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Microbleeds in the logopenic variant of primary progressive aphasia

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Abstract

Background—Microbleeds have been associated with Alzheimer's disease (AD), although it is unclear whether they occur in atypical presentations of AD, such as the logopenic variant of primary progressive aphasia (lvPPA). We aimed to assess the presence and clinical correlates of microbleeds in lvPPA.

Methods—Thirteen lvPPA subjects underwent 3T T2*-weighted and fluid-attenuated inversion recovery MRI and Pittsburgh Compound B (PiB) PET imaging. Microbleeds were identified on manual review and assigned a regional location. Total and regional white matter hyperintensity (WMH) burden was measured.

Results—Microbleeds were observed in four lvPPA subjects (31%); most common in frontal lobe. Subjects with microbleeds were older, more likely female, and had a greater burden of WMH than those without microbleeds. The regional distribution of microbleeds did not match the regional distribution of WMH. All cases were PiB-positive.

Conclusions—Microbleeds occur in approximately 1/3 subjects with lvPPA, with older women at the highest risk.

Keywords

Logopenic variant of primary progressive aphasia; Alzheimer's disease; microbleeds; white matter hyperintensities

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Conflicts of interest: none

1. Introduction

Alzheimer's disease (AD) is associated with amyloid-related imaging abnormalities (ARIA)¹. Microbleeds and superficial siderosis represent part of the spectrum of ARIA and can be identified on gradient-recalled echo (GRE) T2*-weighted MRI. They are thought to represent hemosiderin deposits and occur as a consequence of leakage of blood products from cerebral vessels that have been damaged by amyloid deposition in vessel walls; cerebral amyloid angiopathy (CAA)². The presence of CAA has been particularly associated with AD³, and studies have demonstrated that microbleeds occur in between 12-33% of patients with typical dementia of the Alzheimer's type (DAT)⁴⁻⁹. Microbleeds have however also been associated with white matter hyperintensities (WMH); a marker of cerebrovascular disease, in DAT⁹, suggesting that cerebrovascular disease may be playing some role in the development of microbleeds in AD.

A proportion of patients with AD do not present with episodic memory loss, but instead present with progressive aphasia characterized by impaired naming and sentence repetition, as well as phonological paraphasias. This presenting syndrome has been referred to as the logopenic variant of primary progressive aphasia (lvPPA) (or logopenic progressive aphasia)^{10, 11}. A high proportion of lvPPA subjects have AD pathology^{12, 13}, yet no studies have assessed the occurrence of microbleeds in these patients. The presence of microbleeds may influence anti-coagulation treatment approaches to patients with lvPPA. It is therefore important to understand whether lvPPA subjects are at risk for microbleeds.

We aimed to determine whether microbleeds occur in lvPPA subjects, and to assess whether microbleed burden would be associated with poorer cognition and greater burden of WMH.

2. Methods

2.1. Subjects

Between September 15th 2011 and May 15th 2012 we recruited 13 subjects that met our clinical criteria for lvPPA. All subjects underwent neurological evaluation and a detailed speech and language examination which was video recorded. Clinical diagnosis of lvPPA was rendered based solely on data from speech and language assessments without any reference to neurological or neuroimaging results. The diagnosis of lvPPA was independently determined by two speech-language pathologists (JRD and EAS); hence a consensus diagnosis. The clinical criteria used for lvPPA were as follows: 1) presence of aphasia, 2) impaired sentence repetition and comprehension, 3) presence of anomia with evidence of spared single word comprehension, 4) evidence of phonemic paraphasias, 5) normal rate of verbal expression or slowed verbal expression due to pauses for word retrieval without evidence of motoric slowing, and 6) absence of agrammatic/telegraphic verbal output. All 13 subjects diagnosed as lvPPA also met recently published clinical diagnostic criteria for lvPPA¹¹.

Speech and language assessments included the Western Aphasia Battery, revised¹⁴, Part 1, as the primary measure of global language ability, the Token Test (Part V) as a sensitive measure of verbal comprehension, and the Boston Naming Test¹⁵ as a sensitive measure of confrontation naming ability. All neurological assessments were performed by one Behavioral Neurologist (KAJ) and included testing for global cognitive and functional impairment. The presence/absence of hypertension was also ascertained.

This study was approved by the Mayo Clinic IRB. All subjects provided written informed consent before participating in any research activity.

2.2 MRI analysis

All subjects underwent a standardized MRI imaging protocol at 3T, including 1) a 3D magnetization-prepared rapid-acquisition gradient-echo (MPRAGE) sequence, 2) an axial T2-weighted fluid-attenuated inversion recovery (FLAIR), and 3) a T2*-weighted sequence to detect microbleeds. The majority of cases underwent a 2D GRE T2*-weighted sequence (TR/TE=200/20ms; flip angle=12°; FOV=20cm; in-plane matrix=256x224; phase FOV=1.00; slice thickness=3.3mm; bandwidth=15.63 kHz), although a couple of subjects underwent a 3D Swan T2*-weighted sequence (TR/TE=min/24.8ms; flip angle=30°; FOV=22cm; in-plane matrix=320x224; phase FOV=1.00; slice thickness=2.0mm; bandwidth=62.50 kHz).

Each T2*-weighted MRI sequence was reviewed by an experienced radiologist (CRJ) and each microbleed was marked using in-house software. An in-house 22-region atlas in the space of the MPRAGE was created. The GRE was upsampled 3x in plane and the MPRAGE with its atlas images were registered into the upsampled space and resampled. Each microbleed was assigned a location in the coordinate system of the GRE. White matter hyperintensities were segmented from normal brain tissue on the FLAIR sequences using an automated intensity-based algorithm using methods similar to the software tool Histoseg¹⁶, with additional manual clean-up. A white matter parcellation atlas was transformed into FLAIR space and used to calculate regional burden of WMH. The burden of WMH in each region was divided by white matter volume in that region and multiplied by 100, resulting in a WMH proportion (WMHp) that reflects the percentage of white matter in each region that was affected by WMH.

2.3. PiB-PET analysis

All subjects also underwent Pittsburgh Compound B (PiB) PET imaging using a PET/CT scanner (GE Healthcare, Milwaukee, Wisconsin) operating in 3D mode. Subjects were injected with PiB (average, 614 MBq; range, 414-695 MBq) and after a 40-60 minute uptake period a 20 minute PiB scan was obtained consisting of four 5-minute dynamic frames following a low dose CT transmission scan. Standard corrections were applied. Individual frames of the PiB dynamic series were realigned if motion was detected and then a mean image was created. All voxels in the PiB-PET image were divided by the median PiB uptake of the cerebellum to form uptake ratio images and were visually assessed.

2.4. Statistics

Statistical analyses were performed using JMP computer software (JMP Software version 8.0.0; SAS Institute Inc, Cary, NC). Group comparisons were performed using Mann-Whitney U testing for continuous variables and Chi-squared testing for categorical variables.

3. Results

Microbleeds were identified in 4/13 (31%) subjects (Figure 1). Two of these subjects had multiple microbleeds (14 and 12 microbleeds respectively), while single microbleeds were observed in the other two subjects. Microbleeds were most commonly found in the frontal lobe, although they were also identified in the temporal, parietal and occipital lobe (Figure 2). The right hemisphere was most severely affected.

The subjects with microbleeds were significantly older at onset and time of MRI than those without microbleeds, and had a higher proportion of women (Table 1). No differences were observed across groups in education, time from onset-scan, presence of hypertension or performance on cognitive or language tests. Total WMHp was significantly greater in the subjects with microbleeds compared to those without microbleeds (Table 1), with greater

WMHp burden observed regionally in left and right frontal lobe, left parietal lobe and right occipital lobe (Figure 2). Regional WMHp was greatest in the occipital lobes in both the lvPPA subjects with and without microbleeds (Figure 2). All 13 lvPPA subjects were PiB positive (Figure 1).

4. Discussion

This study demonstrates that microbleeds do occur in subjects with lvPPA and suggests that they may affect approximately 1/3 of lvPPA subjects. This proportion is consistent with the proportion that has been previously observed in subjects with DAT⁹. This is not necessarily surprising given that both lvPPA and DAT are typically associated with AD pathology. Indeed, all lvPPA subjects in our cohort were PiB-positive suggesting the presence of AD pathology. Multiple microbleeds were observed in half of the subjects, with the greatest regional burden observed in the frontal lobes. This contrasts to a recent study of DAT in which microbleed burden was highest in the occipital lobe⁹. This could suggest a different regional predilection in lvPPA, although it is unclear why the frontal lobe would be the most heavily targeted region.

As reported in DAT^{4, 6-9}, we found that the lvPPA subjects with microbleeds were older than the lvPPA subjects without microbleeds. Those with microbleeds were also more likely to be women. Cerebral amyloid angiopathy has indeed been observed more commonly in women in some studies¹⁷. It therefore appears as though older women, especially over the age of 70, are particularly at risk for the development of microbleeds in lvPPA. We did not however observe any association between the presence of microbleeds and cognitive function in lvPPA. While microbleeds have been associated with cognitive decline in healthy subjects¹⁸, many studies have similarly failed to find this association in DAT^{6, 7, 9}.

The lvPPA subjects with microbleeds had a greater burden of WMH. This relationship may suggest a potential cerebrovascular contribution¹⁹. However, microbleeds resulting from cerebrovascular disease are typically identified in deep grey/white matter and brainstem²⁰, whereas the majority of microbleeds in our cases were lobar and hence more suggestive of CAA. Furthermore, the regional distribution of WMH, with greatest burden observed in occipital lobe, did not appear to bear any spatial relationship to the distribution of microbleeds, demonstrating that they are spatially independent biological processes. The greater burden of WMH in the subjects with microbleeds therefore likely reflects the older age of these subjects.

The finding that microbleeds can occur in lvPPA could have important therapeutic consequences, for example whether or not to use anticoagulation therapy in a patient with lvPPA and microbleeds who has atrial fibrillation. While microbleeds are indications of previous bleeds, and are not currently active, patients with microbleeds are at a higher risk of further brain hemorrhage which could be accentuated by anticoagulation therapy. It could also influence prognosis since a higher risk of mortality has been associated with the presence of microbleeds. It is therefore important for microbleeds to be assessed in patients with lvPPA, particularly older women.

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Abbreviations

AD	Alzheimer's disease
lvPPA	logopenic variant of primary progressive aphasia
WMH	white matter hyperintensity
PiB	Pittsburgh Compound B
GRE	gradient recalled echo
CAA	cerebral amyloid angiopathy
MPRAGE	magnetization prepared rapid acquisition gradient echo
FLAIR	fluid-attenuated inversion recovery

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Research in Context

Systematic Review: We performed a pubmed search for articles published in English between Jan 1 1984 and June 1 2012 that contained the search terms “microbleeds”, “Alzheimer”, or “Logopenic”. We specifically reviewed studies that had assessed the presence of microbleeds in Alzheimer’s disease (AD). **Interpretation:** Previous studies demonstrated that microbleeds occur in approximately 1/3 of patients with typical dementia of the Alzheimer’s type (DAT). In the current study, we demonstrate for the first time that microbleeds also occur at a similar rate in patients with an atypical presentation of AD dominated by language impairment, i.e. the logopenic variant of primary progressive aphasia (lvPPA). Microbleeds were associated with older age, female gender and greater burden of white matter hyperintensities in lvPPA. **Future directions:** Future studies will be needed to define the pathological associations of microbleeds in atypical AD, and to determine whether microbleeds are observed in other atypical presentations of AD.

Figure 1. T2*-weighted MRI (top), FLAIR (middle) and PiB-PET (bottom) images for the four lvPPA patients with microbleeds. Microbleeds are shown with arrows.

Figure 2.

Regional microbleed and white matter hyperintensity burden. A) Line plot demonstrating total regional microbleed burden in the four patients with microbleeds; B) total white matter hyperintensity burden in each region for both the IvPPA subjects with and without microbleeds. P values were calculated using Mann-Whitney U test and represent differences in white matter hyperintensity burden between the IvPPA subjects with and without microbleeds. FL = frontal lobe; PL = parietal lobe; OL = occipital lobe; CM = cerebellum; GM = grey matter; WM = white matter; WMHp = white matter hyperintensities as a proportion of white matter volume; L = left; R = right.

Table 1

Summary demographic, clinical and imaging data

	lvPPA without microbleeds (n=9)	lvPPA with microbleeds (n=4)	P value
Female (%)	1 (11%)	3 (75%)	0.02
Education, years	16 (12-18)	14 (12-16)	0.51
Presence of hypertension (%)	4 (44%)	3 (75%)	0.30
Age at MRI, years	65 (47-74)	73 (70-85)	0.02
Age at onset, years	62 (43-72)	70 (64-80)	0.03
Time from onset to MRI, years	4 (2-5)	4 (2-6)	0.56
MMSE (/30)	26.0 (10-30)	24.5 (14-28)	0.78
CDR-SB (/18)	1.5 (0-7)	2.8 (1.5-4.0)	0.21
WAB aphasia quotient	83.0 (55-98.8)	81.4 (64.8-88.6)	0.86
Token Test (/22)	11.0 (1-21)	10.5 (6-14)	0.80
15-item Boston Naming Test	7.5 (4-14)	7.5 (1-9)	0.61
Total number of microbleeds	0	6.5 (1-14)	NA
Total WMHp	1.09 (0.22-2.75)	2.42 (2.20-4.42)	0.03

Data shown as median (range); MMSE = Mini-Mental State Examination; CDR-SB = Clinical Dementia Rating Sum of Boxes; WAB = Western Aphasia Battery; WMHp = White matter hyperintensities proportion, shown as percentage of regional white matter volume. P values were calculated using Mann-Whitney U and Chi-square tests.