Blood-brain barrier and cerebral small vessel disease

J.M. Wardlaw *

SINAPSE (Scottish Imaging Network — A Platform for Scientific Excellence) Collaboration, SFC Brain Imaging Research Centre, Division of Clinical Neurosciences, University of Edinburgh, Western General Hospital, Crewe Rd, Edinburgh, EH4 2EX, UK

**Article Info**

Article history:
Received 14 March 2010
Received in revised form 4 July 2010
Accepted 24 August 2010
Available online 18 September 2010

Keywords:
Blood-brain barrier
MR imaging
Lacunar stroke
Leukoariosis
White matter lesions
Microbleeds

**Abstract**

Increasing evidence from neuro and retinal imaging, neuropathology, epidemiology and experimental models suggests that the primary underlying initiating cause of cerebral small vessel disease is the derangement of the blood-brain barrier. This may start some years before the first symptoms, leads to the small vessel structural changes (vessel wall thickening, disorganisation and eventual breakdown) and perivascular changes (oedema, enlarged perivascular spaces, tissue damage interpreted as “infarcts”) and is fundamentally different to traditional “ischaemic” mechanisms, although small vessel occlusion due to thrombus formation on damaged vessel walls may be a late secondary phenomenon. Space limits a detailed discussion of the epidemiology and experimental evidence, so this brief review will focus on neuroimaging evidence and summarise the appearances, risk factors and associations of different components of cerebral small vessel disease as identified on imaging, discuss potential causes and, in particular, the evidence that disordered blood-brain barrier precipitates or worsens progression of cerebral small vessel disease. This mechanism may also play a role in other common disorders of ageing such as Alzheimer’s disease.

© 2010 Elsevier B.V. All rights reserved.

1. Introduction

“Cerebral small vessel disease” is a general term used to describe a range of different features, all now known to be associated with similar risk factors, pathology and imaging, but for which the cause is, as yet, unknown. Clinical and imaging findings indicate that cerebral small vessel disease is a diffuse condition. Although it may present with discrete focal neurological symptoms in the form of lacunar stroke [1], it may also present with diffuse neurostructural symptoms of progressive cognitive decline, gait disturbance and frank dementia [2]. The appearance on brain imaging, on which much of the understanding of small vessel disease is based, may be of a discrete recent lacunar infarct or small deep haemorrhage in the cerebral hemispheric white matter, basal ganglia or brainstem in patients presenting with focal neurological signs, but imaging frequently also shows evidence of diffuse changes throughout the white matter, basal ganglia and brainstem in the form of lacunes [3,4], leukoariosis, enlarged perivascular spaces (EPVS) and microbleeds [5,6]. Although originally considered to be due to different underlying pathologies, there is increasing evidence of a common underlying small vessel pathology and imaging evidence that these characteristics are all interlinked.

Lacunar stroke makes up about 20% of all strokes (25% of all ischaemic stroke) [7]. Although the symptoms rarely cause death in the acute phase, they are disabling and there is a high risk of late recurrence of lacunar stroke [8] and of cognitive decline and dementia. While a proportion of lacunar stroke may arise from atherothromboembolism, epidemiological and observational studies indicate that the proportion is likely to be small [9,10]. Instead, most lacunar stroke seems to be a distinct subtype of “ischaemic” stroke [9,11] representing a symptomatically discrete form of the diffuse underlying process that causes cerebral small vessel disease. The focus on lacunar stroke as a discrete form of cerebral small vessel disease is useful because the discrete focal symptoms with sudden onset give a point when one can consider that “the clock has started ticking” on the disease. It is then easier to track subsequent disease progression from that inception point.

There are relatively few pathology studies of acute lacunar ischaemic stroke because patients rarely die in the acute phase. In any case, it may be difficult to relate the acute symptoms to a precise small deep brain lesion, particularly if there are other abnormalities in the brain such as old infarcts or white matter lesions (leukoariosis) [12]. The most widely acknowledged original descriptions of the underlying pathology were by Miller Fisher in the 1950s who performed detailed pathological dissections along small deep perforating vessels. He identified that there appeared to be a diffuse abnormality in the small deep vessel wall which he referred to as “segmental arteriolar disorganisation” [13,14]. Others have subsequently referred to this as “lipohyalinosis” if simple and relatively mild, or “fibroinoid necrosis” if advanced and associated with major damage and disintegration of the small vessel wall [15,16]. While occasionally other causes of lacunar stroke have been identified, such as atheroma encroaching on the ostia of the small deep perforating vessels or microemboli occluding them, these would appear to be relatively...
uncommon [17] and indeed often associated with larger infarcts than are traditionally accepted as lacunar ischaemic stroke [18]. The “segmental arteriolar disorganisation” is associated not only with areas of vessel narrowing due to the thickened wall but also of luminal dilatation, loss of normal architecture in the smooth muscle and external layers and extravasation of red cells and other blood components into the perivascular space.

Imaging is not yet at the point of being able to resolve perforating arteriolar appearances reliably, although several emerging methods and use of higher field strength MR scanners may improve this, but even at conventional 1.5 Tesla field strengths, it is possible to see in about 10% of patients with acute lacunar stroke symptoms, using high-definition MR imaging, an abnormal-appearing small deep perforating arteriole with blood products (haemosiderin) in the vessel wall, possibly thrombus in the lumen and altered tissue attenuation surrounding the small vessel (indicating the lacunar ‘infarct’) [19]. There are a few points worth considering here. Small deep perforating vessels or lenticulostrate vessels branch like poplar trees rather than like oak trees [20]. Many lacunar infarcts occur along the line of the lenticulostrate artery [21], rather than at its end (as might be expected and is commonly seen in cortical ischaemic stroke where emboli occlude the blood supply to the distal arterial territory and results in infarction beyond the point of arterial obstruction). Pathologically, a form of “incomplete lacunar infarction” has been seen where there is oedema around a section of a perforating arteriole in the deep white matter or basal ganglia [22,23]. Oedema fluid would have to have entered the brain by crossing the small vessel wall, and is neurotoxic leading to perivascular neuronal damage [24].

Awareness of these features led some years ago to reconsideration of the potential underlying processes leading to the small vessel damage and effects of small vessel disease on the brain. Traditionally, the lipohyalinosis and fibrinoid necrosis have been thought of as some form of microatheroma, or a consequence of vasospasm secondary to hypertension that results in reduced blood flow and creates the small vessel disease and the lacunar infarcts and white matter lesions from interruption of blood flow i.e. from ischaemia [16,25]. However, an alternative possibility is that the vascular endothelium in the small arterioles becomes permeable to substances which would normally remain within the blood and outside the brain and should be regulated by the blood-brain barrier. These substances – proteins, inflammatory biomarkers, inflammatory and red cells – result both in damage to the small vessel wall and in perivascular oedema [22]. This constellation of events could explain the pathological and imaging features of the abnormal small arteriolar walls, lacunar infarcts, white matter lesions, and the EPVS and microhaemorrhages. In contrast, the EPVS and microhaemorrhages are difficult to explain using ischaemic mechanisms. EPVS will be explained in detail later. Microhaemorrhages could arise through an eventual breakdown of the arteriolar wall secondary to other forms of damage. These possibilities are explained diagrammatically in (Fig. 1).

What is the evidence for endothelial, or blood-brain barrier, derangement? Largely the evidence comes from imaging rather than human pathological studies, although there is increasing evidence from animal experimental models of cerebral small vessel disease also. However there is insufficient space to cover the latter topic here and the interested reader is referred to two recent systematic reviews [26,27].

In the human literature, there are numerous studies examining changes in the blood-brain barrier with normal ageing and in dementia and leukoaraiosis [28]. We systematically reviewed the literature and identified 10 studies of changes in the blood-brain barrier with normal ageing (n = 700 subjects), 26 that provided any evidence comparing subjects with any dementia versus no dementia (n = 1060 subjects), 10 studies that compared patients diagnosed as vascular dementia with those diagnosed as Alzheimer’s disease (n = 460 subjects) and 5 studies of different degrees of leukoaraiosis (n = 200 subjects) [28]. This literature data synthesis showed that increasing age was associated with the increasing permeability of the blood-brain barrier (standardised mean difference, SMD, 1.2; 95% confidence interval, CI, 0.6–1.8; p < 0.01); having any dementia (Alzheimer’s, vascular or mixed) was associated with increased blood-brain barrier permeability compared

---

**Fig. 1.** Diagram illustrating the potential mechanisms leading to the microvascular and brain tissue features of cerebral small vessel disease. A) illustrates the “microatheroma ischaemic” hypothesis, which theorises that small vessels are blocked by microatheroma, +/- vasospasm secondary to hypertension, +/- other endothelial dysfunction limiting blood flow which starves oxygen from downstream vessels and the brain. B) illustrates the “blood-brain barrier failure” hypothesis in which the small vessel endothelial walls become leaky, allowing blood proteins and other entities to enter the vessel walls causing thickening and disintegration of the vessel walls; the adjacent brain damage results when the vessel wall is breached and oedema fluid, etc., enters the brain parenchyma itself; thrombosis is a late secondary phenomenon. The figure was designed by Dr. Andrew Farrall, University of Edinburgh.
with normal age-matched controls (SMD 0.8, 95% CI 0.4–1.3, p < 0.01); having vascular dementia as opposed to a diagnosis of Alzheimer’s disease (accepting that there is both considerable overlap between these two entities and that the diagnostic criteria are not robust), was associated with increased blood-brain barrier permeability (SMD 0.7, 95% CI 0.1–1.3, p < 0.01); increasing amounts of leukoaraiosis on imaging was also associated with increasing blood-brain barrier permeability (SMD 0.6, 95% CI 0.3–0.9, p < 0.01) but there were very few studies that provided data on blood-brain barrier changes by the amount of leukoaraiosis and these studies included only 200 subjects, so this latter result is not reliable [28]. Most of the studies used biochemical tests of blood-brain barrier permeability, such as the CSF:plasma albumin ratio. Although there is some debate about whether albumin is actually synthesised within the central nervous system, it is generally accepted that the majority of albumin is synthesised on the plasma side of the blood-brain barrier and therefore any increase in CSF:plasma albumin ratio should indicate increased permeability of the blood-brain barrier. Albumin is a medium-sized protein which crosses the blood-brain barrier passively and so increasing amounts of albumin in the CSF is indicative of a general failure in the blood-brain barrier integrity, rather than of any specific active transport process. A few of the studies used imaging tests, mostly following injection of the MR contrast agent intravenous gadolinium, which is also a relatively non-specific marker of general failure of the blood-brain barrier [28]. Accepting that there is likely to be considerable “noise” in the diagnosis of dementia as well as in the methods used to assess the blood-brain barrier, nonetheless the large number of studies and subjects for most analyses generally points to there being reasonably reliable evidence for an association between failing blood-brain barrier with normal ageing and worsening of blood-brain barrier failure in patients with common forms of dementia and with increasing amounts of leukoaraiosis.

Indeed, new evidence from patients and experimental models has emerged recently emphasising the role of the blood-brain barrier, vascular endothelium and smooth muscle layers in Alzheimer’s disease. In patients with Alzheimer’s disease (and in a corresponding mouse model), blood-brain barrier dysfunction is associated with accumulation of amyloid beta-peptide in the brain, aberrant angiogenesis and reductions in the cerebral microcirculation and this is thought to be related to reduced expression of the vascular restricted mesenchyme homobox gene 2 (MEOX2) in the brain endothelium [29]. There are also problems in the cerebral microvascular smooth muscle in AD which shows increased levels of serum response factor and vascular-specific gene myocardin, two transcription factors that normally regulate vascular smooth muscle cell differentiation. Increased expression of these two transcription factors found in AD is associated with hypercontractile cerebral arterioles and reduced blood flow [30]. This in turn is thought to result in reduced clearance of amyloid beta-peptide with accumulation of amyloid in the arteriolar walls leading to cerebral amyloid angiopathy and microbleeds [31].

Is there any specific evidence of blood-brain barrier failure in patients with definite and specific forms of cerebral small vessel disease? Three recent studies, completed since the systematic review, show that the blood-brain barrier is abnormal in cerebral small vessel disease (including the study by Rosenberg and colleagues presented at this conference; full publication awaited at the time of writing) [32,33]. We studied 97 patients, half with definite clinical and imaging diagnosed lacunar ischaemic stroke and half with cortical ischaemic stroke (to provide controls for a) having a stroke and b) use of various secondary prevention drugs which might have vasoactive properties) [32,34]. We were extremely careful to establish an accurate diagnosis of lacunar versus cortical stroke, as one of the problems with many previous studies of lacunar stroke epidemiology is that about a fifth of patients diagnosed as lacunar stroke probably actually had cortical stroke (and vice versa) due to difficulties in clinical diagnosis [35]. We performed blood-brain barrier imaging at least a month after the stroke to avoid the effects of any acute change in the blood-brain barrier due to the acute stroke lesion. We performed a detailed image processing to look at different tissue sub-regions and used complex statistical modelling to account for numerous overlapping risk factors and other variables. We also analysed just the asymptomatic hemisphere to avoid the acute stroke lesion and found the same results as for the whole brain, therefore used the whole brain results. We found that the lacunar patients had more leaky blood-brain barrier in the white matter than cortical stroke patients (p < 0.0001) and also in CSF (p = 0.003), with no difference between the two stroke subtypes in the grey matter [32]. Interestingly, in addition to the association with lacunar stroke, there was also evidence of worsening blood-brain barrier function with increasing age (confirming the results shown in the systematic review [28]) and also in the presence of increasing numbers of EPVS [5]. In a small proportion of patients it was actually possible to see contrast entering the CSF both in the sulci, basal cisterns, ventricles and EPVS by performing a FLAIR scan 30 min after the MR contrast injection [32].

Two other studies found similar results although the patient and control selection criteria were different. Topkian et al. studied 24 patients with lacunar ischaemic stroke and age-matched controls and found increased blood-brain permeability in normal appearing white matter in subjects with leukoaraiosis [33]. Rosenberg et al. studied patients with vascular cognitive impairment and found evidence of blood-brain barrier failure in areas with leukoaraiosis (data presented at this conference) [36].

Why is the observation of increasing numbers of EPVS in cerebral small vessel disease [5] and also the association between worsening blood-brain function and EPVS [32] important? Perivascular spaces are invaginations of CSF-filled cavities around the small penetrating cerebral arterioles, with some entering the brain substance from the cortex medially and some entering the basal ganglia and running superiorly [37,38]. Experimental studies show that these are important conduits for normal drainage of cerebral interstitial fluid into the ventricles and hence to the venous system and they also act as important conduits for inflammatory processes [38,39]. Pathologically, vessels in the vicinity of EPVS in older subjects show arterial wall thickening and tortuosity, venular widening, features of inflammation and blood-brain barrier failure [40,41].

On imaging, increasing numbers of EPVS are associated with poorer cognitive function during normal ageing [42] and in young diabetics [43], and are also associated with hypertension, inflammation such as in multiple sclerosis [39], a lacunar as opposed to cortical stroke [5] and also increasing amounts of leukoaraiosis [5]. They are, however, a somewhat neglected feature of brain disease, having been completely missed out of all leukoaraiosis rating scales so far (although a few specific scales for quantifying EPVS separately from leukoaraiosis do exist [42,44]) and are regarded by many clinicians and researchers as a normal variant. An association with inflammation was shown recently in patients with multiple sclerosis who were followed from disease quiescence through periods of increased multiple sclerosis plaque inflammation into quiescence [39]. During periods of active inflammation, as identified by contrast-enhancement of MS plaques and elevated inflammatory plasma/CSF markers, the perivascular spaces in the plaques increased visibly in size and then decreased in size as the inflammation subsided [39]. We have observed that MS plaques can extend linearly along the length of an entire EPVS (Fig. 2) which, although anecdotal, would support other studies that indicate an important role for EPVS in neuroinflammation in symptomatic MS [39]. A close examination of age-related leukoaraiosis demonstrates that white matter lesions seem to form around EPVS (Fig. 3). The importance of EPVS and blood-brain barrier derangement is also suggested by careful examination of the distribution of leukoaraiosis. Leukoaraiosis tends to form around the ventricles and to radiate out towards the cortex, exactly following the lines of distribution of the perforating vessels and their corresponding perivascular spaces (Fig. 3). This suggests that EPVS may be an imaging biomarker for early alteration of blood-brain barrier function [45] and may provide a useful marker of
subjects or patients at risk of leukoaraiosis, future stroke and cognitive decline and the adequacy of any treatment. Whether EPVS are also involved in the pathogenesis of Alzheimer’s disease, as might be expected from the abnormal endothelial and smooth muscle cell function resulting from abnormal regulatory transcription factors found in recent molecular studies [29–31], has yet to be determined.

Venular widening is an important, if poorly understood, feature of cerebral small vessel disease. Although we cannot yet accurately distinguish venular changes from other small vessel changes in the brain on imaging, or as yet visualise the venules or arterioles in detail (although some very promising sequences, such as susceptibility-weighted imaging for venules or high field strength MR angiography sequences for arterioles are emerging), we can use the retina as a surrogate for cerebral small vessel changes. Venular widening (and arteriolar narrowing) is seen in the retina in association with lacunar stroke (as opposed to non-lacunar stroke) phenotype [46,47]. As the retina is developmentally closely related to the brain, it provides the one opportunity to visualise repeatedly in life the structural appearance of small vessels. The sequence of retinovascular changes and how they relate to the sequence of changes in the brain [48,49] is not yet well understood as there are insufficient longitudinal data. Nor do we understand yet which retinal vascular and retinopathic changes simply indicate the presence of risk factors that might also affect the brain (such as hypertension and diabetes), or the relation to the pathological process that might drive the brain changes. For example, although some features of retinal disease are associated with blood-retinal barrier breakdown [50,51], other features such as arteriolar narrowing and venular widening could be precipitated by some sort of response to ischaemia, although they bear considerable similarity to the pathological features identified in the brain that relate to blood-brain barrier breakdown in small vessel disease [40,41].

All we have demonstrated so far is evidence that there is blood-brain failure in the presence of existing cerebral small vessel disease. This does not tell us if the blood-brain barrier failure is a cause or a consequence of the small vessel disease. If blood-brain barrier failure was causative, or at least exacerbated the brain features of small vessel disease, then you would predict that the people with the most abnormal blood-brain barrier function at presentation would have the most rapidly progressive features of small vessel disease-related brain damage during follow-up and perhaps also the most recurrent lacunar strokes or cognitive decline and disability. We recently tested this in a pilot study where we performed follow-up imaging and clinical assessment on 50 patients who had participated in our original cross-sectional study [32]. We found that leukoaraiosis had progressed in some patients which was unrelated to age but that was related to having more leukoaraiosis initially. Worsening disability at follow-up was also associated with worse blood-brain barrier integrity at initial presentation. A few patients with particularly striking blood-brain barrier derangement on imaging at original presentation had visibly obvious progression of leukoaraiosis and microhaemorrhages at follow-up. However, quantification of change in leukoaraiosis during follow-up is difficult because, while the leukoaraiosis may increase in extent and number, the original stroke lesion may decrease in size as part
of the natural evolution of lacunar and cortical lesions and contaminate the attempt to measure just the change in leukoaraiosis. New image processing methods will be required to account for this and further analysis is ongoing. One other small study found that blood-brain barrier failure measured using CSF–plasma albumin ratio predated progression of cognitive decline [52]. Clearly further studies with long term follow-up of clinical and imaging parameters are required.

In summary, blood-brain barrier integrity declines slowly with normal ageing and is worse in patients with dementia and with small vessel disease. Failure of the blood-brain barrier plays a key role in lacunar stroke, leukoaraiosis and other features of cerebral small vessel disease, as well as in other age-related diseases such as Alzheimer’s disease, and can explain many of the imaging and pathological observations more completely than can hypotheses that rely primarily on ischaemic mechanisms. Preliminary results suggest that blood-brain barrier failure pre-dates clinical and imaging progressions of small vessel disease. Enlarged perivascular spaces are an important marker of small vessel disease, are a pathway whereby inflammation and other processes can damage the brain, and may be a biomarker of incipient blood-brain barrier failure. Further studies are required to confirm these findings, but the most important messages in studies of lacunar stroke and other features of small vessel disease are that it is extremely important to phenotype lacunar ischaemic stroke and differentiate it from cortical ischaemic stroke very, very carefully; it is important to use risk factor-free definitions of stroke subtype; it is critical to use optimal imaging to identify the acute ischaemic lesion and quantify other features of small vessel disease; it is critical to have an appropriate control group with a different type of stroke as this is the only way that one can control for the effects of drugs, exposure to common vascular risk factors and other features which may otherwise confound any association between lacunar stroke and its underlying mechanism.

Further larger studies with long term follow-up are required to define the role of blood-brain barrier failure in the pathogenesis of cerebral small vessel disease, and to determine what causes the blood-
brain barrier derangement in the first place, as well as to continue to explore alternative mechanistic hypotheses.

Conflicts of interest

The author has various academic grants each totalling more than $10,000 that supported the research described in this review (all disclosed in primary publications) but none of these are considered to represent any significant personal conflict of interest.

Acknowledgements and funding

The author is currently partly funded by the Scottish Funding (SINAPSE) Collaboration (www.sinapse.ac.uk). The author would like to thank colleagues who have participated in the programme of work which produced the evidence described in this review and referenced in the text. In particular, she would like to thank Dr. Andrew Farrall for preparing the original diagram produced in modified form in Fig. 1, and Dr. Susana Munoz-Maniega and Dr. María Valdez Hernandez for creating the image in Fig. 3B.

References


