Perivascular Distribution and Variable Progression of Focal White Matter Hyperintensities in Alzheimer's Disease

Gao, F.Q., Ramirez, J., Masellis, M., Black, S.E.

LC. Campbell Cognitive Neurology Research Unit, Heart and Stroke Foundation Canadian Partnership for Stroke Recovery, Hurwitz Brain Sciences Program, Sunnybrook Research Institute, Department of Medicine (Neurology), Sunnybrook Health Sciences Center, University of Toronto, Toronto, Canada

I. BACKGROUND AND OBJECTIVES

The origin(s) of white matter hyperintensities (WMH) in aging and in Alzheimer's disease (AD) is not fully understood. Previous studies suggest that parenchymal cerebral vessels (e.g. arteries and veins)[1-3] play a role not only in blood circulation but also in homeostasis of interstitial fluid and toxic metabolite clearance.[4] Specifically the perivascular space along the vessels may serve as brain lymphatics.[4] Hence, WMH may signify brain lymphatic dysfunction. The purpose of this study was to investigate whether focal WMH were spatially related to intramedullary vessels, and to map their change over time using magnetic resonance imaging (MRI), so that their dynamic characteristics could be discerned.

II. METHODS

Participants

- 60 subjects (40 AD & 20 NC), mean age=75 yrs.
- Gender: 26 men & 34 women.
- No stroke/lacune.

MR technique

- Two 1.5 T MRIs (3DT1 & PD/T2 scans) at mean interval 1.5 yrs.
- FLAIR and SWI were obtained in some participants.

WMH analysis

1. Focal WMH

- 3D-T1 contrast was set to optimally visualize vessels/venules.
- Focal WMH were identified on T2/PD.
- Co-registered T1-T2/PD revealed the spatial relationship of focal WMH with intramedullary vessels/veins. (Fig2)
- Focal WMH were counted & classified as shown in Fig1.

Fig 1

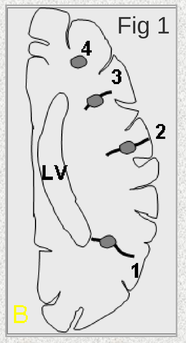


Fig1. The relationship of a focal WMH with a vessel was classified as:
1=centered on a vessel reaching from the pial surface to the lateral ventricle (LV)
2=centered on a vessel leading to the pial surface
3=centered on a vessel which appears to be in between the LV and the pial surface
4= not related to a vessel.

2. Focal WMH change over time

- Focal WMH change over time was recorded as:
  a. Enlarged or newly evident
  b. Smaller or has disappeared
- These were determined after the scan order of baseline vs follow-up was decoded.

III. RESULTS

1. Focal WMH at the baseline (N=757)

1) Focal WMH overall

- 94% (715/757) were designated as perivascular and 6% (42/715) or not-perivascular, based on whether or not they overlapped with or were centered on intramedullary vessels. (Fig 1)
- AD had more focal WMH centered on a vessel than the controls (94.9% vs 90.6%) (χ^2= 5.29, p=0.021).

2) Perivascular focal WMH

- 56.4% (403/715) were associated with vessels emanating from the subependyma (including 321 transcerebral vessels running from the pial surface to the ependyma);
- 28.8% (206/715) were associated with vessels running toward the pial surface only
- AD had more focal WMH centered on a subependymal-related vessel than the controls (57.3% vs 47.2%) (χ^2=5.54, p=0.018).

Fig 2

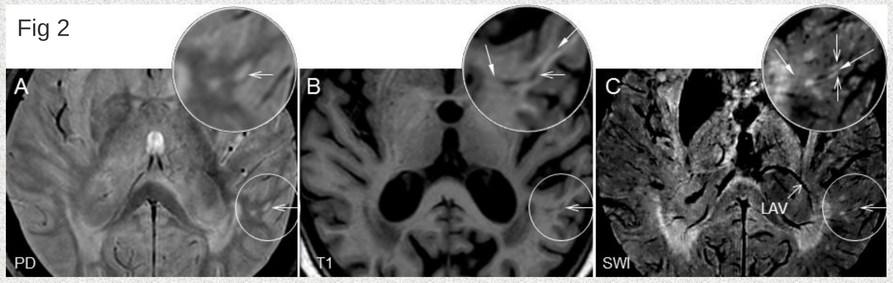
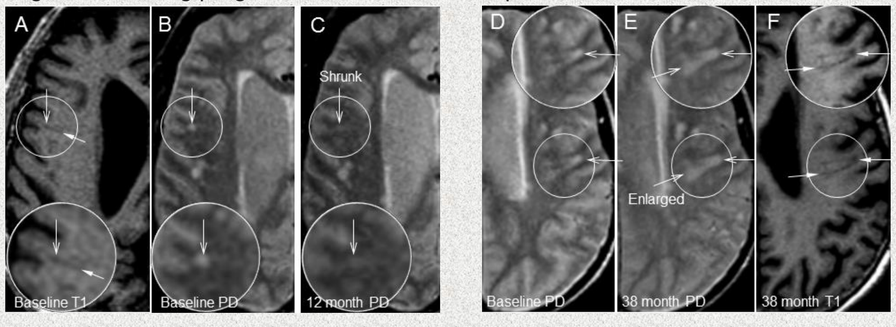


Fig 2. Perivascular distribution of focal WMH
(A) Proton density (PD), (B) T1-weighted, and (C) susceptibility-weighted imaging (SWI) MRI are co-registered at identical anatomical coordinates. The insets are magnifications of the small circles. The focal WMH (arrow in A) is centered on a long vessel (see solid arrows in the inset of B), which is confirmed to be a transcerebral vein on the SWI (arrows in C).

2. Perivascular focal WMH change over time

- 7% of focal WMH significantly decreased (including 10 no longer visible) (Fig3A-C).
- 29% significantly increased concentrically or along a vessel (Fig3 D-F).
- AD had more focal WMH increases over time than the controls (32.1% vs 22.1%) (χ^2=7.36, p=0.007).

Fig 3. Fluctuating progression of focal WMH in patients with AD

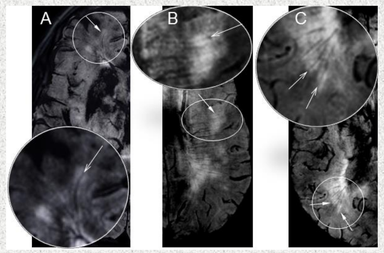


A-C Co-registered to identical coordinates, a focal WMH (arrows in B), centered on a vessel depicted by T1 (solid arrow in A), in one example patient appears to have shrunken significantly at follow-up (open arrow in C).
D-F also co-registered in identical space demonstrating a large focal WMH (arrows in D), centered on a transcerebral vessel (arrows in F), appears in another AD patient to havesignificantly enlarged at follow-up (arrows in E).
The insets are the magnifications of the areas defined in the small circles.

IV. DISCUSSION

- Focal non-lacunar WMH mostly overlapped with or were centered on intramedullary vessels, which suggests their perivenular distribution.
- The majority of intramedullary vessels going through the center of focal WMH are intramedullary veins connected to the subependymal deep venular system. The SWI study demonstrated about 80% focal WMH are peri-venular,[5] which can be easily reproduced (see Fig 4).

Fig 4. Perivenous focal WMH



SWI in axial slices of one hemisphere shows 3 examples of focal WMH centered on the intramedullary veins (arrows). The large circle insets are magnifications of the areas shown in the small circles. Three lesions are shown in the anterior frontal (A), posterior frontal (B), and occipital (C) regions.

- The regression and progression characteristics indicate that focal WMH may reflect perivascular (ie perivenous) edema, blood brain barrier leakage that likely represents regional venous hypertension (due to the venous collagenosis seen pathologically as a substrate of periventricular WMH) and/or perivenous stasis of perivascular lymphatic drainage (due to rigidity of collagenosed venous walls) that goes along perivenous spaces to clear toxins and manage fluid volumes.
- In this study, AD patients had more perivenous focal WMH, which also fluctuated more over time, than controls, suggesting that damage and dysfunction of the brain perivascular lymphatic drainage system are probably more severe in AD.

V. CONCLUSION

- Focal WMH may signify dysfunction of peri-vascular drainage.
- Peri-venous drainage of fluid and toxins appears to be more disturbed in AD than in elder controls.
- How WMH (possibly a marker of brain lymphatic dysfunction) interferes with amyloid clearance in AD warrants further study.

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