

Short communication

Frequency and topography of cerebral microbleeds in dementia with Lewy bodies compared to Alzheimer's disease



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ARTICLE INFO

Article history:

Received 20 March 2015

Received in revised form

19 June 2015

Accepted 13 July 2015

Keywords:

Dementia with Lewy bodies

Cerebral microbleeds

Alzheimer disease

Cerebral amyloid angiopathy

T2* weighted gradient-recalled-echo MRI

ABSTRACT

Aim: To determine the frequency and topographic distribution of cerebral microbleeds (CMBs) in dementia with Lewy bodies (DLB) in comparison to CMBs in Alzheimer disease dementia (AD).

Methods: Consecutive probable DLB (n = 23) patients who underwent 3-T T2* weighted gradient-recalled-echo MRI, and age and gender matched probable Alzheimer's disease patients (n = 46) were compared for the frequency and location of CMBs.

Results: The frequency of one or more CMBs was similar among patients with DLB (30%) and AD (24%). Highest densities of CMBs were found in the occipital lobes of patients with both DLB and AD. Patients with AD had greater densities of CMBs in the parietal, temporal lobes and infratentorial regions compared to DLB (p < 0.05).

Conclusion: CMBs are as common in patients with DLB as in patients with AD, with highest densities observed in the occipital lobes, suggesting common pathophysiologic mechanisms underlying CMBs in both diseases.

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1. Introduction

Hypointense foci on T2* Gradient Recalled Echo MRI associated with cerebral microbleeds (CMBs) are found in approximately 24%–33% of Alzheimer disease dementia (AD) patients [1–4]. Although the number of CMB in patients with dementia with Lewy bodies (DLB) appear to be similar to AD patients, the regional density of CMBs referenced to lobar volumes have not been established in

DLB [5]. Lobar microbleeds, particularly in the occipital, posterior temporal and parietal lobes are typically associated with amyloid deposition and cerebral amyloid angiopathy (CAA) [6–8]. Because a majority of patients with DLB have high amyloid- β (A β) deposition on PET imaging [9–11], we hypothesized that patients with DLB are at an increased risk for CMBs as much as patients with AD. In this study, we investigated the density and topographic distribution of CMB in patients with DLB compared to AD.

2. Methods

2.1. Subjects and clinical evaluations

Consecutive patients with probable DLB (n = 23) with median age of 69 (interquartile range [IQR] 64–74) years from the Mayo

Abbreviations: DLB, dementia with Lewy bodies; AD, Alzheimer disease; CAA, cerebral amyloid angiopathy; CMB, cerebral microbleed; GRE, gradient-recalled-echo MRI.

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Clinic Alzheimer's Disease Research Center (ADRC), underwent a 3T MRI examination from June 2010 until March 2012. Age and sex 2:1 matched patients with AD dementia ($n = 46$) from the ADRC were included as referent group. History of cardiovascular disease, stroke, hypertension and diabetes were recorded through self report at the time of MRI.

Patients with DLB fulfilled the Consortium criteria for probable DLB [12] and patients with AD dementia fulfilled the NINCDS-ADRDA criteria for probable AD [13]. Patients were excluded if they had history of traumatic brain injury, hydrocephalus, intracranial mass, or other neurologic diseases that may influence imaging findings.

This study was approved by the Mayo Clinic Institutional Review Board, and informed consent for participation was obtained from every subject.

2.2. MRI studies

2.2.1. MRI acquisition

A standardized MRI imaging protocol was performed on all subjects included in the study using a 3.0 T scanner, including 1) a 3D magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence (TR/TE/T1 = 2300/3/900 ms; flip angle = 8°; FOV = 26 cm; in-plane matrix = 256 × 256; phase FOV = 0.94; slice thickness = 1.2 mm; and 2) T2* a GRE sequence (TR/TE = 200/20 ms; flip angle = 12°; FOV = 20 cm; in-plane matrix = 256 × 224; phase FOV = 1.00; slice thickness = 3.3 mm).

2.2.2. Identification of CMBs

All CMBs and superficial siderosis were identified by a trained neurologist and secondarily confirmed by two radiologists experienced in reading the T2* GRE images (K.K. and C.R.J.), who were blinded to the diagnostic group. Definite CMBs were defined as small homogenous hypointense lesions up to 10 mm in diameter in the gray or white matter on T2* GRE images as previously described [1]. Occasionally, it was not possible to make a definitive decision, such as distinguishing a CMB from a vascular flow-void. In such instances, the CMB was labeled as "possible CMB" and was not included in the analysis.

2.2.3. Tracking and registration of CMB to a common template

The location of each observed CMB was recorded in the coordinate system of the image on which it was made. Findings observed on these images were propagated into the coordinate system of the image under evaluation. A T1 (MPRAGE) image of the subject was registered and resampled into the space of the image under evaluation. The T1 image carries an in-house modified automated anatomic labeling atlas [14] defining bilateral frontal, parietal, temporal, and occipital lobar regions and deep/infratentorial gray and white matter regions. Because the lobar regions differ in volume, we calculated the regional CMB densities as referenced to the volume of the region rather than simply count per region, combining the right and left hemispheres.

2.3. Statistics

Clinical and demographic characteristics including the frequency of CMB in DLB and AD patients were compared using a Student's *t*-test or a chi-squared test as appropriate. Mean CMB densities in patients with DLB and AD were compared using Student's *t*-tests.

3. Results

Patients with DLB and AD dementia were matched on age and

Table 1
Subject demographics (all subjects).

	DLB ($n = 23$)	AD ($n = 46$)	P-value
No. microbleeds positive (%)	7 (30)	11 (24)	0.56
No. female (%)	3 (13)	13 (28)	0.16
Age at mri yrs.	69 (64, 74)	71 (62, 78)	0.72
Age at onset.	63 (57, 70)	64 (57, 70)	0.63
Disease duration, yrs.	6 (4, 10)	5 (4, 9)	0.63
Education, yrs.	16 (14, 18)	16 (14, 17)	0.90
APOE ϵ carrier, n (%)	9 (41)	33 (73)	0.01
CDR-Sum of boxes score	6 (4, 8)	4 (3, 7)	0.17
Dementia rating scale	124 (104, 130)	118 (103, 126)	0.88
Whole brain density, mean (sd)	1.39 (2.47)	5.51 (17.12)	0.12
Presence of vascular disease and risk factors for vascular disease			
Cardiovascular disease (%)	4 (19)	8 (19)	>0.99
Stroke/TIA (%)	0 (0)	1 (2)	>0.99
Hypertension (%)	7 (32)	25 (54)	0.08
Diabetes (%)	2 (9)	1 (2)	0.55

Unless otherwise indicated, values shown are median (IQR). P values were calculated using Student's *t* test or chi-squared test as appropriate. Abbreviations: CDR, Clinical Dementia Rating. Disease duration is years from onset date to scan date.

sex and they did not differ on education, duration of disease, and clinical severity such as CDR-Sum of Boxes and Dementia Rating Scale and history of cardiovascular risk factors or stroke. A significantly higher proportion of patients with AD dementia (73%) were APOE ϵ 4 carriers, compared to patients with DLB (41%) (Table 1).

There were 67 lesions labeled as definite CMB among the AD and DLB subjects. A total of 18 subjects (7 DLB and 11 AD) had at least one definite CMB identified on the T2* scan. The frequency of total MBs was 24% in the AD group and 30% in the DLB group, with no statistically significant difference among the two groups (Table 1).

One patient with DLB and seven patients with AD dementia had multiple CMBs (2 CMBs in one DLB subject, and respectively 2, 2, 2, 5, 10, 12, 22 MBs in the AD patients. Remaining patients had a single CMB. Three patients with AD (6.5%) had superficial siderosis, in contrast, superficial siderosis was not identified in patients with DLB.

All patients with superficial siderosis were APOE ϵ 4 carriers. CMBs were as common in with APOE ϵ 4 positive DLB patients (2/6; 33%) as APOE ϵ 4 negative (5/17; 29%) ($p = 0.86$; Chi-square test).

Differences in the regional distribution of CMBs were observed among the DLB and AD groups. Considering the regional volumes, within the AD group, CMBs were most densely concentrated in the occipital lobes followed by parietal and temporal lobes, while lower CMBs were observed in the frontal lobes and deep and infratentorial grey and white matter regions. Within the DLB group, CMBs were mostly concentrated in the occipital and frontal lobes, followed by parietal and temporal lobes. No CMBs were found in the deep or infratentorial regions. Patients with DLB showed a significantly lower mean CMB density in the deep or infratentorial regions ($p = 0.046$) and temporal lobes ($p = 0.04$) compared to patients with AD (Fig. 1).

4. Discussion

This study showed that CMBs are common in patients with DLB. Approximately one third of patients with DLB had one or more CMBs. While the frequency of CMBs was similar in AD (24%) and DLB (30%), differences were found in the lobar distributions.

We observed the highest concentration of CMBs in the occipital lobes of patients with AD, which is consistent with the established topographic distribution of CMBs in older adults [1–4]. CMBs that concentrate more in the posterior brain regions, particularly the occipital lobes, are thought to be associated with CAA [2,15,16].

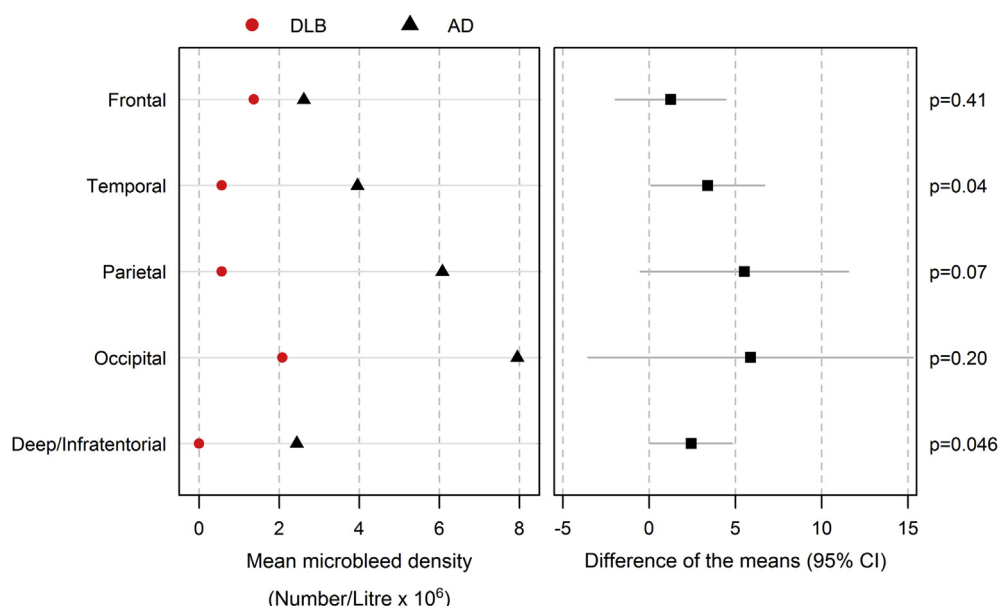


Fig. 1. Mean microbleed density by region and diagnosis (left) and the difference of the Alzheimer's disease (AD) and dementia with Lewy bodies (DLB) group means with 95% confidence intervals (right) P-values are extracted from Student's t-Test.

Although we found the highest concentration of CMBs in the occipital lobes in patients with DLB, it is not possible to link the occipital CMB in patients with DLB to CAA, because distribution of CAA in DLB subjects (with or without AD co-pathology) has not been established.

Interestingly, patients with DLB had a higher concentration of CMBs not only in the occipital region, but also in the frontal lobe. High CMB load in the frontal lobes is consistent with a previous study [5], which reported a higher numbers of frontal CMB in patients with DLB compared to AD. However in contrast to our findings, occipital lobe CMB involvement was less than frontal lobe involvement in DLB patients [5]. This discrepancy may be due to our use of CMB densities in each lobe, normalizing the counts with the lobar volumes. Reporting CMB counts rather than densities in two regions that differ in volume may be misleading. Another possible explanation to the discrepancies could be the variability due to the small sample size in both studies.

In individuals with CAA, lobar CMBs tend to be located in the posterior brain regions. A high occipital CMB density in AD patients supports the hypothesis that CAA is one of the underlying pathologies associated with the occipital CMBs in AD [2]. However, the distribution of CAA in patients with DLB with or without additional AD pathology has not been established. Therefore it is not possible to explain the higher occipital or frontal lobe CMB densities observed in patients with DLB with CAA. However, DLB patients are characterized by A β deposition in the frontal lobes on PET imaging [11], and CMB is associated with A β deposition [1,3]. Therefore CMBs in DLB may be associated with the increased vascular permeability during A β clearance, implicated for amyloid related imaging abnormalities (ARIA) in AD immunotherapy trials [17].

In the current study none of the DLB patients had CMBs in the deep or infratentorial regions. While this could be due to the limitations of our sample size, CMBs located in the deep or infratentorial regions were associated with cardiovascular risk factors, presence of lacunar infarcts and white matter hyperintensities suggesting hypertensive and atherosclerotic microangiopathy is the underlying etiology [18]. Based on the absence of deep or infratentorial CMBs in the current study, hypertensive and atherosclerotic microangiopathy is less likely to be contributing to

CMB pathophysiology in DLB than in AD. Interestingly DLB patients in the current study were less likely to report hypertension in their clinical history (32%) than AD (54%), however this difference did not reach statistical significance ($p = 0.08$).

The main limitation of our study is the relatively small sample size therefore the findings need to be confirmed in a larger cohort. Furthermore, the cases were not pathologically confirmed to have LB disease and AD pathology, and we matched the AD patients to the DLB patients on age and gender. The AD patients in the current study may not be fully representative, and the findings in AD should be interpreted with caution. A high frequency of CMBs in patients with DLB has important therapeutic implications. High numbers of CMBs increase the risk of ARIA with vasogenic edema and effusions (ARIA-E) in amyloid-modifying immunotherapies [19,20]. Patients with DLB with high A β load are candidates for such therapies however; they may be at risk for ARIA-E as much as patients with AD. Furthermore, CMBs have to be considered before starting anticoagulation therapy to elderly adults with dementia because of the higher risk of further brain hemorrhage. Understanding the pathophysiology of cerebral CMB in patients with DLB would help with decisions on such therapeutic approaches in DLB patients.

Disclosure statement

Drs. Gungor, Sarro, Gunter, and Graff-Radford, Ms. Tosakulwong, Mr. Przybelski, and Ms. Zuk report no disclosures.

Dr. Boeve has served as an investigator for a clinical trial sponsored by GE Healthcare. He receives royalties from the publication of a book entitled Behavioral Neurology Of Dementia (Cambridge Medicine, 2009). He serves on the Scientific Advisory Board of the Tau Consortium. He receives research support from the NIH (U01 AG045390, U54 NS092089, P50 AG016574, U01 AG006786, RO1 AG015866, RO1 AG032306, RO1 AG041797), and the Mangurian Foundation for Lewy body research.

Dr. Ferman is funded by the NIH (P50-AG16574/P1) and the Mangurian Foundation for Lewy body research.

Dr. Smith is funded by the NIH (P50-AG16574).

Dr. Knopman 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 TauRx Pharmaceuticals. He receives research support from the NIH.

Dr. Petersen serves on scientific advisory boards for Elan Pharmaceuticals, Wyeth Pharmaceuticals, and GE Healthcare and receives research support from the NIH (P50-AG16574 [PI] and U01-AG06786 [PI], R01-AG11378 [Co-I], and U01-24904 [Co-I]).

Dr. Jack serves as a consultant for Eli Lilly. He receives research funding from the National Institutes of Health (R01-AG011378, R01-AG037551, U01-HL096917, U01-AG032438, U01-AG024904), and the Alexander Family Alzheimer's Disease Research Professorship of the Mayo Foundation Family.

Dr. Kantarci serves on the data safety monitoring board for Pfizer Inc and Johnson Alzheimer Immunotherapy; serves on the data safety monitoring board for Takeda Global Research & Development Center, Inc; and she is funded by the NIH (R01AG040042, P50 AG44170, P50 AG16574, U19 AG10483, U01 AG042791) and Minnesota Partnership for Biotechnology and Medical Genomics (PO03590201).

Acknowledgments

Funding: Financial support for the conduct of the research was provided by the NIH (R01 AG040042, P50 AG016574, R01 AG11378) the Mangurian Foundation for Lewy body research, and the Robert H. and Clarice Smith and Abigail Van Buren Alzheimer's Disease Research Program. Sponsors did not have any role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

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