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Small vessel disease, neurovascular regulation and cognitive impairment: post-mortem studies reveal a complex relationship, still poorly understood

Seth Love and J. Scott Miners

Dementia Research Group, School of Clinical Sciences, University of Bristol,
Learning & Research level 1, Southmead Hospital, Bristol BS10 5NB, U.K.

Correspondence: Seth Love (email seth.love@bris.ac.uk)

Running title: Small vessel disease, neurovascular regulation and cognitive impairment: post-mortem assessment

Abstract

The contribution of vascular disease to cognitive impairment is under-recognised and the pathogenesis poorly understood. This information gap has multiple causes, including a lack of post-mortem validation of clinical diagnoses of vascular cognitive impairment (VCI) or vascular dementia (VaD), the exclusion of cases with concomitant neurodegenerative disease when diagnosing VCI/VaD, and a lack of standardisation of neuropathological assessment protocols for vascular disease. Other contributors include a focus on end-stage destructive lesions to the exclusion of more subtle types of diffuse brain injury, on structural abnormalities of arteries and arterioles to the exclusion of non-structural abnormalities and capillary damage, and the use of post-mortem sampling strategies that are biased toward the identification of neurodegenerative pathologies. Recent studies have demonstrated the value of detailed neuropathology in characterising vascular contributions to cognitive impairment (for example, in diabetes), and highlight the importance of diffuse white matter changes, capillary damage and vasoregulatory abnormalities in VCI/VaD. The use of standardised, evidence-based post-mortem assessment protocols and the inclusion of biochemical as well as morphological methods in neuropathological studies should improve the accuracy of determination of the contribution of vascular disease to cognitive impairment and clarify the relative contribution of different pathogenic processes to the tissue damage.

INTRODUCTION

Pure vascular dementia (VaD) is reported to account for approximately 10-20% of all cases of dementia [1, 2] but this is likely to represent the tip of the iceberg in terms of the contribution of vascular disease to cognitive impairment – vascular cognitive impairment (VCI). Most figures on the epidemiology of vascular dementia have been based on unvalidated clinical assessment. When autopsy data have been available, diagnosis of VaD has usually required post-mortem evidence of multiple cerebral infarcts. Cases that lack infarcts in the histologically sampled tissue or have concurrent neurodegenerative pathology of more than mild severity have usually been excluded, without an understanding of the contribution of the various disease processes to the cognitive impairment, and resulting in substantial underestimation of the prevalence of cognitive dysfunction that has a vascular component. The importance of detailed clinicopathological correlation and the use of a standardised approach for the post-mortem assessment of vascular as well as neurodegenerative abnormalities was highlighted by a recent study of the association between diabetes mellitus and cognitive impairment in a large (n = 2365) autopsy cohort, in which impaired cognition was found to be solely attributable to cerebral small vessel disease (SVD) not Alzheimer's disease (AD) pathology in diabetes [3], contrasting with the findings in a range of purely clinical studies on the basis of which diabetes was reported to be a risk factor for AD [4].

Reasons for underestimating the contribution of vascular disease to cognitive impairment even in post-mortem studies include a tendency to focus

on end-stage destructive lesions (e.g. infarcts) to the exclusion of more subtle types of damage, on obvious structural abnormalities of the vessel wall (e.g. marked arteriolosclerosis and atherosclerosis) to the exclusion of less noticeable changes (e.g. reduction in capillary density), and the use of post-mortem sampling and assessment strategies that are biased toward the identification of neurodegenerative pathologies.

Cerebral perfusion may be compromised at multiple levels: cardiac, arterial, arteriolar and capillary, and the underlying cardiovascular abnormality may be sustained or intermittent, structural or regulatory/non-structural. In general, sustained hypoperfusion results from structural cardiovascular disease and intermittent hypoperfusion reflects abnormal regulation of cardiac output or cerebral vascular tone. However, the distinction is not clear-cut: structural diseases such as cerebral amyloid angiopathy (CAA) can interfere with neurovascular coupling, and some regulatory abnormalities cause chronic mismatch between metabolic demand and blood supply.

In this review we consider what is known, particularly from studies on human brain tissue, about the timing, causes and consequences of arteriolar and capillary compromise in VCI/VaD (and also AD and mixed dementia where the information is relevant to an understanding of VCI/VaD), and what key questions remain to be answered. In keeping with the theme of this issue of Clinical Science, the review does not cover disease of larger arteries, major stroke or cardiac disease, except in the context of mechanisms of brain damage that are shared with intracerebral vascular disease. Also excluded from this review are inherited vasculopathies such as CADASIL.

TIMING OF ARTERIOLAR AND CAPILLARY COMPROMISE IN VCI AND VAD

There is a paucity of information on the timing of development of changes in vascular structure and function in VaD.

Clinical predictors

Several clinical and MRI features predict the development of VaD [5-12]. These include a history of hypertension, heart disease, diabetes mellitus, transient ischaemic attacks (TIAs) and stroke; executive dysfunction, gait disturbances, urinary incontinence or personality changes, often in the absence of memory problems; and white matter hyperintensities or infarcts, often with relative preservation of temporal lobe volume. The prodromal clinical stage is termed vascular-mild cognitive impairment (VMCI), defined by the presence of mixed domains of cognitive impairment other than of memory (although memory impairment may also be present), in someone with a personal or family history of TIAs, strokes (clinically manifest or silent), with strong risk factors for stroke and without a family history of neurodegenerative dementia [5, 8-10]. Over half of patients who develop VaD have preceding VMCI, and about two-thirds of VMCI patients have MRI changes of non-amyloid SVD (NA-SVD) rather than strategic-infarct dementia [5, 8]. It seems very likely therefore that most VMCI patients will therefore have had moderate or marked arteriolosclerosis for some years before they develop dementia.

NA-SVD risk factors versus associations

The general presumption is that cerebral NA-SVD is a consequence of genetic, lifestyle and environmental factors that include cigarette smoking, hypertension, diabetes and age [13, 14]. However, these account for only a small proportion of the attributable risk of NA-SVD. In addition, we should consider the possibility of reverse causality as far as hypertension is concerned, i.e. the possibility that NA-SVD may cause or contribute to the development of hypertension in some people. SVD impairs cerebral perfusion. There is a highly significant negative correlation between the severity of arteriolosclerosis in the cerebral white matter and markers of tissue oxygenation [15, 16]. Elevation of cerebral perfusion pressure, manifesting as systemic hypertension, would be expected as a protective physiological response to reduced arteriolar calibre and impaired cerebral oxygenation [17, 18]. In a large clinical study, Warnet et al. [18] showed that (i) people with hypertension were more likely to have congenital variants of the circle of Willis that were associated with increased cerebral vascular resistance, reduced cerebral blood flow and a higher incidence of lacunar infarcts, (ii) cerebral vascular resistance was elevated before the onset of hypertension and elevated sympathetic nerve activity, and (iii) cerebral blood flow was normal in untreated hypertensive patients but reduced in patients receiving antihypertensive medication.

These observations suggest that hypertension may in some people be mediated by increased sympathetic activity secondary to cerebral hypoperfusion, causes of which would include SVD. Mid-life hypertension is

also associated with (and assumed to be a risk factor for) AD [19, 20]. However, intracerebral accumulation of A β , like arteriolosclerosis, is associated with hypoperfusion and reduced tissue oxygenation [15, 21, 22], and we have shown that cerebroventricular infusion of A β induces or exacerbates hypertension in Dahl rats [23]. Together these clinical and experimental studies suggest that cerebral hypoperfusion as a result of vascular disease, whether structural such as arteriolosclerosis or abnormal regulation of vascular tone as in AD, may cause or contribute to hypertension. Of course, these observations do not preclude hypertension itself as a contributor to NA-SVD and raise the possibility of a vicious cycle in which hypertension initiated by cerebral arteriolosclerosis exacerbates NA-SVD until decompensation occurs and cerebral perfusion can no longer be maintained.

Cerebral infarcts

In several autopsy studies, the presence or severity of cognitive impairment was associated with the number and distribution of microinfarcts and/or lacunar infarcts (see, for example [24-27]). In the Honolulu Asia Aging Autopsy Study, microinfarcts were associated with cognitive function even in the absence of dementia [25]. It is noteworthy that this association seemed to be mediated through reduction in brain weight. Whilst the microinfarcts may have made some direct contribution to the reduction in brain weight, it seems likely that they are focal markers of more diffuse ischaemic brain damage. A recent autopsy study included 343 people who had had a formal diagnosis of MCI or a Clinical Dementia Rating global score of 0.5 within two years of

death [28]. Tangle and neuritic plaque pathology, and moderate to severe vascular pathology (arteriolosclerosis, CAA and lacunar infarcts) were relatively common in this group, and most brains had mixed pathology. However, the pathological findings that discriminated between individuals and those without cognitive impairment were neurofibrillary tangles, neuritic plaques, Lewy body pathology, hippocampal sclerosis and arteriolosclerosis – not microinfarcts, lacunar infarcts or larger infarcts.

Skrobot et al. [29] performed blinded post-mortem assessment of brain tissue from 113 individuals without significant neurodegenerative disease who had had formal cognitive assessments within 12 months of death. Whereas leptomeningeal CAA, large infarcts, lacunar infarcts, microinfarcts, arteriolosclerosis, perivascular space dilation and myelin loss were all individually associated with cognitive impairment, most of these associations were no longer significant on multivariable logistic regression analysis: only leptomeningeal CAA, at least one large infarct, and either myelin loss or arteriolosclerosis in the occipital white matter were retained in the statistical model that predicted cognitive impairment (see PATHOLOGICAL CONSEQUENCES RELEVANT TO VCI/VAD, below).

Together these studies indicate that infarcts (particularly lacunar infarcts and microinfarcts) are present in a sizable proportion of people with MCI and suggest that they often antedate cognitive decline, but that lacunar infarcts and microinfarcts unlikely themselves to be directly responsible for the cognitive decline in most cases but serve rather as markers of cerebral

hypoperfusion that causes cognitive decline through more diffuse brain damage.

Microbleeds

The detection of 'microbleeds' on MRI, particularly if numerous, is associated with cognitive impairment [30-34] and predicts cognitive decline [35, 36]. Both lobar and deep microbleeds are associated with cognitive decline but the underlying vascular pathology probably differs according to the location of the bleeds, as do the mechanisms of cognitive impairment. Lobar microbleeds are associated with clinical and MRI evidence of A β -related small vessel disease (cerebral amyloid angiopathy, CAA), A β deposition and possession of *APOE* ϵ 4 [37-42]. Many of those with lobar microbleeds have concomitant AD pathology, and this is reflected in the pattern of their cognitive impairment, which tends to affect verbal and visuospatial memory. Microbleeds are about twice as prevalent in AD patients (24-29%) as in age-matched controls (12%) [43-45]. It is unclear whether they are independently associated with cognitive decline in AD [43-45]. Although they are often in a predominantly lobar distribution, about 30-40% are non-lobar, suggesting concomitant NA-SVD [46, 47]. This is in keeping with imaging and pathological studies reporting that AD patients have an increased prevalence of ischaemic parenchymal abnormalities in a distribution suggestive of NA-SVD.

Deep microbleeds, particularly those in the thalamus and basal ganglia, are associated with white matter hyperintensities, deep infarcts and microinfarcts, retinal arteriopathy, elevated blood pressure, and smoking [34,

37, 48]. Patients with deep microbleeds are more likely than age-matched controls to show impairment of global cognitive function, psychomotor speed, attention and calculation, and gait [30-32, 41, 49, 50], i.e. a clinical profile typical of VCI.

Post-mortem studies have shown marked heterogeneity in the pathological substrate of microbleeds. Some are foci of recent or old microhaemorrhage involving the perivascular parenchyma, others are clusters of erythrocytes or haemosiderin-laden macrophages in the perivascular space, microinfarcts, or foci of fibrinoid necrosis (Figure 1(A-C)) [51-54]. Most are related to arterioles or capillaries.

Lack of information on other preclinical vascular abnormalities

In summary, imaging and post-mortem studies indicate that VMCI is usually associated with moderate or marked arteriolosclerosis, and often with microhaemorrhages and microinfarcts in the thalamus and basal ganglia. Unfortunately scant neuropathological data are available on other preclinical structural vascular abnormalities (e.g. affecting capillary endothelium or pericytes) or alterations in vascular function (e.g. regulation of vessel calibre or permeability), and we have little information on the timing of vascular abnormalities in relation to the development of clinical disease. It should be noted too that vascular pathology is rarely the sole abnormality in people with MCI, most of whom have mixed neurodegenerative and vascular pathology [28].

CAUSES OF ARTERIOLAR AND CAPILLARY COMPROMISE IN VCI AND VAD

At brain tissue level, multiple processes contribute to the development of VCI and VaD. Ischaemic parenchymal damage is the main cause of VCI or VaD even in people with numerous microbleeds on MRI [52, 53], although inflammation and oxidative stress (e.g. induced by myeloperoxidase and NADPH oxidase activity, and by the formation of hydroxyl radicals through the Fenton reaction) may play a part. Of the various forms of ischaemic pathology, diffuse damage to cerebral white matter is probably a particularly important cause of cognitive impairment (see Pathological consequences relevant to VCI/VaD, below).

Arteriolar changes

NA-SVD and CAA are associated with narrowing of arteriolar lumina, reducing vascular conductance. There is also collagenous thickening of the vessel wall in NA-SVD and loss of smooth muscle cells in both NA-SVD and CAA – alterations likely to contribute to impaired neurovascular coupling in stroke patients and people with hypertension [55, 56] and in those with moderate or severe CAA [57, 58]. CAA is mainly associated with ischaemic cortical damage [24, 59, 60] but can also contribute to diffuse white matter injury, particularly when the A β in the vessel walls elicits an inflammatory reaction [61, 62].

Pericytes and capillaries

Pericytes are important for maintenance of the blood-brain barrier (BBB) and for regulation of perfusion and neurovascular coupling at capillary level.[63-67] Degeneration of pericytes is associated with hypoperfusion in the cerebral cortex. This was demonstrated in mice deficient in platelet-derived growth factor receptor- β which show marked loss of pericytes with age [63, 68], and also in cerebral cortex from non-demented elderly people and even more so in those with cognitive impairment or AD [63, 69]. In parietal white matter hypoperfusion and BBB leakage were not associated with pericyte loss [69] but it is possible that more subtle forms of pericyte damage and dysfunction may occur in the white matter in VCI and VaD.

There is a paucity of information on capillary integrity or loss in VCI and VaD. One way to gauge the density of capillaries is to measure the level of von Willebrand factor, which we showed to correlate closely with conventional morphometric quantification of capillary density [22, 70]. We found the level of von Willebrand factor to be significantly reduced in frontal white matter from people with severe NA-SVD [15], suggesting that NA-SVD causes hypoperfusion not only through structural and non-structural alterations in vessel calibre but also through loss of capillaries, at least in the white matter.

Vasoregulation

Neurochemical abnormalities affecting vasoregulation are well-documented in dementia, particularly AD, and have the potential to cause diffuse white matter ischaemic damage. There is an elevated level of the vasoconstrictor endothelin-1 (EDN1) [15, 22, 71], which acts on vascular smooth muscle and

pericytes to cause vasoconstriction at both arteriolar and capillary level (Figure 2(A-C)) [72-74]. The increase in EDN1 is probably mediated by elevated expression of endothelin-converting enzymes 1 and 2, which catalyse the production of EDN1; these enzymes are upregulated in vitro by A β 40 and A β 42 respectively, and also in post-mortem cerebral cortex from patients with AD [75-77]. Activity of angiotensin-converting enzyme (ACE), which catalyses production of another vasoconstrictor, angiotensin II, is elevated in frontal cortex in AD [78, 79]. We did not find evidence of overproduction of angiotensin II within the white matter in AD or VaD [15, 71] but it would be of interest to examine the cerebral renin-angiotensin system in more detail in VaD, including within the cerebral cortex. It is important to bear in mind that most of the blood that perfuses the subcortical white matter is conveyed through perforating arterioles that traverse the cerebral cortex and that may therefore be affected by intracortical disease processes [13, 21]. We obtained circumstantial evidence that this plays a part in hypoperfusion of the white matter in AD (Figure 3): the reduction in oxygenation of white matter, measured by the increase in vascular endothelial growth factor (VEGF) and the decline in the ratio of myelin-associated glycoprotein (MAG) to proteolipid protein-1 (PLP1), was directly related to the levels of A β 42 and EDN1 in the overlying cerebral cortex [71]. Reduced transcortical perfusion presumably also contributes to white matter damage in severe CAA, in which the vascular disease process is largely restricted to the cortex and overlying leptomeninges, and seems likely to do so in NA-SVD.

Blood-brain barrier

Loss of BBB integrity has the potential to damage both grey and white matter by multiple mechanisms. These include leakage of neurotoxic proteins such as fibrinogen [63, 80-83], induction of inflammation [80-82], and impaired clearance of toxic brain metabolites including A β [63]. Several neuroimaging studies have found evidence of blood-brain barrier (BBB) damage in NA-SVD and VCI [84-87]. Neuropathological studies of the leakage of relatively large molecules such as fibrinogen and IgG have yielded inconsistent findings (see [88] for discussion). We measured fibrinogen content in post-mortem brain tissue by ELISA and found the level to be increased in parietal grey and white matter in AD [69]; in both regions fibrinogen content correlated with the severity of the perfusion deficit (as evidenced by elevation of VEGF and reduction in MAG:PLP1). These findings in human brain tissue are in keeping with observations by Zlokovic and others in mice deficient in platelet-derived growth factor receptor- β [63, 68]. We have preliminary (unpublished) data indicating that there is also fibrinogen leakage in moderate to severe NA-SVD, and work is in progress to assess the relationship of the BBB damage to tissue oxygenation and integrity.

Failure of vascular homeostasis

Whilst we are beginning to understand the contribution of different vascular cell types and biochemical pathways to the regulation of blood flow and tissue oxygenation, and to identify abnormalities in the different cells and pathways in VCI and VaD, we still lack a clear understanding of the aetiology of many of

those abnormalities. There are several examples of failures of vascular homeostasis in association with reduced cerebral oxygenation in dementia, as illustrated by the dissociation between VEGF level and microvessel density in the white matter in NA-SVD [15, 16], and between the level of platelet-derived growth factor and pericyte content in the cerebral cortex AD [69]. If we are to prevent or treat VCI, VaD and mixed dementia, much more work is needed to establish the underlying vascular abnormalities in these diseases, why they occur, and which pathogenic processes might be modifiable.

PATHOLOGICAL CONSEQUENCES RELEVANT TO VCI/VAD

In addition to the obvious focal destructive effects of infarcts and foci of haemorrhage, there is increasing appreciation of the more widespread or remote damage to neurons [89], synapses [90] and white matter tracts [91-95] in VCI and VaD. Cortical disconnection as a result of diffuse damage to cerebral white matter that affects the integrity of cortical association fibres and subcortical tracts seems to be a particularly important contributor to cognitive decline [91, 93, 96]. This is likely to be relevant to cognitive impairment in neurodegenerative as well as vascular disease, partly because neuronal degeneration leads to axonal loss but also because cerebral hypoperfusion is an intrinsic component of AD and Lewy body disease (see Vasoregulation, above). Diffuse white matter damage is well demonstrated by diffusion tensor MRI but difficult to assess and quantify histologically. However, there is some pathological evidence of the important contribution of ischaemic white matter damage to cognitive impairment [97, 98].

In the multicentre neuropathological study by Skrobot et al. [29] of cognitive impairment in the absence of significant neurodegenerative disease, the histological variables that correlated best with ante-mortem cognitive impairment (combined predictive accuracy of 77-78%) were moderate-to-severe occipital leptomeningeal CAA, at least one large (> 10 mm diameter) infarct, and either moderate-to-severe myelin loss in at least one brain region or moderate-to-severe arteriolosclerosis in the occipital white matter. These findings were incorporated into a set of vascular cognitive impairment neuropathology guidelines (VCING) for assessing of the likely contribution of vascular pathology to cognitive impairment. Although VCING represent a major advance in our ability to assess the contribution of vascular pathology to cognitive impairment, the study had several limitations. Some pathologies (e.g. fibrinoid necrosis) were too rare for meaningful analysis. In addition, by excluding brains from people with significant neurodegenerative disease, in whom the threshold at which vascular pathology contributes to cognitive impairment may be reduced, the VCING study may have underestimated the contribution of vascular disease to cognitive impairment in the general population. The VCING model needs to be validated in an independent large cohort, and in the context of mixed neurodegenerative and vascular disease.

It is also worth emphasizing that the guidelines are largely an indirect approach to assessing vascular brain damage; most of the abnormalities that are scored in this scheme are not themselves directly responsible for cognitive impairment. In particular, occipital CAA and white matter arteriolosclerosis are likely to be markers/proxy indicators of ischaemic white

matter damage. A more sensitive and specific approach to post-mortem determination of the contribution of vascular disease – and more specifically hypoperfusion – to cognitive impairment may come from adjunctive biochemical studies, in which ischaemic white matter damage can be measured biochemically [94]. Our expectation is that the use of biochemical as well as morphological methods for post-mortem assessment, in combination with efforts to identify better in vivo biomarkers and more specific clinical indicators of VCI, will not only improve the accuracy of determination of the contribution of vascular disease to cognitive impairment but also will also clarify the relative contribution of different pathogenic processes to the tissue damage and facilitate the identification of therapeutic targets.

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Figures

Figure 1. Pathological abnormalities reported to underlie microbleeds.
(A) Region of old microhaemorrhage, associated with accumulation of haemosiderin in the perivascular parenchyma and vessel wall.
(B) Larger cluster of haemosiderin-laden macrophages, with more

sparsely distributed accumulations of haemosiderin in the adjacent parenchyma. **(C)** Focus of fibrinoid necrosis in a cortical arteriole (note that this patient did not have CAA).

Figure 2. Abnormal cerebral perfusion in association with vasoconstriction.

(A) This schematic diagram illustrates a normal capillary bed, fed by the arteriole on the left and draining into the venule on the right. Vascular smooth muscle cells are represented as yellow bands and pericytes are coloured green. (B) Elevated production of vasoconstrictors such as endothelin-1 (EDN1) causes contraction of smooth muscle cells and pericytes. This reduces blood flow and slows the transit of blood through arterioles and capillaries, causing oxygen desaturation. (C) In the cerebral cortex in Alzheimer's disease there is also some loss of pericytes, and reduced oxygenation reflects a combination of cortical hypoperfusion and impaired neurovascular regulation.

Figure 3. Vascular disease in the cerebral cortex affects perfusion of the cerebral white matter.

Perforating arterioles that arise from meningeal branches of the major cerebral arteries supply both the cerebral cortex and the underlying white matter. Excessive vasoconstriction within the cerebral cortex in Alzheimer's disease (AD) affects not only cortical arterioles but also perforating arterioles that traverse the cortex. Reproduced from [13, 14].