Alzheimer's & Dementia 13 (2017) 257-266

Featured Article

An investigation of cerebrovascular lesions in dementia with Lewy bodies compared to Alzheimer's disease

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Abstract

Introduction: Cerebrovascular lesions on MRI are common in Alzheimer's disease (AD) dementia, but less is known about their frequency and impact on dementia with Lewy bodies (DLB).
Methods: White-matter hyperintensities (WMHs) and infarcts on MRI were assessed in consecutive DLB (n = 81) and AD dementia (n = 240) patients and compared to age-matched and sex-matched cognitively normal subjects (CN) from a population-based cohort.
Results: DLB had higher WMH volume compared to CN, and WMH volume was higher in the occipital and posterior periventricular regions in DLB compared to AD. Higher WMH volume was associated with history of cardiovascular disease and diabetes but not with clinical disease severity in DLB. Frequency of infarcts in DLB was not different from CN and AD dementia.
Discussion: In DLB, WMH volume is higher than AD and CN and appears to be primarily associated with history of vascular disease.
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Keywords: MRI; Dementia with Lewy bodies; Alzheimer's disease; White matter hyperintensities; Infarcts; Cerebrovascular disease; Sex differences

1. Introduction

Alzheimer's disease (AD) and Lewy body disease are the two most common causes of neurodegenerative dementia in older adults. Cerebrovascular disease (CVD) may coexist with both AD and Lewy body disease [1–6], particularly in the oldest old [7,8]. Infarcts and white-matter hyperintensities (WMH) on T2-weighted MRI are considered indicators of CVD in patients with or without dementia [9], although WMH could also be due to vascular amyloidosis [10]. The underlying pathophysiology of WMH is complex indeed [11–13], with potential contribution from both vascular and neurodegenerative pathologies [14–16].

http://dx.doi.org/10.1016/j.jalz.2016.07.003
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Patients with AD dementia have more WMH and a higher frequency of cerebral infarcts than cognitively normal (CN) subjects [6,16–20]. However, the prevalence and the clinical impact of CVD in dementia with Lewy bodies (DLB) are not established, with conflicting reports about the frequency of cerebrovascular lesions on MRI in patients with DLB compared to CN subjects and patients with AD dementia [19,21–24]. Therefore, the first objective of the present study was to assess the frequency and distribution of cerebrovascular lesions (WMH and cerebral infarcts) on MRI in patients with DLB and AD dementia patients, compared to a population-based cohort of CN subjects separately matched to DLB and AD patients. The second objective was to compare the frequency and distribution of cerebrovascular lesions in DLB compared to AD and investigate the impact of cerebrovascular lesions on the disease severity and the clinical features of DLB.

2. Methods

2.1. Subjects

Consecutive patients with probable DLB (n = 90) according to the Third Consortium Criteria for DLB, and AD dementia (n = 262) according to the NIA-Reagan criteria [25,26] for probable AD dementia were recruited to the Mayo Clinic Alzheimer's Disease Research Center (ADRC) and from the population-based Mayo Clinic Study of Aging (MCSA) [27] between August, 2005 and November, 2014 and underwent an MRI at 3 Tesla.

Clinical evaluations included a neurological examination and the administration of standardized measures of cognitive and functional performance such as Mini Mental State Examination (MMSE), Mattis Dementia Rating Scale (DRS), and the Clinical Dementia Rating scale Sum of Boxes (CDR-SOB). Clinical features characteristic of DLB were assessed in the patients as follows: (1) Unified Parkinson's Disease Rating Scale, part III (UPDRS-III); (2) visual hallucinations characterized by being fully formed, not restricted to a single episode and not related to another medical issue; (3) fluctuations classified with a score of 3 or 4 on the Mayo Fluctuations Questionnaire [28]; and (4) probable rapid eye movement (REM) sleep behavior disorder (pRBD) as defined by the International Classification of Sleep Disorders-II diagnostic criteria [29]. On completion of the evaluation, a consensus committee composed of the behavioral neurologists, neuropsychologists, and nurses who evaluated the subjects established the clinical diagnosis. For each patient, data concerning history of vascular disease and vascular risk factors were collected by the clinicians based on patient's and caregiver's report, medical records and observation through the standardized uniform data set form A5, from the National Alzheimer's Coordinating Center (NACC; https://www.alz.washington.edu). The exclusion criteria were history of traumatic brain injury, hydrocephalus, or intracranial mass; neurologic and psychiatric diseases other than AD dementia or DLB, history of chemotherapy, head radiation therapy, or substance abuse. Patients were not excluded if they had a history of cerebrovascular disease (Fig. 1).

For comparison, we included two groups of CN subjects who were matched by age and sex to the DLB and to the AD groups, from the population-based MCSA [27] who underwent 3T MRI examinations. Similar to the ADRC cohort, we excluded subjects with a history of traumatic brain injury, hydrocephalus, or intracranial mass; neurologic and psychiatric diseases, history of chemotherapy, head radiation therapy, or substance abuse. We did not exclude CN subjects for cerebrovascular disease.

Written informed consent was collected from each subject before the participation in any research activity.

L.S., C.G.S., J.G.-R., T.G.L., R.I.R., M.E.M., J.E.P., D.W.D., N.T., S.A.P., S.M.Z., and M.R.R. report no disclosures. B.F.B. has served as an investigator for a clinical trial sponsored by Cephalon. He has received honoraria from the American Academy of Neurology. He receives research support from the National Institute on Aging (P50-AG16574 [Co-I], U01 AG06786 [Co-I], R01-AG15866 [Co-I], and U24-AG26395 [Co-I]), and the Alzheimer's Association (IIRG-05–14,560 [PI]). T.J.F. is funded by the NIH (Mayo Clinic Alzheimer's Disease Research Center/Project 1-P50-AG16574/P1 [Co-I]). D.S.K. serves as Deputy Editor for Neurology®; serves on a Data Safety Monitoring Board for Lundbeck Pharmaceuticals and for the Dominantly Inherited Alzheimer's Disease Treatment Unit. He is participating in clinical trials sponsored by Lilly Pharmaceuticals and Tau Rx Pharmaceuticals. He receives research support from the NIH. G.C. has received honoraria from Teva, Sanofi, Genzyme, Merck Serono, Biogen, Bayer, Serono Symposia International Foundation, Excemed, Roche, Almirall, Chugai, Receptos, Forward Pharma, outside the submitted work. M.F. is Editor-in-Chief of the Journal of Neurology; serves on scientific advisory boards for Teva Pharmaceutical Industries; has received compensation for consulting services and/or speaking activities from Biogen Idec, Excemed, Novartis, and Teva Pharmaceutical Industries; and receives research support from Biogen Idec, Teva Pharmaceutical Industries, Novartis, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, CurePSP, Alzheimer's Drug Discovery Foundation, the Jacques and Gloria Gossweiler Foundation (Switzerland), and ARiSLA (Fondazione Italiana di Ricerca per la SLA). R.C.P. chaired a Data Monitoring Committee of Pfizer and Janssen Alzheimer Immunotherapy and serves as a consultant for Hoffman-La Roche., Merck, Genentech, Inc., Biogen, Eli Lilly and Co. and receives research support from the NIH (P50 AG016574 [PI] and U01 AG006786 [PI], R01 AG011378 [Co-I], and U01 AG024904 [Co-I]). C.R.J. reports consulting services for Eli Lilly Co, funding from the NIH (R01 AG011378, U01 AG024904, RO1 AG041851, R01 AG037551, R01 AG043392, and U01 AG006786) and research support from the Alexander Family Professorship of Alzheimer's Disease Research. K.K. serves on the data safety monitoring board for Pfizer Inc., Takeda Global Research & Development Center, Inc.; and she is funded by the NIH [R01AG040042 (PI), R21 NS066147 (PI), Mayo Clinic Alzheimer's Disease Research Center/Project 1 P50 AG16574/P1 (PI), P50 AG44170/Project 2 (PI) and R01 AG11378 (Co-I)].

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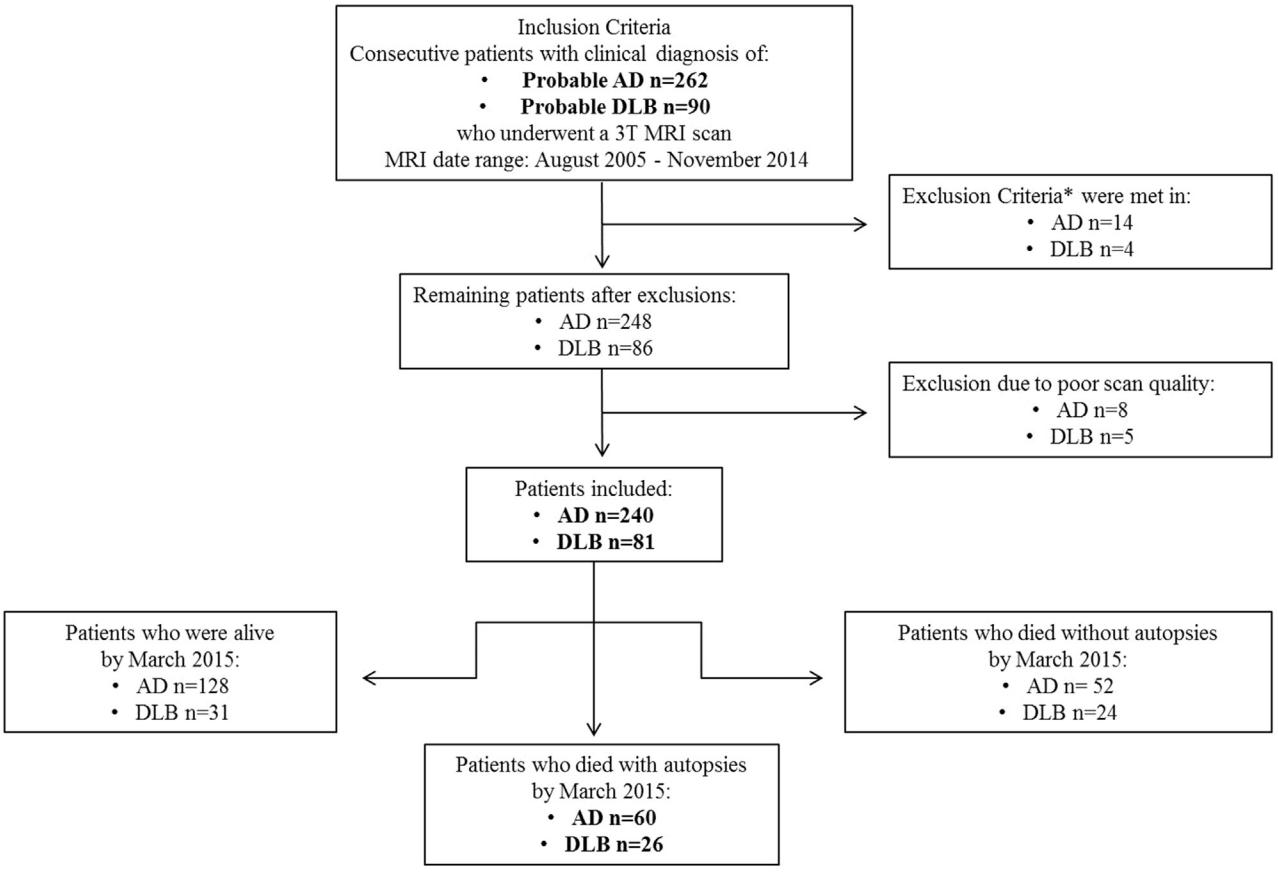


Fig. 1. Flow chart summarizing the prospective cohort in study by March 2015. Abbreviations: AD, Alzheimer's disease; DLB, dementia with Lewy bodies. *Exclusion Criteria: history of traumatic brain injury (n = 3), hydrocephalus (n = 1), or intracranial mass (n = 2), neurologic and psychiatric diseases other than AD dementia or DLB (n = 5), history of chemotherapy (n = 1), head radiation therapy (n = 1) or substance abuse (alcohol, n = 5).

2.2. MRI

A standardized MRI imaging protocol at 3T (GE Healthcare) was performed on all subjects included in the study from both ADRC and MCSA cohorts including a T1-weighted 3D magnetization prepared rapid acquisition gradient-echo (MPRAGE) sequence and an axial T2-weighted fluid attenuated inversion recovery (FLAIR) sequence. MRI scans underwent a standardized quality control procedure, and we excluded 13 MRI (8 AD; 5 DLB) examinations due to poor scan quality.

WMH were quantified using a semiautomated algorithm on FLAIR as described previously using a semiautomated segmentation algorithm [30]. A whole-brain voxel-based analysis (VBA) of detected WMH voxels was conducted. First, each subject's FLAIR scan was affine aligned to their corresponding T1 image using SPM12 [31]. A nonlinear registration was then computed between each subject's T1 scan and an in-house population-specific template using the ANTs SyN algorithm [32]. Each scan's mask of detected WMH voxels was transferred through both registrations and resampled using nearest neighbor before blurring with a Gaussian kernel of width 8 mm full width at half maximum. Voxel-wise statistics were computed on these resampled, blurred WMH images in template space, over all voxels considered WM according to the template, using SPM12. False Discovery Rate (FDR) correction for multiple comparisons was applied with a threshold of $P < .05$ and a minimum cluster size of 100.

Supratentorial cortical and subcortical infarcts, as well as infratentorial infarcts were identified and recorded on FLAIR scans by a trained neurology resident (L.S.) and confirmed by a radiologist (K.K.). Both were blinded to the diagnosis. Cortical infarcts were hyperintense lesions involving the cerebral cortex, with the longest diameter >3 mm. Subcortical infarcts and infratentorial infarcts were characterized by focal tissue loss, visible on FLAIR sequences as a hypointense lesion with diameter > 3 mm and surrounded by a hyperintense rim. Hyperintensities on FLAIR images associated with infarcts were marked and were not included in the WMH volume count because of the different underlying pathophysiology.

2.3. Neuropathology

Sampling was done according to the Consortium to Establish a Registry for Alzheimer's disease (CERAD) protocol [33] and the Third Report of the DLB Consortium [26]. The pathologic diagnosis was made by a neuropathologist (J.E.P. or D.W.D.) in accordance with the Third Report of the DLB Consortium criteria and the NIA-Reagan criteria

[26,34]. Patients were subsequently classified on the basis of their pathologic diagnosis into "DLB" if the pathological diagnosis was high-likelihood DLB; "AD" if the diagnosis was intermediate to high-likelihood AD; and "mixed AD/DLB" if they were diagnosed with low-to-intermediate likelihood DLB.

2.4. Statistical analysis

Fisher exact tests and Student *t* tests were used as appropriate to compare demographics and clinical characteristics between the DLB and AD groups. The DLB group was compared to age-matched and sex-matched CN subjects using McNemar tests, paired *t* tests, and repeated-measures linear regression (for log-transformed WMH adjusted for total intracranial volume, TIV) as appropriate. The AD group was compared to a group of age-matched and sex-matched CN subjects in the same way. Associations between WMH volume and age were determined using multiple linear regression analyses, adjusting for sex and TIV. Owing to a skewed distribution, WMH volume was log transformed to meet model assumptions. Age and sex interactions were also tested in these models but found not to be significant. Linear regressions were used to compare log-transformed WMH volume between the groups, adjusting for TIV. Linear regressions were again used to assess associations of WMH volume with UPDRS-III, DRS, visual hallucinations, and fluctuations as well as history of vascular risk factors in DLB subjects after adjusting for TIV and sex. Logistic regressions, adjusting for age and sex, were used to test for associations between infarcts and diagnosis of DLB or AD. Interactions of sex with infarcts were assessed in the logistic regression models but found not to be significant. Statistical analyses were run in R, version 3.1.3, and SAS, version 9.3. *P* values <.05 were considered statistically significant.

3. Results

Patients with DLB (n = 81) and AD dementia (n = 240) did not differ on age and sex compared with their respective CN group due to matching; however, the AD dementia and DLB groups had a higher proportion of apolipoprotein E (*APOE*) ε4 carriers and lower MMSE scores when compared to the matched CN subjects (Supplementary Table 1). DLB patients were younger ($P = .01$) and had a higher frequency of men ($P < .001$), but a lower frequency of *APOE* ε4 carriers ($P = .05$) compared to the AD dementia patients. Dementia severity on DRS, CDR-SOB, and MMSE was not different between the AD and DLB groups, and they had a similar frequency of cardiovascular disease and risk factors (Table 1).

WMH volume was higher in patients with DLB and AD dementia compared to their matched CN group, after adjusting for TIV ($P < .001$; Table 2). As expected, age was significantly associated with higher WMH volume, both in AD dementia, DLB, and the pooled AD dementia and DLB groups ($P < .001$). Women had higher WMH volume in AD dementia ($P < .001$), DLB ($P = .04$), and the pooled AD dementia and DLB groups ($P < .001$) compared to men, after accounting for age. A trend of higher WMH volume was observed in patients with DLB compared to AD dementia after adjusting for age, sex, and TIV ($P = .054$; Fig. 2). WMH did not differ in *APOE* ε4 carriers and noncarriers in DLB ($P = .47$) and AD dementia ($P = .41$) groups after adjusting for TIV.

Table 1
Demographic and clinical characteristics of patients with dementia with Lewy bodies (DLB) and Alzheimer's disease (AD) dementia

	DLB, n = 81	AD, n = 240	*P* value
Women, n (%)	14 (17)	105 (44)	<.001
Age at MRI, y	72 (8) [52, 89]	75 (10) [48, 96]	.005
Education, y	15 (3) [7, 20]	15 (3) [7, 20]	.39
APOE ε carrier, n (%)	36 (46)	139 (60)	.048
CDR-SOB score	6 (3) [1, 17]	5 (3) [0, 18]	.53
MMSE score	21 (6) [1, 30]	20 (5) [1, 30]	.48
DRS total score	116 (18) [56, 140]	114 (18) [47, 141]	.40
UPDRS-III	10 (7) [0, 29]	2 (3) [0, 13]	<.001
Visual hallucinations, n (%)	52 (64)	7 (4)	<.001
Fluctuations, n (%)	58 (72)	15 (8)	<.001
Parkinsonism, n (%)	76 (94)	26 (14)	<.001
REM sleep behavior disorder, n (%)	65 (80)	21 (11)	<.001
Any smoking, n (%)	36 (47)	94 (41)	.35
Cardiovascular disease, n (%)	23 (29)	43 (24)	.35
Stroke, n (%)	4 (5)	18 (10)	.33
Hypertension, n (%)	35 (44)	123 (52)	.24
Diabetes, n (%)	7 (9)	16 (7)	.62

Abbreviations: CDR-SOB, Clinical Dementia Rating scale Sum of Boxes; MMSE, Mini Mental State Examination; DRS, Dementia Rating Scale; UPDRS-III, Unified Parkinson's Disease Rating Scale, part III; REM, rapid eye movement.

NOTE. Unless otherwise indicated, values shown are mean (SD) [range]. *P* values are assessed using Student *t* test or Fisher exact tests. *P* values of infarction and WMH are form logistic regression models adjusted for total intracranial volume, age at the MRI scan, and sex.

On voxel-wise analysis, both AD dementia and DLB patients had significantly higher WMH volume throughout the deep, periventricular, and subcortical WM compared to their matched CN groups, symmetrically involving both hemispheres but not the brainstem and cerebellum ($P < .05$; FDR corrected). After adjusting for age, patients with DLB had higher WMH volume in the occipital lobe WM bilaterally compared to AD dementia. When the same comparison was repeated adjusting for both age and sex, patients with DLB showed higher WMH not only in the occipital lobes, but also in the right-posterior periventricular WM when compared to AD dementia. On the contrary, patients with AD dementia did not have regionally higher WMH volume compared to DLB after adjusting for age and sex ($P < .05$; FDR corrected; Fig. 3).

We found no association between WMH volume and the presence of DLB core clinical features (visual hallucinations, parkinsonism, and fluctuations), DRS or UPDRS-III scores,

Table 2
Cerebrovascular lesions on MRI in patients with dementia with Lewy bodies (DLB) and Alzheimer's disease (AD) dementia compared respectively to age and sex-matched cognitively normal (CN) subjects and to each other

	DLB, n = 81	CN, n = 81	*P* value*	AD, n = 240	CN, n = 240	*P* value*	*P* value†
Any infarct, n (%)	22 (27)	24 (30)	.72	83 (35)	64 (27)	.046	.69
Cortical infarct, n (%)	3 (4)	5 (6)	.50	28 (12)	12 (5)	.006	.06
Subcortical infarct, n (%)	16 (20)	18 (22)	.68	58 (24)	49 (20)	.28	.94
Infratentorial infarct, n (%)	6 (7)	2 (2)	.16	27 (11)	12 (5)	.009	.64
WMH (cm^3)	25.3 (21.1) [2.6–95.2]	15.6 (15.7) [0.9–84.6]	<.001	24.3 (21.9) [1.9–119.4]	17.4 (17.1) [0.8–134.1]	<.001*	.054

Abbreviations: MMSE, Mini Mental State Examination score; WMH, white-matter hyperintensities.

Unless otherwise indicated, values shown are mean (SD) [range].

**P* values are from a conditional logistic regression models comparing AD and DLB patients to each of their age and sex-matched CN group where the log transformation was done on WMH volume and an adjustment for total intracranial volume (TIV) was included in the model.

†*P* values are form logistic regression models comparing AD and DLB where the log transformation was done on WMH volume and an adjustment for TIV, age at the MRI scan and sex was included in the model.

whereas the presence of pRBD was associated with lower WMH volume after adjusting for TIV and sex ($P = .05$) in patients with DLB. Furthermore, in DLB patients, a positive history of cardiovascular disease ($P = .05$) and diabetes ($P = .04$) was associated with higher WMH, after adjusting for TIV. In patients with DLB, history cardiovascular disease (n = 23) included a history of heart attack or cardiac arrest (n = 7); atrial fibrillation (n = 3); coronary artery disease (n = 14); cardiac bypass (n = 6), congestive heart failure (n = 1); and other cardiac disease (n = 4).

Overall frequency of infarcts was not different between DLB and matched CN subjects. Frequencies of cortical ($P = .50$), subcortical ($P = .68$), and infratentorial infarcts ($P = .16$) were similar between the DLB and matched CN subjects. Patients with AD dementia showed a higher overall frequency of infarcts than their matched CN subjects ($P = .05$). Also, AD dementia patients had a higher frequency of cortical ($P = .01$) and infratentorial infarcts ($P = .01$) but not subcortical ($P = .28$) infarcts compared to their matched CN subjects (Table 2 and Fig. 4). Frequency of infarcts was not different among the *APOE* ε4 carriers and noncarriers in DLB ($P > .99$) and AD dementia groups ($P = .89$). DLB patients with infarcts were older compared to those without infarcts ($P < .01$), and the frequency of infarcts did not differ by sex ($P = .75$). We found no difference in DRS ($P = .14$) in DLB patients with infarcts and without infarcts. Similarly, AD dementia patients with infarcts were older ($P < .001$) and had a lower education ($P = .01$) compared to those without infarcts, and the frequency of infarcts did not differ by sex ($P > .99$) in patients with AD dementia.

In the logistic regression analyses, we found no interaction between sex and the presence of cortical infarcts ($P = .22$), subcortical infarcts ($P = .17$), or infratentorial

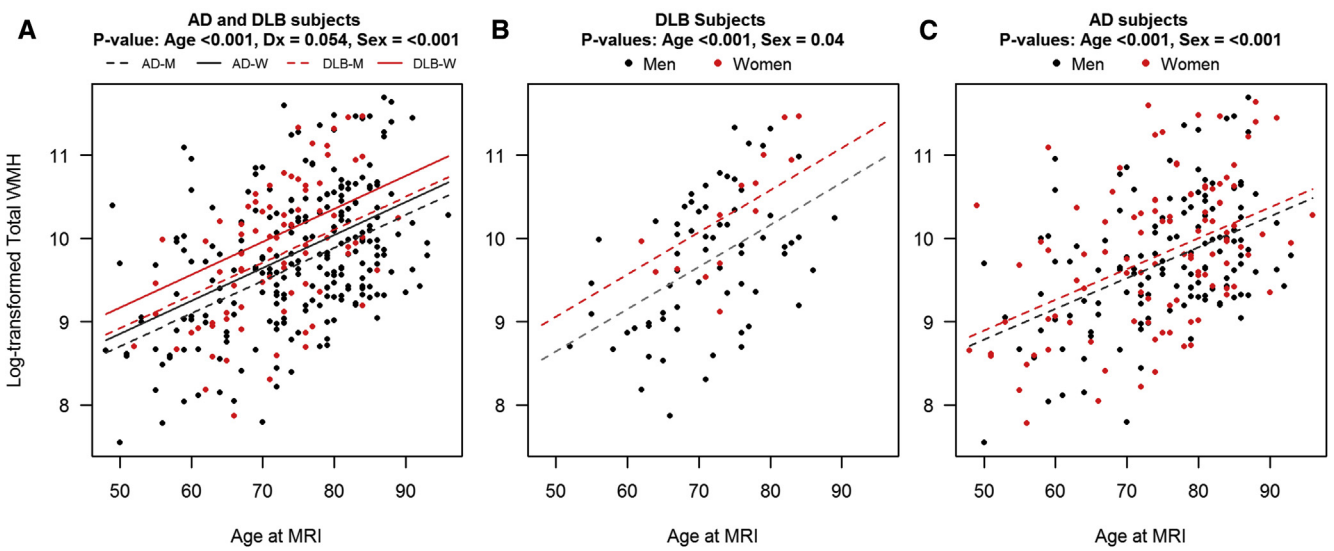


Fig. 2. Plots of age at MRI and log-transformed WMH volume adjusted for TIV in patients with diagnosis (Dx) of: (A) probable dementia with Lewy bodies (DLB, in red) and Alzheimer's disease dementia (AD, in black), women represented with solid and men represented with dashed lines; (B) patients with dementia with Lewy bodies, women represented with red and men represented with black-dashed lines; (C) probable Alzheimer's disease dementia, women represented with red and men represented with black-dashed lines. *P* values from the linear regression analysis (adjusted for TIV) are reported in the image.

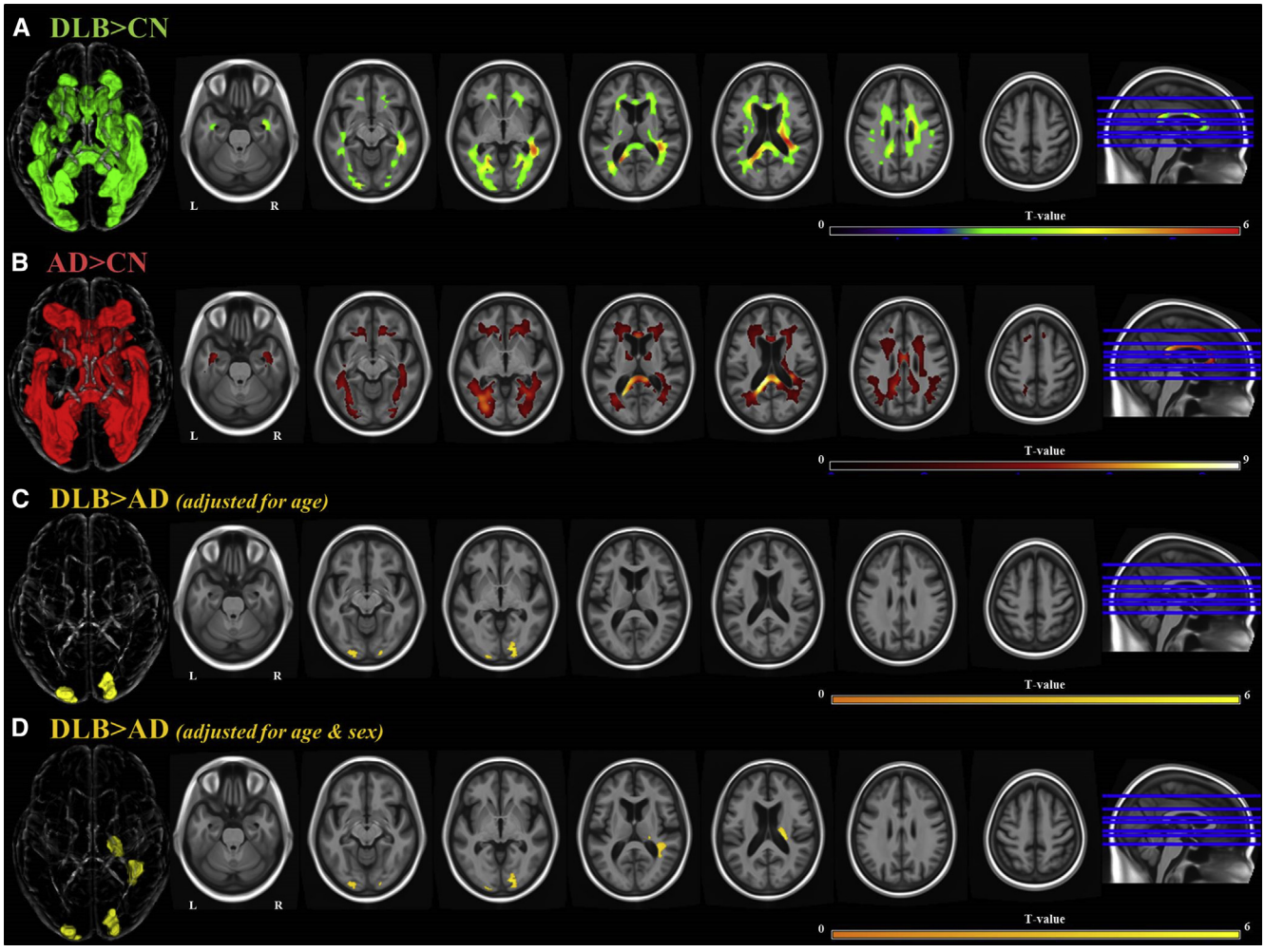


Fig. 3. Voxel-wise comparison of white-matter hyperintensities (WMH) volume differences in (A) patients with dementia with Lewy bodies (DLB) compared to age-matched and sex-matched cognitively normal (CN) subjects: DLB patients had higher WMH volume in the deep, periventricular, and subcortical white matter, which symmetrically involved the supratentorial regions in both hemispheres; (B) patients with Alzheimer's Disease (AD) dementia compared to their matched CN subjects: AD patients had higher WMH volume in the deep, periventricular, and subcortical white matter, which symmetrically involved the supratentorial regions in both hemispheres; (C) patients with DLB compared to patients with AD dementia, after adjusting for age: DLB had higher WMH volume limited to the occipital lobes bilaterally; (D) patients with DLB compared to patients with AD dementia, after adjusting for age and sex: DLB had higher WMH volume in the occipital lobes bilaterally, and additionally showed higher WMH in the right-posterior periventricular region. Results are shown at $P < .05$ FDR corrected, cluster size >100. L indicates left, and R indicates right.

infarcts ($P = .16$) after adjusting for age. Both age and sex were significant in the logistic regressions when the sex by infarcts interactions were removed. Using models without the interaction terms, we found no differences in the frequency of any infarcts ($P = .69$), subcortical infarcts ($P = .94$), and infratentorial infarcts ($P = .64$) between DLB and AD dementia patients after adjusting for age and sex. However, patients with DLB had a trend of lower frequency of cortical infarcts compared to AD patients ($P = .06$).

From the current cohort, by March 2015, 60 probable AD and 26 probable DLB patients died and underwent an autopsy (Fig. 1). Patients with a clinical diagnosis of probable DLB, had a pathological diagnosis of DLB (n = 13; 50%), mixed DLB/AD (n = 10; 38.5%), and AD (n = 3; 11.5%). Among patients with a clinical diagnosis of probable AD, none of them received a pathologic diagnosis of DLB, whereas they had a pathologic diagnosis of AD (n = 30; 50%) or mixed DLB/AD (n = 25; 41.7%). Other pathologic diagnoses in the clinical AD dementia group included tangle-only dementia (n = 1; 1.7%), TDP-43 pathology with low-likelihood AD (n = 2; 3.3%), tauopathy with features of corticobasal degeneration (n = 1; 1.7%), and a case with a low-likelihood AD and cerebrovascular disease (n = 1; 1.7%).

4. Discussion

The principal findings in this study were as follows. (1) Patients with DLB, when compared to age and sex-matched CN subjects, had a higher WMH volume but a similar frequency and distribution of infarcts, whereas

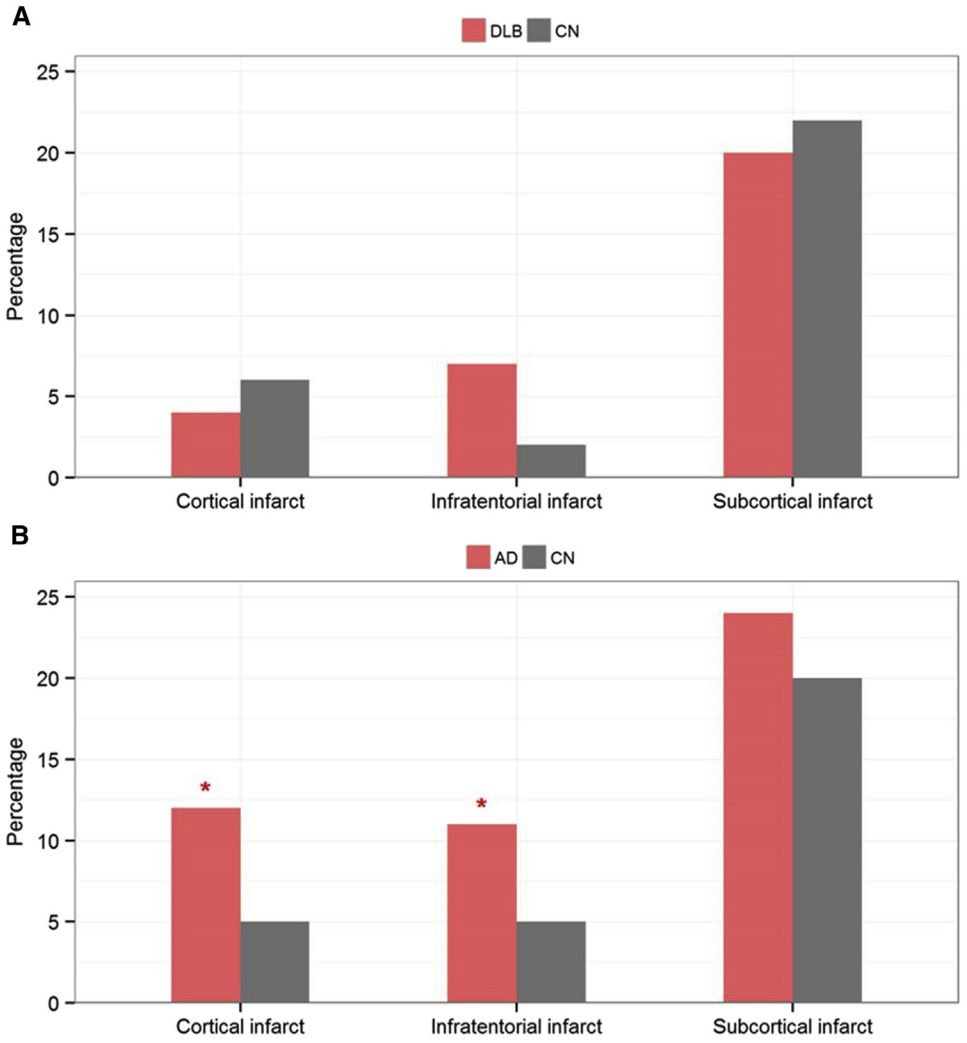


Fig. 4. Bar graphs showing the percentage of subjects with cortical, infratentorial, and subcortical infarcts (A) in patients with dementia with Lewy bodies (DLB) versus age-matched and sex-matched cognitively normal (CN) subjects and (B) in patients with Alzheimer's disease (AD) dementia versus their matched CN subjects. * indicates $P < .05$ from Fisher exact test.

patients with AD dementia showed both higher WMH volume and a higher proportion of cortical and infratentorial infarcts as compared to their matched CN subjects. Furthermore, we found that in both patient groups, not only older age but also female sex was associated with greater WMH volume; (2) Compared to patients with AD dementia, those with DLB had higher WMH volume in the occipital lobes, after adjusting for age, and showed additional WMH increase localized in the posterior periventricular WM after adjusting for both age and sex; (3) Higher WMH volume was associated with a history of diabetes and cardiovascular disease but not with the core clinical features in patients with DLB.

In our cohorts, both patients with DLB and AD dementia had higher WMH volume than age-matched and sex-matched CN subjects, which is an established finding in AD [14,17], but the literature is conflicting in patients with DLB. In one study including 27 subjects with probable DLB and 26 CN subjects, DLB patients had more WMH on visual inspection than CN subjects [19], whereas another neuroimaging study including 14 probable DLB and 33 CN subjects showed no difference in WMH volume between the two groups [21]. Such inconsistency may be explained by the small sample size, different criteria for clinical diagnosis of DLB and different WMH measurement techniques. Furthermore, both AD and DLB patients when compared to their matched CN subjects, had a pattern of increased WMH volume involving the periventricular, subcortical, and deep WM but sparing the brainstem and cerebellum. These findings are in agreement with studies performed on AD subjects, which demonstrated a predilection for WMH to occur in periventricular WM [35], a hypoperfused region [17,36].

Little is known about frequency of infarcts on MRI in patients with DLB. Neuropathologic studies in DLB reported infarct frequency of 25%–67% [4,37,38]. In our cohort,

27% of patients with DLB had at least one infarct at MRI, and the distribution in cortical, subcortical, and infratentorial locations was similar to the matched CN subjects, which is in agreement with neuropathology literature [5,38]. Frequency of infarcts was 35% in patients with AD dementia in our cohort, which is consistent with autopsy studies in AD [2,20,39]. In the community, patients with mixed AD and vascular pathology tend to have a higher frequency of dementia than those with a single pathology [2]. Furthermore, in our cohort, patients with AD dementia showed higher frequency of infarcts in the cortical and infratentorial regions compared to CN subjects, in agreement with a previous autopsy study [3] but not in the subcortical region. The pathophysiological mechanisms for the differences in the distribution of infarcts between AD dementia and CN groups need further investigation. Higher prevalence of cortical infarcts in AD could be due to the effect of vascular amyloidosis in AD, but infratentorial infarcts are hard to explain on this basis. Furthermore, no differences in frequency and distribution of infarcts were found among patients with DLB and AD dementia except for a trend of higher frequency of cortical infarcts in AD patients compared to DLB ($P = .06$). Small number of infarct counts in the DLB and lack of statistical power may be responsible for the absence of differences between DLB and AD groups. Larger cohorts may be needed to understand the regional distribution of infarcts in patients with DLB compared to AD.

In our study, female sex and older age were associated with higher WMH volumes in both DLB and AD dementia groups. A higher prevalence of WMH in women compared to men has been reported in the Rotterdam study [40]. Even more consistently, older age has been associated with a higher WMH volume [7,12,40]. Therefore, in comparing cerebrovascular lesions among DLB and AD dementia, we had to take into account the expected differences in sex and age among the two cohorts of patients. The linear regression analysis showed that WMH volume was higher in DLB when compared to AD dementia after accounting for age and sex. Studies with smaller sample sizes have reported lack of differences in WMH among DLB and AD dementia [19,24], but some observed higher WMH volume in DLB compared to AD dementia patients, which did not reach statistical significance [22]. When we performed a voxel-based analysis of the differences in WMH volume among DLB and AD dementia, we found that DLB patients had higher WMH in the occipital lobes when compared to patients with AD dementia, after accounting for age. Furthermore, after adjusting for both age and sex, besides the occipital locations, additional areas of increased WMH were present in the right-posterior periventricular WM in DLB compared to AD dementia. The VBA data suggest that patients with DLB have higher WMH volume in the posterior brain compared to patients with AD dementia, which is influenced not only by older age but also by female sex. Furthermore, higher occipital WMH volume in patients with DLB compared to those with AD dementia is consistent with occipital microstructural WM disruption on diffusion MRI in DLB in an earlier study [41], which remained significant even after adjusting for amyloid-β load on PET as a marker of additional AD pathology [42]. The greater involvement of the occipital lobe WM in DLB also suggests a relationship between the disruption of occipital WM and hypometabolism observed in patients with DLB on PET studies [42].

To assess the clinical impact and investigate the underlying pathophysiology of WMH in DLB, we analyzed the association of WMH volume with the clinical characteristics of DLB. Although DLB patients with a history of cardiovascular disease and diabetes tended to have higher WMH than those who did not have this history, we found no association between WMH volume and DRS, UPDRS-III scores, or any of the core clinical features of DLB. Interestingly, the presence of pRBD was associated with lower WMH volume in patients with DLB. Because pRBD is closely related to presence of Lewy body disease (LB) pathology [43–46], our finding suggests an inverse relationship between WMH volume and LB deposition in patients with DLB. This interpretation is supported by an inverse correlation found between cerebrovascular lesions and LB deposition at autopsy [5] and calls for further investigations. Because pRBD is not as common in patients with AD as DLB, we could not test this relationship in our AD sample.

This study was performed primarily in a referral clinic-based cohort of patients with probable DLB and AD dementia, which limits the external validity and generalizability of our findings to the population. Indeed, it has been shown that referral clinic-based cohorts of patients with AD pathology have a lower frequency of infarcts compared to the community-based cohorts [47]. A key strength of our study was the inclusion of a matched CN sample from a population-based cohort. Ideally, AD dementia and DLB subjects would be recruited from the same population. However, it may not be possible to achieve a DLB sample as large as the current sample due to the relatively low prevalence of DLB in the population [48,49]. Finally, a subset of our AD dementia and probable DLB cohorts underwent autopsies, and several of them had mixed AD/DLB pathology. The presence of mixed pathology may obscure the between-group differences in clinically diagnosed patients with probable DLB and AD dementia.

In conclusion, patients with probable DLB had higher WMH volume compared to CN subjects, with greater involvement of the posterior periventricular regions compared to patients with AD dementia. Our results underline the influence of age and sex differences on WMH, which are important confounders in studies comparing AD dementia and DLB. WMH volume was associated with the history of cardiovascular disease and diabetes in DLB patients but not with the core clinical features of DLB, suggesting that vascular disease is influencing higher WMH volumes in patients with DLB.

Acknowledgments

This study was funded by the NIH [R01 AG040042, R01 AG11378, P50 AG16574, U01 AG06786, AG44170, C06 RR018898], Foundation Dr. Corinne Schulerand, the Mangurian Foundation, The Elsie and Marvin Dekelboum Family Foundation, and the Robert H. and Clarice Smith and Abigail Van Buren Alzheimer s Disease Research Program. The funding sources had no role in study design, collection, analysis, interpretation, or decision to submit this article. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jalz.2016.07.003.

RESEARCH IN CONTEXT

1. Systematic review: Review of the literature was performed using PubMed and Google Scholar. Articles focusing on the frequency, distribution, and clinical impact of cerebrovascular lesions in DLB and AD were selected for citation.
2. Interpretation: Cerebrovascular disease is common in patients with DLB. Frequency of cerebral infarcts is similar, but WMH volume is higher in DLB compared to cognitively normal elderly. WMH volume increases with age and is higher in women than men in DLB and AD. Occipital and posterior periventricular white matter is particularly involved in DLB compared to AD after accounting for age and sex.
3. Future directions: Further studies are needed to confirm our results in a population-based cohort of patients with DLB and AD and preferably with autopsy-confirmed diagnosis in the entire cohort.

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