1mm, 60% of lacunes > 2x2mm).
Matsusue 2006 ⁶⁴	Not specified.	HE, LFB, axon staining	GFAP	1.5T	Description of old lacune: cystic cavity with ill-defined and irregular margin, with surrounding mild loss of myelin and axons with mild gliosis.

neur (-) controls = non-demented subjects without neurological disease, neur (+) controls = non demented patients with neurological disease, VaD = vascular dementia. HE = Haematoxylin-Eosin, LFB = Luxol Fast Blue, LFB-PAS = Luxol Fast Blue/ periodic acid-Schiff, KB = Klüber-Barrera, EvG = Elastic van Gieson, GFAP = glial fibrillary acidic protein, PTAH = Phosphotungstic Acid Hematoxylin, VRS = Virchow Robin spaces, WM = white matter.

Table 3. Postmortem studies on characterization of microbleeds using postmortem MRI – pathology correlation.

Reference	Subjects	Histochemistry	MRI	Main findings
Fazekas 1999 ⁷⁹	11 subjects with intracerebral hemorrhage	HE, Masson trichrome, KB, congo red, iron	1.5T	MRI signal loss in 7/11 subjects. 2 pts: only cortical-subcortical, 1 pt only basal ganglia/infratentorial, 4 pts both locations. WMH in all patients, lacunes in 5/7 pts. In 62% of MRI signal loss: focal accumulation of hemosiderin-containing macrophages adjacent to small blood vessels, sometimes minute areas of tissue necrosis. The remainder of MRI signal loss: no pathological substrate. Also MR-negative hemosiderin deposits: smaller, only a few perivascular, hemosiderin-laden macrophages. No calcification or vascular malformations. 2 subjects had cerebral amyloid angiopathy of variable extent in multiple vessels, associated with foci of remote blood leakage. Brains with fibrohyalinosis showed microbleeds preferentially in the basal ganglia/thalami, but also cortical-subcortical.
Tanaka 1999 ⁸⁰	3 neur (+) controls, with MRI signal loss	HE, Masson trichrome, KB, Berlin Blue	1.0T In vivo MRI	Foci of old hemorrhages caused by rupture of arteriosclerotic microvessels <200 µm, surrounded by gliosis and incomplete ischemic necrosis. Identified as hemosiderin pigments within the perivascular space and as an organised pseudoaneurysm (1 case).
Tatsumi 2008 ⁸¹	1 neur (+) control	HE, Berlin Blue	1.5T, both postmortem and in vivo MRI	9 MRI hypointensities: all could be identified as brown spots on the cut surface. 8 hemosiderin-laden macrophages, 1 vascular pseudocalcification (left pallidum). 5/8 had vascular abnormalities: degenerated endothelial lining and hyalinosis. Size of hemosiderin deposit similar with MRI hypointensity. Associated with tissue rarefaction, gliosis or arteriolar changes. Some hemosiderin deposits not observed on MRI. Ante- and postmortem MRI comparable.
Schrag 2009 ⁸²	8 AD (of which 6 advanced CAA), 2 neur (-) controls	Aβ1-42, CD68, HO-1, complement C6, CD3, CD20, Prussian Blue, fluorescent study (HO-1 + MAP-2), TUNEL	3.0T	38 MBs: correspond to variety of pathological changes = 16 old hematomas, 7 small cavities, 3 microscopic hemosiderin granules + hematoxin deposition, 1 dissection vessel wall, 1 microaneurysm. Location: 79% grey-white junction, 21% superficial cortex. CAA related vascular damage: thickened, acellular, arteriolar walls with βamyloid deposition and lacking muscularis layer. Activated microglia (CD68), evidence of heme degradation (HO-1), late complement activation, apoptosis. Inflammatory reaction along local microvasculature.

neur (+) controls = non demented patients with neurological disease, CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. MB = microbleed HE = Haematoxylin-Eosin, KB = Klüber-Barrera, EvG = Elastic van Gieson, HO-1 = heme oxygenase 1.

Figure legends

Figure 1.

MRI expressions of small vessel disease. Axial Fluid Attenuated Inversion Recovery (FLAIR)-images with periventricular and deep white matter hyperintensities (A); and an illustration of two lacunes in the right hemisphere (arrows) and deep white matter hyperintensities (B). T2*-gradient echo image with multiple cortical-subcortical microbleeds (C).

Figure 2.

A schematic representation of small vessel disease (SVD) expressions is shown including illustrative postmortem MRI and histological sections. SVD expressions that are visible on MRI are illustrated as: a pre-frontal coronal FLAIR image and a matching Bodian Silver stained section of white matter hyperintensities (WMH); a parietal coronal FLAIR image and a Klüver-Barrera stained section of two lacunes (two arrows in the magnification); and a cerebellar axial T2*-image and Haematoxylin Eosin-stained section of a microbleed (reproduced with permission from Fazekas, AJNR 1999 ⁷⁹). SVD expressions that are not readily detected by conventional MRI include: cortical microinfarcts, illustrated by microglial/macrophage activation on a HLA-DR stained section; and changes in the normal appearing white matter, e.g. astrogliosis (GFAP stained section). Future studies should be directed to assess the whole spectrum of SVD, because all expressions may contribute to clinical symptoms in the elderly subject.

Figure 3.

Prefrontal coronal FLAIR image (A) of an 88-year-old female Alzheimer's disease patient. Regions of interest represent white matter hyperintensities (WMH) in the periventricular area (green; B1 to E1); WMH in the deep white matter (yellow; B2 to E2); and an area of normal appearing white matter (white, B3 to E3). Bodian Silver stained sections (B, original magnification 200x) showed lower axonal density in WMH (B1 and B2) than in NAWM (B3); more microglial activation (C) was observed in WMH (C1 and C2) than in NAWM (C3) on HLA-DR immunohistochemical sections (original magnification 200x); WMH also showed more myelin loss (D1 and D2) compared to NAWM (D3) in Luxol-Fast-Blue/Cresyl-Violet stained sections (original magnification 100x); the severity of astrogliosis (E) (GFAP-immunostained sections, original magnification 400x) was not clearly different between WMH and NAWM in this patient. Adapted with permission from Gouw, Brain 2008 ⁵².

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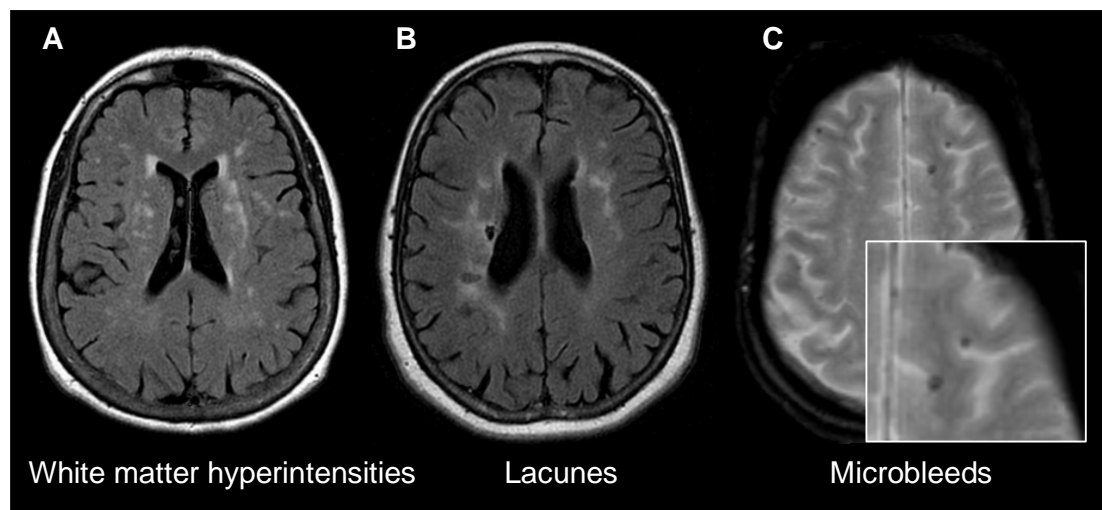
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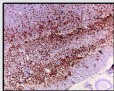
Figure 1.



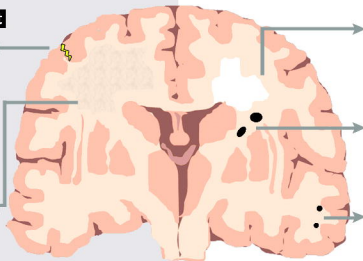
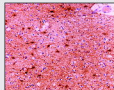
“invisible” SVD

“visible” SVD

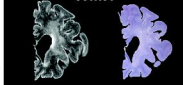
Cortical Microinfarct



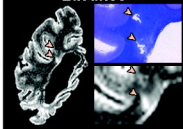
NAWM changes



WMH



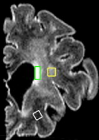
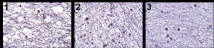
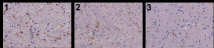
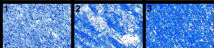
Lacunes



Microbleeds



Clinical Symptoms

A**B****C****D****E**