Title:

The influence of cerebrovascular disease in dementia with Lewy bodies and Parkinson's disease dementia

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Abstract:

Introduction: Lewy body dementia (LBD), including dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), is a common form of neurodegenerative dementia. The frequency and influence of comorbid cerebrovascular disease is not understood but has potentially important clinical management implications.

Methods: A systematic literature search was conducted (Medline and Embase) for studies including participants with DLB and/or PDD assessing cerebrovascular lesions (imaging and pathological studies). They included white matter changes, cerebral amyloid angiopathy (CAA), cerebral microbleeds (CMB), macroscopic infarcts, micro-infarcts and intracerebral haemorrhage.

Results: Of 4411 articles, 63 studies were included. Cerebrovascular lesions commonly studied included white matter changes (41 studies) and CMB (18 studies). There was an increased severity of white matter changes on magnetic resonance imaging (visualized as white matter hyperintensities, WMH), but not neuropathology, in LBD compared to PD without dementia and age-matched controls. CMB prevalence in DLB was highly variable but broadly similar to Alzheimer's disease (AD) (0-48%), with a lobar predominance. No relationship was found between large cortical or small subcortical infarcts or intracerebral haemorrhage and presence of LBD.

Conclusion: The underlying mechanisms of WMH in LBD require further exploration, as their increased severity in LBD was not supported by neuropathological examination of white matter. CMB in LBD had a similar prevalence as AD. There is a need for larger studies assessing the influence of cerebrovascular lesions on clinical symptoms, disease progression and outcomes.

Introduction

Lewy body dementia (LBD), including dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), is a common form of neurodegenerative dementia. Clinical features of DLB include fluctuating cognition, recurrent visual hallucinations, rapid eye movement sleep behavior disorder and parkinsonism [1]. PDD has similar features to DLB but is diagnosed when the onset of dementia is at least one year after established parkinsonism[1]. Lewy body pathology, involving

aggregation of the synaptic protein α-synuclein, characterizes LBD and is prevalent in is up to 5% in the general population and up to 30% in people with dementia [1-3].

Comorbid pathology, including amyloid-β, tau and cerebrovascular disease occurs commonly in dementia, including LBD [4]. Cerebrovascular disease is of particular interest as there are potential prevention and treatment options. In dementia, it is unclear whether cerebrovascular disease interacts with the neurodegenerative process or whether its effect is purely additive, although in Alzheimer's disease, the trajectory of cognitive decline may be accelerated by the presence of cerebrovascular disease [5]. Cerebrovascular disease has multiple manifestations that can be detected on neuroimaging and neuropathological examination. The following cerebrovascular lesions will be examined in this review and have been associated with cognitive decline: white matter changes, cerebral microbleeds and minibleeds, cerebral amyloid angiopathy, cortical and subcortical infarcts and intracerebral haemorrhage and microinfarcts [6-17].

White matter changes can be seen either on MRI ("white matter hyperintensities", WMH) or detected on neuropathological examination ("white matter lesions", WML). WMH may represent ischaemic tissue damage, with disruption of the blood brain barrier and leakage of plasma and may develop from small clinically silent infarcts [18-21]. They may have different aetiologies based on location (fig 2); peri-ventricular WMH may be caused by ischaemic damage due to atherosclerosis, while deep subcortical WMH are associated with small vessel disease and presence of lacunar infarcts [18,22].

Cerebral microbleeds (CMB), which consist of haemosiderin and are associated with lipofibrohyalinosis of the cerebral vasculature, have also been associated with cognitive impairment [23] [10-14]. CMB have an increased prevalence in AD (18-32%), which may be due to an increased prevalence of CAA as CMB in the lobar regions are associated with CAA [23-25]. They are seen on MRI as black round or ovoid lesions with a blooming effect on susceptibility-weighted MRI, usually between 2-10mm in diameter [26,27]. Mini-bleeds, another type of small cerebral bleeds, are defined as an accumulation of erythrocytes or siderophages in the perivascular region and are only visible microscopically [11,28]. CMB quantification in research can be through manual

counting or a semi-quantitative ranking scale. More recently, automated methods have been explored and may have increased sensitivity, although specificity is limited [29-31].

CAA is another cerebrovascular lesion that, although associated with the presence of AD pathology, may contribute to cognitive decline independently of AD pathology [15,16]. CAA results from deposition of β-amyloid (Aβ) in the cerebral and meningeal vasculature (mainly arteries and arterioles), with an increasing prevalence with age [32]. It can be diagnosed on cerebral imaging using certain criteria (e.g. the Boston criteria), but the gold standard is histopathological diagnosis [33].

Cerebral microinfarcts (definitions vary from microscopic infarcts to infarcts that up to 5mm in size) have been linked with development of dementia, even in the absence of other pathology (e.g. Alzheimer's disease) [17]. They are detected on microscopic examination at autopsy (e.g. with a semi-quantitative scale), although more recently studies have detected micro-infarcts using 7T and 3T MRI [34].

This comprehensive review examines the frequency and influence of cerebrovascular disease in LBD. Results of neuroimaging and neuropathological studies of vascular brain disease in LBD are discussed and recommendations for future work are provided.

Methods

A systematic literature search was conducted as per the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [35] using the electronic databases Medline and Embase for articles in English from the database inception to 21st July 2021. Reference lists were also systematically checked for relevant articles. Studies included assessed the presence and/or location of cerebrovascular lesions on either magnetic resonance imaging (MRI) or neuropathological studies of DLB or PDD. Case reports, conference abstracts and studies including < 5 participants with LBD were excluded. The search terms included both keywords and subject headings. The Embase search strategy (from inception until July 2021 when the search was run) was as follows:

((white matter lesion* or white matter hyperintensit* or cerebral amyloid or angiopathy or vascular or cerebrovascular or stroke or infarct* or microinfarct* or microvascular or h$emorrhage* or microbleed* or micro-bleed*).tw or white matter injury/ or white matter lesion/ or vascular amyloidosis/ or cerebrovascular accident/ or occlusive cerebrovascular disease/ or brain infarction/ or intracerebral bleeding/ or intracerebral haemorrhage/) AND ((Parkinson* or Lewy).tw or parkinson disease/ or parkinson dementia complex/ or symptomatic parkinson disease/ or diffuse lewy body disease/ or lewy body/) AND (autopsy/ or nuclear magnetic resonance imaging/ or (magnetic resonance imaging or neuropatholog* or autopsy).mp) AND limit to (human and English language). We conducted a narrative review of the literature based on the findings of the systematic literature review.

Results

Sixty-three studies were included (fig 1), with studies on white matter lesions (N=42), cerebral microbleeds and mini-bleeds (N=18), cerebral amyloid angiopathy (N=16), large cortical and small subcortical infarcts (N=17), microinfarcts (N=12) and intracerebral haemorrhage (N=8). There was commonly more than one lesion examined in each particular study.

White matter lesions of presumed vascular origin

Studies on white matter lesions included MRI studies (N=31) and neuropathological studies (N=11). MRI studies (LBD participant numbers ranged from N=8 - 165) compared LBD participants to healthy controls, AD, and PD. Most MRI studies showed an increased prevalence and/or severity of deep and peri-ventricular WMH in LBD compared to PD without dementia and age-matched controls (table 1) [36-49]. Sarro et al (2017) included one of the largest DLB participant groups (n=81) and used 3T MRI with a semi-automated method of WMH quantification (corrected for brain volume), which was increased in DLB compared to aged-matched controls [36]. Several longitudinal studies found an association between WMH in PD and progression to PDD, but in others, WMH was not associated with progression to PDD after accounting for other confounding variables (e.g. age, CSF Aβ and hippocampal volume) [47,50-56].

Although some studies suggested an increased severity of MRI WMH in DLB compared to PDD, particularly in the parietal and occipital regions [40,57], others did not find a statistically significant difference; the differing results may be due to a different WMH measurement method, differing population groups or a relatively small sample size of DLB participants [38,42].

There was a similar prevalence and severity of MRI WMH in DLB and AD in the peri-ventricular [37,40,41,58-60] and deep white matter [37,40,41,58,59], with the posterior periventricular and occipital regions being more affected in DLB compared to AD [36]. However, a study by Kenny et al (2004) suggested that only the deep WMH (but not peri-ventricular or basal ganglia hyper-intensities) were more severe in DLB (n=38) than AD (n=52) [60]. This finding suggests the possibility of a separate mechanism for development of peri-ventricular WMH in AD, such as an increased water content in the peri-ventricular white matter related to cortical degeneration [22]. It has been suggested that WMH in AD may be a core feature involved in its pathogenesis, although the mechanism is yet unknown [61].

Neuropathological studies included between 8 and 48 LBD participants and mainly compared WML to controls. They examined a selected number of brain sections and used a semi-quantitative rating scale (table 2) [11,28,62-64]. The prevalence of WML in LBD ranged from 25-48%, compared to 4-31% in controls. Types of WML were mostly unspecified, but in some studies were defined as axonal or myelin loss. Unlike MRI studies, neuropathology studies mostly found similar rates of WML in LBD compared to age-matched controls [11,28,62,63,65,66]. Other studies suggested a relationship between WML and LBD, although interpretation of some of the results may have been confounded by other variables such as age of participants [6,67,68 69].

There does not appear to be a clear correlation between WML and clinical outcomes in LBD, either in the presence of core clinical features, dementia severity or motor scores, although REM sleep behaviour disorder has been associated with lower WMH volume in DLB [36,70]. Ferreira et al (2021) studied 165 DLB participants and reported that a higher WMH burden was associated with presence of visual hallucinations in DLB [71]. Conversely, Barber (1999) reported that occipital WMH

were associated with the absence of visual hallucinations and delusions, but this was a smaller study (27 DLB participants) and also included other dementia types in the analysis [37]. Two cross-sectional studies found that WMH severity correlated with reduced scores on neuropsychiatric testing (including Mini Mental State Examination, Clinical Dementia Rating and the Seoul Verbal Learning Test) [38,71]. Furthermore, there may be an association between autonomic dysfunction, which is a supportive feature for the clinical diagnosis of DLB, and the severity of deep but not periventricular WMH[1,72].

Cerebral microbleeds and mini-bleeds

Eighteen studies examined CMB and mini-bleeds in LBD (N=7 – 91 participants), but there were some conflicting results and possible study biases. Most studies compared DLB to controls, but the other comparison groups also included AD, PD and PDD. The prevalence of CMB in DLB ranged from 0-48% and in controls from 0-50% (table 3). Four autopsy studies reported similar rates of CMB in DLB compared to age-matched controls, although mini-bleeds had an increased frequency [11,28,63,66,73]. In contrast, other studies reported an increased prevalence of CMB in DLB (45%) compared to PDD (26%) and controls (17%) and in PDD (35%) compared to PD with mild cognitive impairment and PD (prevalence of 15% in both) [42 44,46]. Variability in characteristics between LBD participants and controls may have contributed to the differences in these results, for example differences in age and prevalence of cardiovascular risk factors between groups in some of the studies [28,67]. In comparison to AD, several studies showed a similar prevalence of CMB in DLB [58,64,73-76]. CMB and mini-bleeds were more prevalent in lobar rather than deep and infra-tentorial regions, where rates were similar to controls [11,28,42,67,75-77]. Although this suggests that CMB in LBD may be related to AD-related pathology, including CAA, studies have not supported this theory. Donaghy et al (2020) examined 30 DLB participants using MRI and amyloid PET imaging and did not find an association between amyloid and presence of CMB [75]. Two smaller neuropathological studies by de Reuck et al (2013 and 2015) also explored this and found no significant difference was found in CMB and mini-bleeds between DLB participants with AD and CAA pathology and those without [63,67]. Mendes et al (2021) included 91 DLB participants and did not find an association between CMB in DLB and presence of cerebrospinal

fluid AD biomarkers, including tau, phosphorylated tau and amyloid-ß (1-42) [76]. An alternative proposed theory is that CMB in LBD may be associated with increased angiogenesis related to Lewy body pathology [67,78].
Fukui et al (2013) assessed clinical and imaging correlations of CMB in DLB. An increased number of CMB was associated with cognitive rather than motor impairment at onset of the disease [58]. In some studies, DLB participants with CMB had lower scores on neuropsychological testing than those without, but this association was not found in other studies [75,76,79].

Cerebral amyloid angiopathy (CAA)

Sixteen studies examined CAA in LBD (N=13 - 110 participants) by examining a certain number of brain regions and most studies used a semi-quantitative ranking scale [80]. CAA prevalence was compared between DLB, PDD, AD and controls. Some studies distinguished between DLB with coexisting AD pathology and those without. The prevalence and severity of CAA in LBD appeared to be increased compared to participants with PD without dementia [47,81-83628485]. Prevalence of CAA ranged from 6-100% in LBD, 58-100% in AD, and 0-50% in controls (table 4). In an autopsy study by Jellinger et al (2021) including 170 LBD cases, the prevalence of CAA was higher in DLB (93%) than PDD (50%) and PD (22%)[84]. It is important to note that several studies that controlled for AD co-pathology in LBD suggest that CAA prevalence may be related to AD co-pathology, as the prevalence was lower in LBD without AD co-pathology [868783] and in some cases was similar to the prevalence in healthy controls [88]. Whether CAA itself is a contributor to cognitive decline in LBD or whether these results are indicative of AD co-pathology in those with dementia is yet to be explored.

Large Cortical Infarcts and small subcortical infarcts

Seventeen studies examined large cortical and small subcortical infarcts (N=8 - 165 LBD participants) and comparison groups included controls, AD and PD. Most reported a similar prevalence of these changes in LBD and controls [11,28,36,39,42,63,67,86,89,90]. Ferreira et al (2021) included 165 DLB participants and noted that infarcts (>3mm) assessed on MRI were more common in subcortical than

cortical regions (13% vs 2%, respectively) and were associated with presence of WMH [71].

One study by Ghebremedhin et al (2010) raised the possibility of an inverse relationship between cerebrovascular lesions (including small vessel disease and atherosclerosis in the circle of Willis assessed using a semi-quantitative scale and infarct prevalence in brain sections) and the extent of Lewy body pathology in DLB (n=13) compared to controls (n=53) [1,62]. However, these findings differ from other findings in the literature and the authors note that the association observed in this study could be a result of cerebrovascular lesions lowering the threshold for developing clinical symptoms of DLB.

In comparison to AD, three studies reported no statistically significant difference in the prevalence of infarcts in LBD [39,64,73]. One neuropathological study by Londos et al (2000) examined frontal white matter changes, including both non-specific white matter changes and infarcts, and found that overall these were increased compared to AD [91].

Microinfarcts

Twelve studies assessed micro-infarcts in LBD (N=7 - 25 LBD participants), mainly in comparison with controls. There may be an increased prevalence of microinfarcts in LBD (range 15-80%) compared to controls (range 10-35%, table 6). In two neuropathological studies, the severity of microinfarcts was greater in DLB than controls and in the study by Ghebremedhin et al (2010), microinfarcts were more common in participants with severe Lewy body pathology [62,67]. Although other studies did not find a statistically significant difference in microinfarcts in DLB compared to controls, their sample sizes were relatively small[11,28,63,90].
There were conflicting results regarding the prevalence of microinfarcts in DLB compared to AD. De Reuck et al (2017) found an increased number of microinfarcts in both neuropathological and post-mortem MRI examination of brains with Lewy body pathology (either “pure” DLB or with AD co-pathology) compared to those with pure AD pathology [64]. In contrast, Isojima et al (2006) found microinfarcts to be less prevalent on neuropathological examination of DLB brains (40%) compared to AD

brains (68%) [73]. The reason for these conflicting results is unclear, but in the study by De Reuck et al (2017), there were differences between participant groups in prevalence of hypertension, which may be a risk factor for microinfarcts [92].

Intracerebral haemorrhage

In comparison with controls, most of the eight studies examining intracerebral haemorrhage reported a similar prevalence in LBD compared to controls (table 5) [11,28,63,66,67,86,90]. Isojima et al (2006) reported increased prevalence of intracranial haemorrhage in DLB compared to AD, but this also included non-cerebrovascular causes (i.e. subdural haemorrhage) [73].

Discussion and conclusions

Studies examined a range of cerebrovascular lesions in LBD. There was an increased severity of WMH changes on MRI in LBD compared to PD without dementia and age-matched controls, but this result was not found for neuropathological WML. CMB prevalence in LBD was highly variable but broadly similar to AD (0-48%), with a lobar pattern. Microinfarcts were found to be more prevalent in LBD compared to controls in some studies. No relationship was found between large cortical or small subcortical infarcts or intracerebral haemorrhage and presence of LBD.

The most widely studied cerebrovascular change in LBD was WMH of presumed vascular origin on MRI brain, where most studies reported an increased burden in LBD compared to age-matched controls. There was also a possible relationship between WMH burden and progression from PD to PDD in longitudinal studies. The pathogenesis of WMH may be closely related to AD, and whether this is the case with LBD remains unknown [61]. There was increasing use of more advanced imaging methods in the more recent studies (3T MRI or 7T post-mortem MRI). Some studies used an automated approach to WMH quantification, which although are more complex to implement than VRS (e.g. Fazekas or Scheltens scales), may have increased accuracy and reproducibility [22,93-96]. Interestingly, neuropathology studies did not support the increased prevalence of WML of presumed ischaemic origin in LBD compared to controls, which raises the importance of clarifying the underlying pathology of the WMH visualised on MRI in LBD. One possibility is that an alternate

pathology to cerebrovascular disease, such as inflammation or demyelination, results in the appearance of the WMH on MRI [97]. Alternatively, MRI may be more sensitive in detecting white matter changes compared to neuropathology which examines selected brain sections.

Another commonly studied lesion was CMB and mini-bleeds, where conclusions were difficult due to variable study methodology, for example in controlling for cerebrovascular risk factors. Some studies reported an increased prevalence in LBD compared to age-matched controls while others did not, and there appeared to be a similar prevalence of CMB in LBD compared to AD. There was an increased prevalence of CMB in the lobar rather than deep and infra-tentorial regions in LBD. The data suggested that CAA in LBD may be increased compared to those without LBD, but may be related to AD co-pathology. Microinfarcts, which were studied both on neuropathological examination and post-mortem MRI, were found to be more prevalent in some studies but not others, with differing participant groups between studies and small sample sizes.

The prevalence of other cerebrovascular lesions, including large cortical infarcts, small subcortical infarcts and intracerebral haemorrhage, did not appear to differ between people with LBD and age-matched controls.

Within the studies, methods of lesion detection and definition of lesions varied. There was also variability in the participant population between studies and many had a relatively small sample size. As a result, there were inconsistencies between studies, with no clear relationship arising between the prevalence of a specific cerebrovascular lesion type and the diagnosis of LBD or clinical outcomes. However, certain patterns were observed with some cerebrovascular lesions that may inform future studies. Future research in this area would benefit from more consistent cerebrovascular lesion definitions and lesion detection methods. Recommendations for imaging standards for cerebrovascular disease research are available and include suggestions regarding minimum essential MRI sequences and VRS use [98]. Future research should also have consistent adjustment for both clinical and pathological variables to determine the effect of cerebrovascular lesions on LBD and its progression.

In conclusion, there may be an increased prevalence of certain cerebrovascular lesions (WMH, CMB and CAA) in LBD compared to age-matched controls. LBD did not appear to affect the prevalence of large cortical or small subcortical infarcts or

intracerebral haemorrhage. Data were lacking with regards to the effect of the presence of such lesions on clinical outcomes in LBD. There is a need for larger studies assessing the influence of cerebrovascular lesions on clinical symptoms, disease progression and outcomes.

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