The vascular risk factors and vascular neuropathology in subjects with autopsy-confirmed dementia with Lewy bodies

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Abstract

Background: The frequency of vascular risk factors (VRFs) and the relationship between vascular pathology and cognitive function in neurodegenerative disease remains incompletely understood.

Objective: The purpose of this study was to describe the frequency of VRFs and vascular pathology and explore the relationship between vascular pathology and cognitive function in dementia with Lewy bodies (DLB).

Methods: This study included 363 autopsy-confirmed DLB and 753 Alzheimer's disease (AD) patients from the National Alzheimer's Coordinating Center (NACC) database. We used chi-squared test and analysis of variance (ANOVA) to compare the VRFs and related factors in DLB and AD. Multinomial logistic regression and Spearman's correlation test were used to examine the relationship between vascular pathology and cognitive function.

Results: No significant differences of VRFs were identified between DLB and AD. AD patients had higher rates of microinfarcts (23.5% vs. 16.3%, $p = 0.005$) and moderate to severe amyloid angiopathy (45.9% vs. 36.1%, $p = 0.002$). In DLB patients, only cerebral amyloid angiopathy (CAA) pathology was negatively correlated with memory domain ($r = -0.263$, $p < 0.001$) and language ($r = -0.112$, $p = 0.034$). The rates of APOE ε4 allele carriers (60.0% vs. 44.9%, $p = 0.004$) and CAA pathology (45.9% vs. 23.4%, $p < 0.001$) were much higher in the group with an intermediate likelihood of DLB than in the group with a high likelihood. There was a negative correlation between CAA pathology and memory (logical memory) in the group with an intermediate likelihood of DLB.

Conclusion: No difference of VRFs was identified between autopsy-confirmed DLB and AD. CAA was shown to be an important pathology in DLB, which specifically correlated with memory

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and language. The groups with high and intermediate likelihood of DLB differed in terms of CAA pathology, and CAA pathology may play an important role in the development of DLB.

Keywords

1. Introduction

The association between cognitive impairment and vascular risk factors (VRFs) has been studied for a long time. In the absence of a disease-modifying treatment or cure, reducing the risk of developing dementia takes on added importance. Family history and genetic susceptibility genes, such as the Apolipoprotein E (APOE) ɛ4 allele, cannot be modified by medical interventions or by individual behavior [1]. However, it is important to find evidence of risk factors that can be modified, such as diabetes and hypertension. Growing evidence has supported the influence of VRFs on the incidence of dementia due to Alzheimer's disease (AD) as well as vascular dementia (VaD). Approximately half of clinically probable AD subjects have mixed brain pathology, most commonly Alzheimer's disease pathology and microvascular infarcts [2][3]. However, for dementia with Lewy bodies (DLB), the second most common neurodegenerative disease after AD, there has been insufficient evidence for the relationship between vascular factors/lesions and DLB in a large sample. Some researchers used white-matter hyperintensity (WMH) to estimate the presence of cerebrovascular lesions, and found that the WHM volume was higher in DLB than in the AD group [4]. In addition, neuropathological studies in LBD showed that mini-bleeds are more frequent in LBD brains than in controls [5]. However, the sample sizes in the above studies were small, not exceeding 100 participants. Some results of comparisons of the presence of VFRs and vascular pathology (like infarcts) between AD and DLB have been reported. For example, one study including 55 DLB, 34 PDD (Parkinson's disease dementia), and 78 AD patients showed that a history of VFRs did not differ significantly among these three groups [6]. However, another study found a significant difference between AD and DLB in the frequency of microscopic infarcts, whereas no significant difference in hemorrhages was noted [7].

Considering the lack of evidence about the prevalence and characteristics of VFRs and vascular pathology in DLB, the aim of this study was to explore the vascular characteristics in a large sample of autopsy-confirmed DLB cases. In addition, given that only a few studies have focused on differences in the level of neuropathological likelihood of DLB, our study investigates the differences of VRFs and vascular pathology between the high- and intermediate-likelihood DLB phenotypes. Moreover, we compare the neuropsychological battery between these phenotype groups. Finally, we explore whether cognitive function is correlated with the vascular pathology in DLB.

2. Methods

2.1 Subjects

Data on the subjects were obtained from the National Alzheimer's Coordinating Center's (NACC) dataset (https://naccdata.org/) from 2005 to 2015. This database contains the results of standardized clinical evaluations, detailed descriptions of which have previously been published [8–10]. Neuropathology (NP), genetic data, and uniform data sets (UDS) were included in this study. All participants underwent a neuropathological assessment and were rated as "high likelihood" or "intermediate likelihood" of having exhibited a DLB phenotype antemortem [11]. For convenience, a high or intermediated likelihood of exhibiting a DLB phenotype is described as "high or intermediate likelihood of DLB" below. Those with a high likelihood of DLB have either (a) diffuse neocortical LB pathology with no, low, or intermediate likelihood of AD neuropathologic change (Braak tau stage < V) or (b) limbic LB pathology with no or low likelihood of AD neuropathologic change (Braak tau stage < III). Those with an intermediate likelihood of DLB have either (a) diffuse neocortical LB pathology with high likelihood of AD neuropathologic change (Braak tau stages V–VI) or (b) limbic LB pathology with intermediate likelihood of AD neuropathologic change (Braak tau stages III–IV). AD patients were classified as having a "high" or "intermediate" likelihood of dementia due to AD by the NIA-Reagan Institute criteria. High AD neuropathologic change was defined as a high amyloid-β plaque score (Thal phase 4 or 5), moderate to high neuritic plaque score [Consortium to Establish a Registry for Alzheimer's Disease (CERAD) score 2 or 3] and high neurofibrillary (NFT) score (Braak stage V or VI). Intermediate AD neuropathologic change was defined as (a) low amyloid-β plaque score (Thal phase 1 or 2), moderate to high neuritic plaque score (CERAD 2 or 3), and intermediate to high NFT score (Braak stage > II); (b) intermediate amyloid-β plaque score (Thal phase 3), any neuritic plaque score (CERAD 0–3), and intermediate to high NFT score (Braak stage > II); (c) high amyloid-β plaque score (Thal phase 4 or 5), zero or low neuritic plaque score (CERAD 0 or 1), and intermediate to high NFT score (Braak stage > II); or (d) high plaque score (Thal phase 4 or 5), moderate or high neuritic plaque score (CERAD 2 or 3), and intermediate NFT score (Braak stage III or IV). Patients with other diagnoses (Parkinson's disease, multiple system atrophy, frontotemporal degeneration) were excluded from our study.

This study was approved by the institutional review board at each institution. Written informed consent was obtained from all NACC participants and informants.

2.2 Clinical data

Information on the demographic and VRFs in the AD and DLB groups was derived from the NACC UDS data set at the first visit. The vascular risk factors included hypertension, diabetes, hypercholesterolemia, history of stroke, history of transient ischemic attack (TIA), heart attack, atrial fibrillation (AF), congestive heart failure, angioplasty/endarterectomy/stent, and cardiac bypass procedure. These factors were divided into two categories: 0 for no and 1 for yes (including a recent situation or one in the more distant past). Cognitive functioning was assessed using a standardized neuropsychological battery. Clinical Dementia Rating (CDR) scale was used to estimate the global cognitive decline.

Global cognitive functioning was measured using the Mini-Mental State Examination (MMSE). To assess memory, we used logical memory story A, parts 1 and 2, from the Wechsler Memory Scale. Attention was measured using digit span forward and processing speed by Trail Making Test A. Digit span backward, digit symbol from the Wechsler Adult Intelligence Scale - Revised (WAIS-R), and Trail Making Test B were used to measure executive functioning. Fluency (animals and vegetables) and the Boston Naming test were used as measures for language.

2.3 Vascular pathological data

Data on the presence of infarcts and lacunae, microinfarcts, hemorrhages, and microbleeds were collected from the NP data set. All of these cerebrovascular pathological findings were divided into two categories: 0 for no and 1 for yes. Cerebral amyloid angiopathy (CAA) pathology was divided into grades 0–3 in the NP data set [12]. For convenience in the subsequent analysis, we assigned grades 0–1 as low CAA pathology and grades 2–3 as high CAA pathology.

2.4 APOE genotype

Data for the APOE genotype were collected from the NACC genetic data set. Based on whether or not the participants possessed the APOE ε4 and ε2 allele, we divided them into carriers and noncarriers.

2.5 Statistical analysis

After excluding the subjects with missing data for the above variables, 363 subjects with DLB and 753 subjects with AD from NACC were finally included in our study. Among the 363 DLB subjects, 205 had a high likelihood of DLB and the other 158 had an intermediate likelihood of it based on the neuropathology.

IBM Statistical Package for the Social Sciences (SPSS) for Windows (version 25.0; IBM Corporation, Armonk, NY) was used for the statistical analyses. Descriptive analyses were conducted using percentages for categorical variables and mean ± standard deviation (SD) for quantitative variables. We used chi-squared test in the comparison between AD and DLB with regard to sex, vascular risk factors, APOE ε4 and APOE ε2 allele carriers, and vascular neuropathology. Other demographic information such as education, age at visit, age at onset of cognitive decline, age at death, and the scores of neuropsychological assessments was compared between AD and DLB using analysis of variance (ANOVA). We used multiple logistic regression to analyze the value of vascular risk factors and vascular pathology for the differential diagnosis of DLB and AD. Odds ratios (OR) of having dementia with 95% confidence intervals (CIs) were obtained from the fitted models. The analysis of the correlation between vascular pathology and neuropsychological assessment in DLB was performed using Spearman's correlation test. The analytical methods used for comparisons between the groups with intermediate and high likelihood of DLB were the same as those used for the AD and DLB group comparisons. A p-value of less than 0.05 was considered significant, and all tests were two-sided.

3. Results

3.1 Demographics of DLB and AD patients

Overall, 363 DLB and 753 AD patients were finally included in this study. The demographic information and vascular risk factors of autopsy-confirmed AD and DLB cases are presented in Table 1. The DLB group had a higher proportion of males than the AD group (69.4% vs. 57.1%, $p < 0.001$). Meanwhile, the two groups did not differ significantly in age at visit, years of education, and age at onset of cognitive decline. Subjects in the DLB group (80.21 ± 8.91) died at a younger age than those in the AD group (82.07 ± 8.57). The CDR (0.84 ± 0.46) of the DLB group was slightly higher than that of the AD group (0.73 ± 0.37). In the 363 DLB patients, 194 had at least one copy of the ε4 allele. The proportion of AD patients carrying APOE ε4 alleles was significantly higher than that of DLB patients (63.3% vs. 53.4%, $p = 0.002$), while there was no significant difference in the frequency of APOE ε2 carriers. The prevalence of hypertension was slightly higher in AD than in DLB (48.7% vs. 46.0%, $p = 0.392$), but this did not reach statistical significance. There was no significant difference in the frequency of all listed vascular risk factors between the two groups ($p = 0.577$).

3.2 Vascular neuropathology in DLB and AD patients

A comparison of the results on vascular neuropathology of the DLB and AD groups is shown in Table 2. DLB and AD patients had similar frequencies of infarcts and lacunae (12.7 vs. 12.7, $p = 0.971$). The prevalence of hemorrhages and microbleeds also did not differ significantly between DLB and AD (6.3% vs. 5.7%, $p = 0.678$). However, AD patients had higher rates of microinfarcts (23.5% vs. 16.3%, $p = 0.005$) and moderate to severe amyloid angiopathy (45.9% vs. 36.1%, $p = 0.002$). We performed logistic regression analysis to explore the factors that could potentially be used to distinguish DLB from AD (Table 3). We found that, after adjusting for sex, education, and vascular risk factors, possession of an APOE ε4 allele (OR: 0.745, CI: 0.569–0.975; $p = 0.032$) and CAA pathology (OR: 0.686, CI: 0.523–0.898; $p = 0.006$) may be associated with a lower risk of developing DLB than AD.

3.3 Correlation between vascular pathology and neuropsychological assessment in DLB

As shown in Table 4, we compared the memory, language, attention, and executive functions between DLB and AD. MMSE score was slightly higher in AD (24.20 ± 4.02) than in DLB (23.61 ± 4.79). AD patients performed worse in memory and language, while DLB patients performed worse in attention and executive function domains. In DLB patients, we found that only CAA pathology was negatively correlated with memory (r = −0.263, $p < 0.001$) and language (r = −0.112, $p = 0.034$) (Table 5). Hemorrhages and microbleeds were positively correlated with digit span forward length (r = 0.148, $p = 0.005$). The other two vascular pathologies did not show a relationship with cognitive domains in this study.

3.4 Differences of vascular risk factors, vascular pathology, and neuropsychological assessment between high and intermediate likelihood of DLB phenotypes

Table 6 indicates that there was a higher proportion of males among patients with the high likelihood of DLB phenotype than among those with an intermediate likelihood. The rates of APOE ε4 allele carriers (60.0% vs. 44.9%, $p = 0.004$) and those with CAA pathology (45.9% vs. 23.4%, $p < 0.001$) were higher in the intermediate likelihood group than in the high likelihood group. No other demographic information, vascular risk factors, or vascular pathology differed significantly between the two groups. Adjusted logistic regression analysis showed that only those with a CAA pathology (OR: 0.367, CI: 0.225–0.597; p < 0.001) may be less prone to develop a high rather than an intermediate likelihood of DLB phenotype (Table 7). When there was no significant difference between the two groups regarding MMSE scores, we demonstrated that those with the high likelihood of DLB phenotype performed worse in Trail Making Test Part A ($p = 0.001$) and Trail Making Test Part B ($p = 0.041$) (Table 8). In the memory and language domains, scores of the intermediate group were lower than those of the high group (all $p < 0.001$). Table 9 indicates that there was a negative correlation between CAA pathology and memory (logical memory) in the intermediate likelihood of DLB group. There was no correlation between CAA pathology and neuropsychological assessment in the high likelihood of DLB group.

4. Discussion

This study showed that the prevalence of VRFs was similar in autopsy-confirmed DLB and AD, although there were more males in the DLB group than in the AD group. Previous studies mostly focused on the association between Lewy body disease [include DLB, Parkinson's disease (PD), and Parkinson's disease dementia (PDD)] and VRFs, which reported conflicting results. Some of them reported that factors associated with a reduced risk for vascular disorders were found in patients with Lewy body disease [13]. Meanwhile, some others suggested that the risk of Parkinson's disease was not significantly associated with a history of hypertension, hypercholesterolemia, or diabetes [14]. As for research focusing on the comparison of VRFs between LBD and AD, the results were not completely consistent. Our findings are somewhat consistent with the results of previous studies regarding the VRFs for DLB [15], and that the prevalence of VRFs in LBD may be close to that in AD [16]. However, Chan et al. showed that vascular risk factors like hypertension and diabetes are significantly less common in PDD and DLB than in AD [6].

Despite the rates of total infarcts and lacunae not differing significantly between AD and DLB, the DLB group had lower rates of microinfarcts (16.3% vs. 23.5%) and CAA pathology (36.1% vs. 45.9%). Logistic regression analyses also confirmed lower rates of microinfarcts and CAA in DLB than in AD. However, our study showed a lower rate of microinfarcts than previously reported in dementia (about 20%–50%) [17] [18]. Previous studies mostly emphasized the relationship between microinfarcts and all-cause dementia or cognitive impairment. A cohort of 425 community-dwelling older adults showed that both single and multiple cortical microinfarcts are associated with lower cognition, especially perceptual speed and semantic memory [19]. Another study also using NACC data indicated significant relationships of global, old, acute/subacute, and regional cerebral vascular

pathologies (microinfarcts included) with the onset and severity of Alzheimer's disease [20]. Our results provide evidence that vascular risk factors and vascular pathology may contribute less to DLB than to AD. Both AD and DLB are associated with orthostatic hypotension (OH), and DLB may have a somewhat higher rate of OH than AD [21]. Because we could not obtain information about the autonomic nervous system in our participants, we could not causally attribute the differences of small vessel disease pathological changes (microinfarcts and CAA included) to OH. The APOE ɛ4 allele is known to play an important role in neurodegenerative disease. It has been reported as a risk factor for microinfarcts and CAA in older adults [22]. Moreover, it may affect the blood–brain barrier, the innate immune system, and synaptic function and cause the accumulation of amyloid-β (Aβ), which indirectly affects vascular function [23]. CAA is very common in AD with prevalence of up to 97% [24]. However, CAA also occurs in Lewy body dementias and an association between CAA and cognitive decline in PDD and DLB has been demonstrated [25]. Our results regarding CAA are consistent with other studies showing that the AD group had a higher frequency of CAA than the DLB group [26].

Few studies have explored the relationship between the neuropsychological battery and vascular pathology in DLB. Our results fill this gap to some extent. Specifically, CAA was shown to be negatively correlated with the memory and language domains in DLB. The domains whose impairment correlated with CAA did not match those in previous studies. For example, a prospective cohort study found that those with CAA had significantly lower memory and executive functions, and processing speed than normal subjects [27]. A previous community-based study with autopsy-based confirmation of all the participants revealed that CAA was associated with increased rates of decline in global cognition, perceptual speed, episodic memory, and semantic memory [28]. CAA may work via multiple pathways to affect cognition. In imaging studies, individuals with CAA were shown to exhibit diverse markers of small vessel disease, including cerebral microbleeds, white-matter hyperintensity, microstructural tissue changes, and associated cognitive impairment [29] [30]. Recently, Subotic et al. demonstrated that CAA was associated with lower cortical thickness than that in controls and that the lower cortical thickness was associated with lower memory scores [31]. In addition, cases of CAA with an amnestic presentation tended to have a smaller hippocampal volume than their non-amnestic counterparts [32]. Another study revealed that, in sporadic CAA, decreased basal ganglia volume was independently correlated with greater cortical gray matter atrophy ($r = 0.45$, $p < 0.0001$) and worse performance on language processing ($r = 0.35$, $p = 0.003$), but not with the results of cognitive tests of executive function or processing speed [33]. DLB always has a mixed pathology of both Lewy body and AD-like features, and is charactered by the impairment of executive and attention domains. Our results provide evidence that the CAA pathology is related to memory and language, but not executive and attention domains, in DLB. We hypothesized that the CAA pathology is correlated with memory and language in neurodegenerative diseases that are not limited to AD or CAA, but also include DLB. However, further study is needed to explore the relationship between structural MRI changes and CAA pathology in DLB.

We initially compared the VRFs and vascular pathology between intermediate and high likelihood of DLB phenotypes. Cases with an intermediate likelihood of DLB showed a significantly higher rate of CAA pathology than the high likelihood group. In addition,

logistic regression analysis showed that CAA could distinguish the high and intermediate likelihood groups. A possible explanation for this is that the intermediate likelihood group had more severe AD-like pathology. Generally, CAA is characterized by the deposition of β-amyloid (Aβ) in leptomeningeal vessels and penetrating arterioles. Recently, researchers have confirmed the contribution of tau pathology to the pathology of CAA [34]. Upon comparing the cognitive impairment domains between the high and intermediate likelihood groups, the intermediate likelihood group showed worse performance in memory and language domains. A possible reason for this is that the high likelihood DLB cases have normal hippocampal volumes, in contrast to the intermediate likelihood of DLB cases [35]. According to the criteria of DLB pathology, the intermediate likelihood group showed a higher level of AD-like pathology. Aβ was previously reported to be associated with decline in memory plus language and executive functions [36]. Moreover, a study using tau PET imaging showed that deposition of tau in the middle temporal lobe was associated with poor memory test results irrespective of the coexistence of Aβ [37]. Our results showed that CAA was negatively correlated with memory and language domains in the intermediate group, rather than in the high group. Those with a high likelihood of DLB had a higher rate of Lewy-like pathology and a lower rate of CAA pathology than those with intermediate likelihood of DLB, so the correlation of CAA and memory is not obvious. In future, more studies should focus on the differences in vascular pathology between intermediate and high likelihood of DLB cases.

The main strength of this study is that it featured a large sample size including participants with autopsy-confirmed DLB based on the NACC date. We not only compared the frequency of VRFs and vascular pathology in DLB and AD, but also evaluated the correlations between the neuropsychological test results and vascular pathology. Moreover, we explored the differences of VRFs and vascular pathology between the intermediate and high likelihood of DLB groups for the first time, which may provide evidence for further studies. However, this study has several limitations. For example, owing to the missing data in the DLB group, we did not add the results of visuospatial domains in our study. Moreover, given the lack of information about OH, we could not confirm whether there was a difference in OH between the DLB and AD groups in our study. We also did not describe the differences between APOE ε4 homozygous and heterozygous groups as such data were unavailable. In future work, we should collect more information about OH and blood pressure, and perform in-depth analysis on the roles of vascular factors in neurodegenerative disease.

Conclusions

This study suggested that there is no difference in VRFs between autopsy-confirmed DLB and AD. It also showed that CAA is an important pathology in DLB, which specifically correlated with the memory and language domains in DLB. Additionally, there were differences in APOE genotype and CAA pathology between high and intermediate likelihood of DLB groups. Moreover, the results suggested that CAA pathology may play an important role in development of DLB. Further studies should obtain more information such as structural and perfusion images and data on the autonomic nervous system to explain the similarities and differences in DLB and AD. There is also a need for more focus on the differences between high and intermediate likelihood of DLB phenotypes.

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Table 1.

Demographic information and vascular risk factors in autopsy-confirmed Alzheimer's disease and dementia with Lewy bodies

	DLB (n=363)	AD (n=753)	*p*-value
Sex, male (yes, n, %)	252 (69.4%)	430 (57.1%)	< 0.001 [***]
Years of education (years, mean ± SD)	15.57 ± 3.02	15.63 ± 2.94	0.749
Age at visit (years, mean ± SD)	74.79 ± 8.59	74.65 ± 8.15	0.798
Age at cognitive decline (years, mean ± SD)	70.56 ± 8.70	70.56 ± 8.53	0.999
Age at death (years, mean ± SD)	80.21 ± 8.91	82.07 ± 8.57	0.001 [**]
Hypertension (yes, n, %)	167 (46.0%)	367 (48.7%)	0.392
Diabetes (yes, n, %)	30 (8.3%)	61 (8.1%)	0.925
Hypercholesterolemia (yes, n, %)	201 (55.4%)	419 (55.6%)	0.932
History of stroke (yes, n, %)	18 (5.0%)	28 (3.7%)	0.329
History of TIA (yes, n, %)	16 (4.4%)	37 (4.9%)	0.710
Heart attack (yes, n, %)	33 (9.1%)	50 (6.6%)	0.144
Atrial fibrillation (yes, n, %)	32 (8.8%)	75 (10.0%)	0.543
Congestive heart failure (yes, n, %)	11 (3.0%)	15 (2.0%)	0.281
Angioplasty/endarterectomy/stent (yes, n, %)	36 (9.9%)	73 (9.7%)	0.906
Cardiac bypass procedure (yes, n, %)	25 (6.9%)	37 (4.9%)	0.178
CDR (mean ± SD)	0.84 ± 0.46	0.73 ± 0.37	< 0.001 [***]
APOE *e*4 allele carriers (yes, n, %)	194 (53.4%)	477 (63.3%)	0.002 [**]
APOE *e*2 allele carriers (yes, n, %)	33 (9.1%)	61 (8.1%)	0.577

AD, Alzheimer's disease; DLB, Dementia with Lewy bodies; TIA: Transient ischemic attack; CDR: Clinical dementia rating; APOE, Apolipoprotein E

[*] $p < 0.05$

[**] $p < 0.01$

[***] $p < 0.001$

Table 2.

Comparison of vascular neuropathology between autopsy-confirmed Alzheimer's disease and dementia with Lewy bodies

	DLB (n=363)	AD (n=753)	*p*-value
Infarcts and lacunae (yes, n, %)	46 (12.7)	96 (12.7)	0.971
Microinfarcts (yes, n, %)	59 (16.3)	177 (23.5)	0.005 [**]
Hemorrhages and microbleeds (yes, n, %)	23 (6.3)	43 (5.7)	0.678
CAA (yes, n, %)	131(36.1)	346 (45.9)	0.002 [**]

AD, Alzheimer's disease; DLB, Dementia with Lewy bodies; CAA, Cerebral Amyloid Angiopathy

[*]
$p < 0.05$

[**]
$p < 0.01$

[***]
$p < 0.001$

Table 3.

Vascular risk factors and vascular pathology on differential diagnosis for autopsy-confirmed dementia with Lewy bodies and Alzheimer's disease

	OR	95% CI		p-value
		Lower bound	Upper bound	
Male	0.589	0.445	0.780	< 0.001 ***
Education	0.968	0.925	1.012	0.149
Hypertension	0.900	0.684	1.186	0.455
Diabetes	0.957	0.592	1.546	0.856
Hypercholesterolemia	0.925	0.717	1.193	0.546
History of stroke	0.852	0.541	1.342	0.489
History of TIA	0.732	0.460	1.166	0.189
Cardiovascular disease	1.151	0.841	1.573	0.380
APOE ε4 allele carrier	0.745	0.569	0.975	0.032 *
Infarcts and lacunae	1.132	0.758	1.690	0.546
Microinfarcts	0.609	0.432	0.859	0.005 **
Hemorrhages and microbleeds	1.151	0.668	1.983	0.612
CAA	0.686	0.523	0.898	0.006 **

TIA: Transient ischemic attack; APOE, Apolipoprotein E; CAA, Cerebral Amyloid Angiopathy

*
$p < 0.05$

**
$p < 0.01$

***
$p < 0.001$

Table 4.

Comparison of neuropsychological assessment of DLB and AD

	DLB (n=363)	AD (n=753)	*p*-value
MMSE (mean ± SD)	23.61 ± 4.79	24.20 ± 4.02	0.031 [*]
Memory			
Total number of story units recalled (mean ± SD)	6.08 ± 4.23	5.71 ± 4.11	0.164
Logical Memory IIA — Delayed — Total number of story units recalled (mean ± SD)	4.25 ± 4.10	3.30 ± 4.03	< 0.001 [***]
Logical Memory IIA — Delayed — Time elapsed since Logical Memory IA (mean ± SD)	22.76 ± 6.41	22.13 ± 6.35	0.125
Language			
Animals (mean ± SD)	12.18 ± 5.41	13.45 ± 5.34	< 0.001 [***]
Vegetables (mean ± SD)	7.46 ± 3.79	8.5 ± 3.85	< 0.001 [***]
Boston Naming (mean ± SD)	23.18 ± 5.72	23.01 ± 5.88	0.659
Attention			
Digit span forward length (mean ± SD)	6.07 ± 1.18	6.19 ± 1.21	0.119
Trail Making Test Part A (seconds) (mean ± SD)	75.82 ± 40.65	52.34 ± 28.26	< 0.001 [***]
Executive function			
Digit span backward length (mean ± SD)	3.72 ± 1.23	4.07 ± 1.14	< 0.001 [***]
WAIS-R Digit Symbol (mean ± SD)	25.02 ± 13.24	31.02 ± 12.82	< 0.001 [***]
Trail Making Test Part B (seconds) (mean ± SD)	213.25 ± 85.34	186.56 ± 88.24	< 0.001 [***]

MMSE, Mini-Mental Status Exam; AD, Alzheimer's disease; DLB, Dementia with Lewy bodies; WAIS-R: Wechsler Adult Intelligence Scale - Revised

[*] $p < 0.05$

[**] $p < 0.01$

[***] $p < 0.001$

Table 5.

Correlation between vascular pathology and neuropsychological assessment in DLB (n=363)

	Infarcts and lacunae		Microinfarcts		Hemorrhages and microbleeds		CAA	
	r	*p*-value	r	*p*-value	r	*p*-value	r	*p*-value
Memory								
Total number of story units recalled	0.046	0.385	0.071	0.176	0.035	0.503	−0.263	< 0.001 ***
Logical Memory IIA — Delayed — Total number of story units recalled	0.033	0.531	0.098	0.063	−0.069	0.192	−0.263	< 0.001 ***
Logical Memory IIA — Delayed — Time elapsed since Logical Memory IA	−0.065	0.222	−0.078	0.145	−0.075	0.161	0.008	0.885
Language								
Animals	0.020	0.707	0.081	0.123	0.079	0.131	−0.112	0.034 *
Vegetables	−0.007	0.891	0.055	0.299	0.022	0.676	−0.048	0.362
Boston Naming	−0.052	0.320	−0.061	0.249	0.039	0.453	−0.091	0.082
Attention								
Digit span forward length	−0.042	0.421	0.032	0.540	0.148	0.005 **	0.050	0.340
Trail Making Test Part A (seconds)	−0.003	0.951	−0.003	0.954	−0.074	0.157	−0.006	0.907
Executive function								
Digit span backward length	0.038	0.466	−0.017	0.751	0.003	0.953	0.010	0.853
WAIS-R Digit Symbol	−0.029	0.592	0.004	0.937	0.052	0.336	−0.020	0.720
Trail Making Test Part B (seconds)	0.047	0.425	0.023	0.688	−0.088	0.133	0.004	0.945

DLB, Dementia with Lewy bodies; CAA, Cerebral Amyloid Angiopathy; WAIS-R: Wechsler Adult Intelligence Scale - Revised

*
$p < 0.05$

**
$p < 0.01$

***
$p < 0.001$

Table 6.

Demographic information and vascular risk factors in high and intermediate likelihood of dementia with Lewy bodies

	High (n = 158)	Intermediate (n = 205)	p-value
Sex, male (n, %)	122 (77.2)	130 (63.4)	0.005[**]
Age at visit (years, mean ± SD)	74.63 ± 7.85	74.91 ± 9.14	0.758
Years of education (years, mean ± SD)	15.46 ± 3.32	15.66 ± 2.77	0.526
Age at cognitive decline (years, mean ± SD)	70.31 ± 8.16	70.75 ± 9.11	0.636
Age at death (years, mean ± SD)	79.30 ± 8.06	80.90 ± 9.48	0.090
Hypertension (n, %)	76 (48.1)	91 (44.4)	0.482
Diabetes (n, %)	17 (10.8)	13 (6.3)	0.130
Hypercholesterolemia (n, %)	82 (51.9)	119 (58.0)	0.243
History of stroke (n, %)	7 (4.4)	11 (5.4)	0.684
History of TIA (n, %)	6 (3.8)	10 (4.9)	0.619
Heart attack (n, %)	13 (8.2)	20 (9.8)	0.616
Atrial fibrillation (n, %)	14 (8.9)	18 (8.8)	0.979
Congestive heart failure (n, %)	3 (1.9)	8 (3.9)	0.270
Angioplasty/endarterectomy/stent (n, %)	15 (9.5)	21 (10.2)	0.813
Cardiac bypass procedure (n, %)	9 (5.7)	16 (7.8)	0.432
CDR (mean ± SD)	0.87 ± 0.48	0.82 ± 0.44	0.303
APOE e4 allele carriers (n, %)	71 (44.9)	123 (60.0)	0.004[**]
APOE e2 allele carriers (n, %)	17 (10.8)	16 (7.8)	0.332
Infarcts and lacunae (n, %)	23 (14.6)	23 (11.2)	0.343
Microinfarcts (n, %)	29 (18.4)	30 (14.6)	0.341
Hemorrhages and microbleeds (n, %)	14 (8.9)	9 (4.4)	0.083
CAA (n, %)	37 (23.4)	94 (45.9)	< 0.001[***]

TIA, Transient Ischemic Attack; CDR, Clinical Dementia Rating; APOE, Apolipoprotein E; CAA, Cerebral Amyloid Angiopathy

[**] $p < 0.01$

[***] $p < 0.001$

Table 7

Vascular risk factors and vascular pathology on differential diagnosis for high and intermediate likelihood of dementia with Lewy bodies

	OR	95% CI		*p*-value
		Lower bound	**Upper bound**	
Male	0.470	0.282	0.786	0.004 [**]
Education	0.961	0.890	1.038	0.315
Hypertension	1.242	0.823	1.875	0.302
Diabetes	1.674	0.789	3.548	0.179
Hypercholesterolemia	0.784	0.510	1.206	0.268
History of stroke	0.711	0.393	1.287	0.260
History of TIA	0.942	0.438	2.025	0.877
Cardiovascular disease	0.930	0.542	1.594	0.792
APOE *e4* allele carriers	0.760	0.479	1.205	0.243
Infarcts and lacunes	1.068	0.508	2.247	0.862
Microinfarcts	1.221	0.641	2.323	0.544
Hemorrhages and microbleeds	1.880	0.740	4.779	0.185
CAA	0.367	0.225	0.597	< 0.001 [***]

TIA, Transient Ischemic Attack; APOE, Apolipoprotein E; CAA, Cerebral Amyloid Angiopathy

[**]
$p < 0.01$

[***]
$p < 0.001$

Table 8

Comparison of neuropsychological assessment of high and intermediate likelihood of dementia with Lewy bodies

	High (n= 158)	Intermediate (n= 205)	*p*-value
MMSE (mean ± SD)	24.11 ± 4.77	23.22 ± 4.78	0.081
Memory			
Total number of story units recalled (mean ± SD)	7.21 ± 4.09	5.20 ± 4.13	< 0.001 ***
Logical Memory IIA — Delayed — Total number of story units recalled (mean ± SD)	5.41 ± 4.19	3.37 ± 3.81	< 0.001 ***
Logical Memory IIA — Delayed — Time elapsed since Logical Memory IA (mean ± SD)	22.53 ± 5.95	22.94 ± 6.8	0.548
Language			
Animals (mean ± SD)	12.47 ± 5.56	11.95 ± 5.30	0.367
Vegetables (mean ± SD)	7.59 ± 3.69	7.37 ± 3.88	0.579
Boston Naming (mean ± SD)	24.61 ± 4.33	22.07 ± 6.39	< 0.001 ***
Attention			
Digit span forward length (mean ± SD)	6.08 ± 1.16	6.05 ± 1.21	0.820
Trail Making Test Part A (seconds) (mean ± SD)	84.02 ± 42.25	69.50 ± 38.29	0.001 **
Executive function			
Digit span backward length (mean ± SD)	3.65 ± 1.26	3.78 ± 1.20	0.323
WAIS-R Digit Symbol (mean ± SD)	24.23 ± 13.14	25.54 ± 13.31	0.374
Trail Making Test Part B (seconds) (mean ± SD)	225.45 ± 83.51	204.78 ± 85.82	0.041 *

DLB, Dementia with Lewy bodies; CAA, Cerebral Amyloid Angiopathy; WAIS-R: Wechsler Adult Intelligence Scale - Revised

*
$p < 0.05$

**
$p < 0.01$

***
$p < 0.001$

Table 9

Correlation of cerebral amyloid angiopathy pathology and neuropsychological assessment in high and intermediate likelihood of dementia with Lewy bodies

	High (n= 158)		Intermediate (n= 205)	
	r	*p*-value	r	*p*-value
Memory				
Total number of story units recalled	−0.116	0.145	−0.290	< 0.001 ***
Logical Memory IIA — Delayed — Total number of story units recalled	−0.134	0.094	−0.282	< 0.001 ***
Logical Memory IIA — Delayed — Time elapsed since Logical Memory IA	0.049	0.543	−0.011	0.874
Language				
Animals	−0.014	0.858	−0.166	0.018 *
Vegetables	0.050	0.535	−0.100	0.155
Boston Naming	−0.027	0.739	−0.050	0.478
Attention				
Digit span forward length	0.025	0.752	0.073	0.299
Trail Making Test Part A (seconds)	−0.005	0.955	0.067	0.343
Executive function				
Digit span backward length	0.010	0.896	−0.011	0.874
WAIS-R Digit Symbol	0.005	0.958	−0.053	0.453
Trail Making Test Part B (seconds)	−0.120	0.189	0.117	0.124

DLB, Dementia with Lewy bodies; CAA, Cerebral Amyloid Angiopathy; WAIS-R: Wechsler Adult Intelligence Scale - Revised

*
$p < 0.05$

***
$p < 0.001$