Towards defining the neuropathological substrates of vascular dementia

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Abstract

Cerebrovascular disease is highly heterogeneous but can culminate in vascular cognitive impairment or vascular dementia (VaD). As much as the clinical diagnosis warrants scrutiny, the neuropathological substrates of VaD also need to be better defined. Atherosclerosis and small vessel disease are the main causes of brain infarction. Lacunar infarcts or multiple microinfarcts in the basal ganglia, thalamus, brainstem and white matter are associated with more than half of VaD cases consistent with subcortical ischaemic VaD. White matter changes including regions of incomplete infarction are usually widespread in VaD, but their contribution to impairment is not explicit. Other pathologies including hippocampal injury and Alzheimer type of lesions may also modify the course of dementia. Similar to other common dementias consensus criteria for VaD need unambiguous definition to impact on preventative and treatment strategies and are critical for selective recruitment to clinical trials.

Keywords: Alzheimer’s disease; Cerebral amyloid angiopathy; Dementia; Hyalnosis; Small vessel disease; Cerebrovascular degeneration; Vascular dementia

Vascular dementia (VaD) remains the second most common cause of age-related dementia. VaD may result from all forms of cerebrovascular injury, which sometimes may include post-stroke syndromes [1]. The challenge of defining the pathological substrates of VaD is complicated by the heterogeneous nature of cerebrovascular disease and coexistence of other pathologies including Alzheimer type of lesions. Blood vessel size and origin of vascular occlusion are critical factors in defining subtypes of VaD. Multi-infarct dementia is caused by large vessel disease, whereas Binswanger type of VaD involving subcortical regions including the white matter results from small vessel changes. Subcortical ischaemic VaD appears the most significant subtype of VaD [2]. Other factors that may define the subtype and degree of impairment include multiplicity, size, anatomical location, laterality and age of the lesion (Table 1). It is imperative to recognise subtypes of VaD yet not devise numerous categories to make the task overly complicated [3].

1. Cerebrovascular disease, VaD and mixed dementia

It is long understood that the clinical diagnosis of VaD in demented patients with evidence of cerebrovascular lesions applies only when other causes of dementia are ruled out [4]. As with diagnosis of other causes of dementia consensus may be derived from a range of investigations including a detailed clinical history, timing of event, neuropsychometric tests, neuroimaging and neuropathological reports in accord with the DSM criteria. Perhaps inevitably as in the Alzheimer’s disease (AD) model, diagnostic criteria based on the pathological findings should be quantified and related to the progression of cognitive impairment [5].

In addition to VaD, the diagnosis of mixed dementia (AD and VaD or less frequently dementia with Lewy bodies and VaD) particularly among the oldest old (>85 years of age) is a challenge. Clinical and pathological evidence indicates combined neurodegenerative and vascular pathologies...
worsen presentation and outcome of dementia [6,7]. A high proportion of individuals fulfilling the neuropathological diagnosis of AD have significant cerebrovascular lesions including silent infarcts and extensive white matter disease upon imaging [8–11]. Conversely, clinically diagnosed VaD patients frequently show extensive AD-type neuropathological changes [12–14]. Nolan et al. [14] reported that 87% of the patients enrolled in a prospective series to examine VaD in a dementia clinic were found to have AD either alone (58%) or in combination with cerebrovascular disease (42%) at postmortem. All of the patients with signs of cerebrovascular disease were also found to have some concomitant neurodegenerative disease (Fig. 1). Similarly, another study indicated that large numbers of VaD cases without coexisting neuropathological evidence of AD suggests that “pure” VaD is very uncommon [13]. Therefore, current clinical diagnostic criteria serve to detect pathology but not “pure” pathology. Early validation studies indicated that while mixed dementia could be distinguished from AD, it could not be separated from VaD [15]. Recent studies suggest that 30–50% of mixed AD and VaD cases are misclassified as VaD [16,17], and the neuroimaging component of the NINDS-AIREN criteria does not distinguish between people with and without dementia in the context of cerebrovascular disease [18]. The potential overlap of pathologies is therefore complex, with different types of cerebrovascular lesions including cortical and subcortical infarction and small vessel disease [19,20], and different types and severity of neurodegenerative changes involving tau, amyloid and α-synuclein pathology. While evidence-based pathological criteria for the diagnosis of mixed dementia remains to be perfected the diagnosis should be made when a primary neurodegenerative disease known to cause dementia exists with one or more of the pathological lesions defining the VaD subtypes (Table 2). Thus, a combination of the nominal three or more infarctions and Alzheimer pathology above stage III may warrant such a diagnosis.

From the essential information derived at autopsy (Table 1), in Newcastle, we have proposed the neuropathological diagnosis of probable VaD or less popular “pure VaD” be based on the exclusion of a primary neurodegenerative disease known to cause dementia and the presence of cerebrovascular pathology that defines one or more of the VaD subtypes (Table 2). These would include dementia among post-stroke survivors who fulfil the NINDS-AIREN [3] criteria for probable VaD. Those stroke survivors with mild cognitive impairment could be classed as exhibiting vascular cognitive impairment but the criteria for this extension are not widely accepted [1]. The diagnosis of possible VaD may be used when the brain contains vascular

![Fig. 1. Pathological diagnosis of clinical cases originally classed as VaD. Mixed type 1 revealed large infarcts, whereas mixed type 2 predominantly exhibited small vessel disease with microinfarction. Other included dementia with mild Parkinson disease and depression. Abbreviations: AD, Alzheimer’s disease; DLB, dementia with Lewy bodies.](image-url)

Table 1
Key variables to define the pathology of VaD

<table>
<thead>
<tr>
<th>Vascular dementia subtypes related to</th>
<th>Subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large infarct or several infarcts (&gt;50 ml loss of tissue); MFD</td>
<td>I</td>
</tr>
<tr>
<td>Multiple small or microinfarcts (&gt;3 with minimum diameter 5 mm); small vessel disease* (involving greater than three coronal levels; hyalinisation, CAA, lacunar infarcts, perivascular changes)</td>
<td>II</td>
</tr>
<tr>
<td>Strategic infarcts (e.g., thalamus, hippocampus)</td>
<td>III</td>
</tr>
<tr>
<td>Cerebral hypoperfusion (hippocampal sclerosis, ischaemic–anoxic damage, cortical laminar necrosis, borderzone infarcts involving three different coronal levels)</td>
<td>IV</td>
</tr>
<tr>
<td>Cerebral haemorrhages (lobar, ICH or SAH)</td>
<td>V</td>
</tr>
<tr>
<td>Cerebrovascular changes with AD pathology</td>
<td>VI</td>
</tr>
<tr>
<td>(above Braak III), Mixed dementia</td>
<td></td>
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</tbody>
</table>
pathology, which does not fulfil the criteria in one of the subtypes but where no other explanation for dementia is found.

2. Brain vascular lesions and VaD

Majority of arterial territory infarctions, which may be admixed in cortical and subcortical regions, result from atherothrombembolism. This may be responsible for up to 50% of all ischaemic strokes, whereas intracranial small vessel disease causes 25% of the infarcts [21]. Small vessel alternations involve arteriosclerosis and hyalnosis and associated with lacunar infarcts and lacunes predominantly occurring in the subcortical structures. White matter disease or subcortical leukoencephalopathy with incomplete infarction and small vessel disease are common pathological changes in cerebrovascular disease. Other features include borderzone (watershed) infarctions, laminar necrosis and amyloid angiopathy (Table 2). Complicated angiopathies such as fibromuscular dysplasia, arterial dissections, granulomatous angiitis, collagen vascular disease and giant-cell arteritis are rarer causes of cerebrovascular disease [21] and VaD.

Previous studies have recorded ischaemic, oedematous and haemorrhagic lesions affecting the brain circulation or perfusion to be associated with VaD (Table 3). In four studies where VaD was diagnosed, 75% of the cases revealed cortical and subcortical infarcts suggesting other vascular pathologies involving incomplete infarction or borderzone infarcts could be important factors. Among other lesions 25% of cases had cystic infarcts, whereas 50% of cases had lacunar infarcts or microinfarcts. Lacunar infarcts, however, appear to be a common category of infarcts and currently recognised as the most frequent cause of stroke [21]. Severe amyloid angiopathy was present in 10% of the cases. Most interestingly, 55% of the cases revealed hippocampal atrophy in one study [22]. One of the studies concluded that ischaemic vascular disease appears to correlate with widespread small ischaemic lesions distributed throughout the CNS [22].

2.1. Large infarction and large vessel pathology

Large infarction or macroinfarction is normally defined as that visible upon gross examination of the brain at autopsy. As indicated above atherosclerosis is considered the main cause of large vessel occlusion leading to large infarcts. The stages of atherosclerosis may vary from accumulation of foam cells causing fatty streaks to complicated atheromas involving extracellular matrix components and even viral or bacterial infections. Occlusion of the extracranial arteries such as the internal carotid artery and the main intracranial arteries of the circle of Willis including the middle cerebral artery can lead to multi-infarct dementia, which forms approximately 15% of VaD [23]. In severe cases, medium-sized arteries in the leptomeninges and proximal perforating arteries could be involved. The damage could be worse depending upon the presence of hypertension. Artery-to-artery embolism involves breaking of thrombi from the often ulcerated lesions in the extracranial arteries, e.g., at the bifurcation of common carotid artery or the heart. The thrombi may contain, in addition to coagulated blood and platelets, cholesterol and calcified deposits from the underlying atheromatous plaque. Various types of cardiogenic emboli may also find their way to the anterior or particularly the posterior cerebral circulation to cause infarcts in the territory of the posterior cerebral artery or superior cerebellar artery.

Arterial territorial infarctions involve four principal areas particularly those supplied by the major arteries: anterior, middle cerebral artery, posterior artery and the territory between the anterior and middle cerebral artery [21]. The size of these infarctions is determined by assessing the two largest diameters of each lesion (Table 1). The typical infarct comprises the central core with complete infarction surrounded by a narrow perifocal hypoperfused (or penumbra) zone of incomplete infarction, which may be oedematous, leads into normal appearing tissue. The core may involve both the cortex and underlying white matter that is devoid of functional components such as neurones, axons and oligodendrocytes and may in time form cavitated lesions or scars devoid cells or haemosiderin. Prior to scar formation between 3 and 14 days, infarct cores attract neutrophils, lipid-laden macrophages or microglia and astrocytes in the lesion, which is easily assessed upon routine staining. The intensity of gliosis, both astrocytic and microgliosis, is an important consideration in judging the degree and age of infarction. Degrees of gliosis or glial scars may be seen in brains subjected to global ischaemia, i.e., after transient cardiac arrest where responses may be observed in vulnerable neuronal groups within the hippocampus or neocortical laminae (Table 1).

2.2. Lacunes and lacunar infarcts

Lacunar infarcts and microinfarcts appear central to the most common cause of VaD [19–22]. Lacunes are complete

Table 3

<table>
<thead>
<tr>
<th>Pathological feature</th>
<th>% cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete infarctions (cortical and subcortical)</td>
<td>75</td>
</tr>
<tr>
<td>Lacunar infarcts (mostly WM and BG)</td>
<td>50</td>
</tr>
<tr>
<td>Small or microinfarcts</td>
<td>50</td>
</tr>
<tr>
<td>Cystic infarcts</td>
<td>25</td>
</tr>
<tr>
<td>Cerebral amyloid angiopathy</td>
<td>10</td>
</tr>
<tr>
<td>Intracerebral haemorrhages</td>
<td>2</td>
</tr>
<tr>
<td>Hippocampal atrophy and sclerosis</td>
<td>55</td>
</tr>
</tbody>
</table>

Data compiled from 70 cases reported in previous studies ([12,19,20]; Kalaria et al., unpublished observations), % cases are averaged from two or more reported studies. Cystic infarcts (possibly also lacunar) with typically ragged edges were admixed in both cortical and subcortical structures. Abbreviations: BG, basal ganglia; WM, white matter.
or cavitating infarcts as defined above, measuring up to 15 mm in diameter seen radiologically and upon gross examination at autopsy. These lesions are largely confined to the cerebral white matter and subcortical structures including the thalamus, basal ganglia and brainstem. Most lacunes, as remnants of small infarcts, are detected in the cystic or chronic stage with no viable central tissue but could have perifocal regions with incomplete infarction, particularly in the white matter. A few lacunes may represent healed or reabsorbed as minute or petechial haemorrhages. Microlacunes have also been described which essentially should be thought of as large cystic microinfarcts. To distinguish perivascular cavities, it has been suggested that lacunes be classed into three subtypes: lacunar infarcts, lacunar haemorrhages and dilated perivascular spaces [21]. Lacunar infarcts usually result from progressive small vessel disease manifested as hypertensive angiopathy that may involve stenosis caused by hyalinosis. Small vessel disease in a perforating artery, for example, may also reveal regions of incomplete infarction, attenuation or rarefaction usually recognised by pallor upon microscopic examination. However, lacunar lesions can also be caused by infections and neoplasms. Lacunes are associated with small perivascular cavities up to 2 mm in width often found in the basal ganglia and the white matter. Perivascular cavities or empty spaces resulting from distortion or elongation of small arteries collectively referred to as etat lacunaire in the grey matter and etat crible in the white matter may be numerous in older subjects.

2.3. Microinfarction

Microinfarcts have been variably described but are widely attributed to small ischaemic lesions visible only upon light microscopy (Fig. 2A). These lesions of up to 4 mm diameter may or may not involve a small vessel at their centre but are foci with pallor, neuronal loss, axonal damage (white matter) and gliosis. Sometimes these may include regions of incomplete infarction or rarefied (subacute) change. Microinfarcts have also been described as attenuated lesions of indistinct nature occurring in both cortical or subcortical regions. Such lesions or combination of these should be reported when they are multiple or at least greater than three present in any region (Table 2).

2.4. Small vessel disease

Small vessels, including intracerebral end-arteries and arterioles, undergo progressive age-related changes [24], which may result in lacunar or microinfarcts. These range from wall thickening by hyalinosis, reduction or increment of the intima to severe arteriosclerosis and fibroid necrosis (Fig. 2B). Uncomplicated hyalinosis is characterised by almost complete degeneration of vascular smooth muscle cells (becomes acellular) with concentric accumulation of extracellular matrix components like the collagens and fibroblasts [24]. These changes are most common in the small vasculature of the white matter (Fig. 2B). Small vessel changes likely promote occlusion or progressive stenosis with consequent acute or chronic ischaemia of the tissue behind it. Alternatively, arteriosclerotic changes located in small vessels in the deep white matter and basal ganglia may cause vessels to loose their elasticity to dilate and constrict in response to variations of systemic blood pressure or loss of auto-regulation. This, in turn, causes fluctuations in blood flow response and changes in cerebral perfusion. The deep cerebral structures would be rendered most vulnerable because the vessels are end arteries almost devoid of anastomoses. Small vessel pathology could lead also to oedema and damage of the blood–brain barrier (BBB) with chronic leakage of fluid and macromolecules in the white matter [25].

2.5. Cerebral amyloid angiopathy

While CAA is most common in AD and consistently present in Down’s syndrome [8], it also occurs in elderly subjects with cerebrovascular disease in the general absence of Alzheimer lesions [26]. Amyloid β protein accumulation within or juxtaposed to the vasculature may lead to degeneration of vascular cells in both larger perforating arterial vessels as well as cerebral capillaries that represent...
the BBB. These likely result in microinfarctions and perivascular cavities similar to those seen in hyalinised vessels in subcortical structures. CAA is an important cause of intracerebral and lobar haemorrhages leading to profound ischaemic damage [27]. CAA also appears to be causally related to white matter changes described by subcortical leuencephalopathy in patients with CAA, who lacked changes characteristic of AD [24]. Genetic factors, such as the APOE 4 allele associated with severity of CAA may modify or attenuate the perfusion of the white matter [28].

2.6. Alzheimer pathology

Alzheimer lesions, including amyloid plaques and neurofibrillary pathology, occur more often in cases of cerebrovascular disease than normal ageing elderly [11]. VaD cases may also bear other AD type lesions including cholinergic neuronal deficits [11]. If the location of the Alzheimer pathology in such cases is restricted to the hippocampus and the density of neuritic plaques or tangles does not exceed stage III of the criteria defined by Thal et al. [29] and Braak and Braak [30], they could be diagnosed as VaD. This is similar to the converse where dementia cases meeting CERAD criteria for probable AD may exhibit infarctions or white matter changes. However, cases of cerebrovascular disease fulfilling the criteria for the diagnosis of VaD (Table 2) with concomitant Alzheimer pathology above stage III for plaques and tangles should be designated as mixed dementia.

2.7. White matter disease

White matter lesions (or subcortical leuencephalopathy) incorporating myelin loss are considered a consequence of vascular disease. The frequency of white matter changes is increased in patients with cerebrovascular disease and those at risk for vascular disease including arterial hypertension, cardiovascular disease and diabetes mellitus [1]. White matter lesions occur in ~30% of AD and dementia with Lewy body (DLB) cases and may be present irrespective of the focal lesions in VaD [31]. It is often argued that white matter damage in patients with AD might simply reflect Wallerian changes secondary to cortical loss of neurons. However, this is unlikely since histological changes characteristic of Wallerian degeneration are not evident as white matter pallor. Conversely, in AD patients with severe loss of cortical neurones similar white matter lesions are not apparent [31].

Lesions in the deep white matter have been correlated with dementia including VaD [1,11]. Although the boundary between the periventricular and deep white matter depends on the coursing of the fibres within the plane for purposes of quantification, the deep white matter is considered to be 0.5–1 cm from the ventricle wall. Lacunar infarcts are produced when the ischaemic damage is focal and of sufficient severity to result in a small area of necrosis whereas diffuse white matter change is considered to be a form of rarefaction or incomplete infarction where there may be selective damage to some cellular components. While the U-fibres are usually spared, white matter disease comprises several patterns of alterations including pallor or swelling of myelin, loss of oligodendrocytes, axons and myelin fibres, cavitations with or without the presence of macrophages and areas of reactive astrogliosis, where the astrocytic cytoplasm and cell processes may be visible with standard stains. Lesions in the white matter also include spongiosis, i.e., vacuolisation of the white matter structures and widening of the perivascular spaces. A standard method of grading the degree of both the periventricular and deep white matter regions including the U-fibres is warranted. In vitro imaging methods may be devised using conventional myelin stains such as Luxol Fast Blue and Loyez, which are cheap but sometimes capricious.

2.8. Hippocampal sclerosis

Hippocampal neurones in the Sommer’s sector are highly vulnerable to disturbances in the cerebral circulation or hypoxia caused by systemic or cardiovascular disease. Severe loss of hippocampal neurones within the CA fields and infarctions along Ammon’s horn are evident in a proportion (10–20%) of usually older (>80 years) VaD cases. The loss of cells should be graded when this is evident together with any microinfarctions within the hippocampal formation [32]. Hippocampal sclerosis is likely a major contributing factor in the hippocampal atrophy described at gross examination.

2.9. Borderzone (watershed) infarcts

The borderzone or watershed infarctions mostly occur from haemodynamic events, usually in patients with severe internal carotid artery stenosis. They can occur bilaterally or unilaterally and disposed to regions between two main arterial territories, deep and superficial vessel systems. Typical borderzone infarctions may be 5 mm or more wide as wedge-shaped regions of pallor and rarefaction extending into the white matter. The white matter usually develops larger areas of such rarefaction or subacute change [21,23].

2.10. Laminar necrosis

Laminar necrosis is characterised by neuronal ischaemic changes leading to neuronal loss and gliosis in the cortical ribbon. This is particularly apparent in cases where global ischaemia or hypoperfusion has occurred as in cardiac arrest. Typical topographic distribution of spongiform form change can be readily apparent with standard stains. They appear more commonly at the arterial border zones [21,23] that may fall into the subtype IV of VaD pathology (Table 2).
3. Conclusions

The heterogeneous nature of cerebrovascular disease compels better understanding of the neuropathological substrates of VaD for wide application. Small vessel disease leading to lacunes or multiple microinfarcts in the subcortical structures appear most involved in a major subtype of VaD. White matter pathology is frequent in VaD, but it needs evaluation to enable correlation with cognitive decline. Whether hippocampal changes remote from sites of ischaemic injury or Alzheimer pathology contribute to the disease progression is unclear. The systematic classification of VaD pathological subtypes should be applied universally. The clear definition of the neuropathological correlates of VaD would be useful for preventative and treatment strategies.

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References
