Focal white matter hyperintensities in fluctuating progression and perivascular distribution in aging and Alzheimer's disease: interstitial edema or ischemia?

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I. BACKGROUND AND OBJECTIVES

- Non-specific white matter hyperintensities (WMH) in Alzheimer's disease (AD) are usually attributed to small arterial occlusive disease.[1]
- However, venulopathy may also be implicated,[2,3] by interfering with interstitial fluid (ISF) circulation along perivascular pathways.[4,5] We investigated whether focal WMH have a perivascular/perivenous location, representing perivascular leakage which can fluctuate over time, seen in both aging and AD on MRI.
- Objectives are using a cross-sectional and longitudinal design:
  - To investigate relationship between WMH and deep intramedullary venules.
  - To investigate change of WMH over time.
  - To correlate MRI with pathology, and explore a potential under-appreciated pathophysiology of non-specific incidental WMH.

II. METHODS

Participants:

- 60 subjects (40 AD & 20 NC), mean age=72 yrs.
- 28 men & 14 women, no history of stroke.
- Interval between baseline and follow-up MRIs = 1.5 yrs.

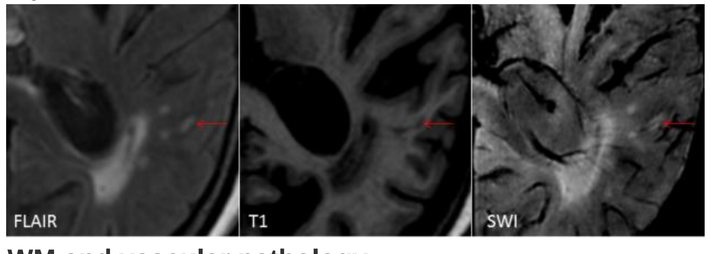
MR technique

- 3D-T1-weighted MRI with voxel size = 0.86x0.86x0.86 mm.
- T2/PD images co-registered to T1 space.
- Susceptibility weighted images (SWI) and FLAIR images were obtained for illustration purpose.

WMH analysis:

- Focal WMH < 10mm in diameter were identified and counted on T2/PD images.
- Vessels were visualized on 3D-T1 or inverted T2 images by darkening image contrast.
- Spatial relationship: whether a focal WMH was centered on a intramedullary vessel was determined on the co-registered T1 and T2/FLAIR, co-registered images (Fig1)
- Each focal WMH change over time was recorded as: unchanged; enlarged; decreased.

Fig 1. Focal WMH (arrows) identified at the same location in the space of co-registered FLAIR, T1 and SWI



WM and vascular pathology

- Histopathology was obtained in 4 AD patients from this series.

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III. RESULTS

Focal WMH and peri-vascular distribution

- 762 focal WMH were identified, mean count/subject = 14 in AD vs 9 in NC.
- 715 (94%) were superimpposed on intramedullary vessel.
- 391 out of 715 (55%) were superimposed on an intramedullary subependymal vessel, suggesting venular origin. (Fig 2,4-5).

Fig 2. Focal WMH (arrows on FLAIR) with centralized veins (arrows on SWI & the magnified inset).

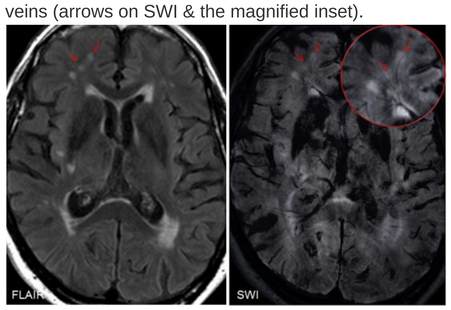
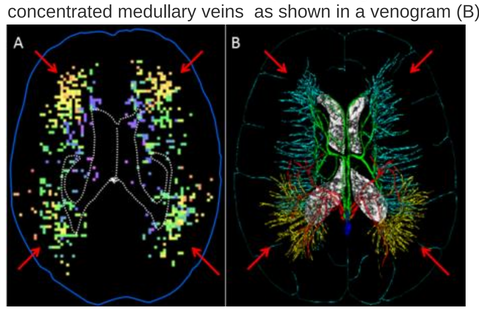


Fig 3. Distribution of focal WMH (A) mapping with areas of concentrated medullary veins as shown in a venogram (B).



Focal WMH distribution (Fig 3)

- Focal WMH from all subjects were distributed more abrandantly at the angles of the frontal and occipital horns of the lateral ventricles (arrows in Fig 3A), the areas have dense concentrations of medullary veins (arrows in Fig 3B) which drain frontal, parietal, occipital and temporal white matter (into deep venous system.

Focal WMH change over time

- Unchanged = 64%; Enlarged = 30% (Fig4); decreased = 6% (Fig5-6).

Fig 4. Focal WMH enlarged over 1 yr (arrows on FLAIR) centralized by a vein (arrow on SWI & magnified inset).

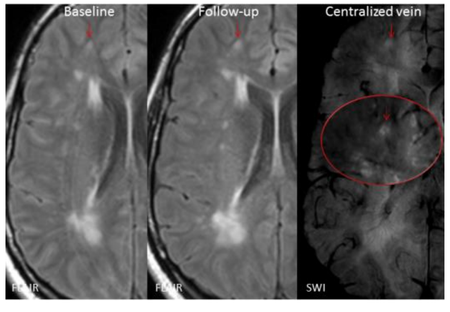


Fig 5. Focal WMH shrunk over 1 yr (arrows on FLAIR) centralized by a vein (arrow on SWI & magnified inset).

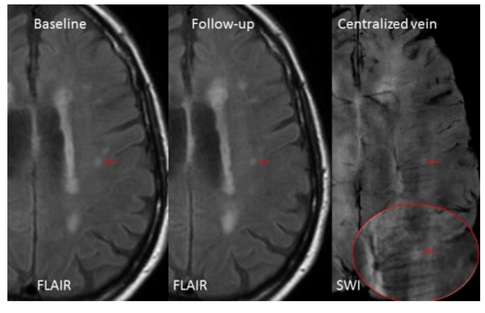
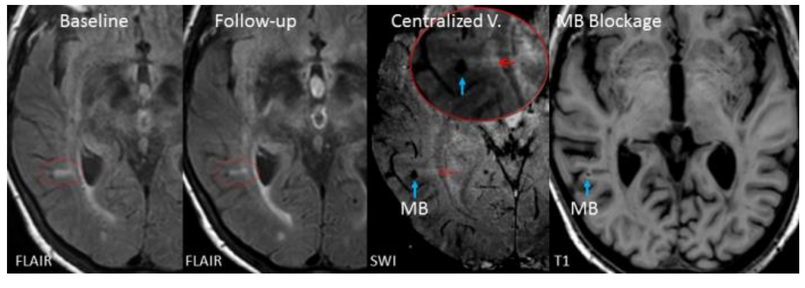


Fig 6. Focal WMH shrinking over 1 yr (circles on FLAIR) centered by a vein (red arrows on SWI & magnified inset), & related to perivenous fluid retention attributable to blockage by a microbleed (MB) (blue arrows) at the cortex (T1)



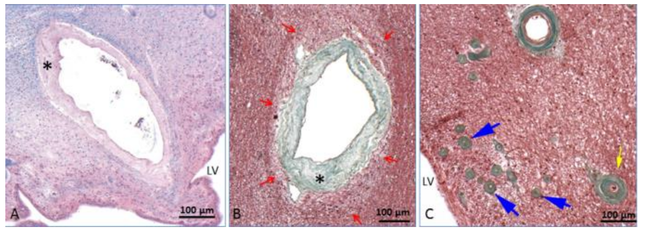
Characteristics of focal WMH in AD compared to NC

- No differences in mean focal WMH count, distribution and spatial relationship with vasculature between AD and NC.

WMH Pathology (Preliminary)

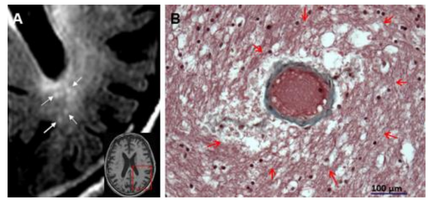
- **Vascular pathology**
  - Both small & large venous collagenosis

Fig 7. H&E/LFB (A) and trichrome stained sections (B,C) of periventricular white matter show collagenosis of large calibre (asterisks in A&B) and small calibre veins (blue arrows in C, contrast with arteriolosclerosis at yellow arrow). Some large calibre veins were surrounded by a region of myelin pallor (A).



- **Tissue pathology**
  - Perivascular pallor, demyelination & edema (Fig7A,B,Fig8B)

Fig 8. Focal WMH on FLAIR (arrows in A) in the region defined by the rectangle in the inset, and a trichrome stained histologic section of this region shows focal spongiform tissue transformation (arrows in B), suggesting edema, surrounding a white matter vessel.



IV. DISCUSSION

- Most non-specific (i.e. non-lacunar) WMH were located along medullary vessels, the majority of which were medullary venules.
- Variable progression of focal WMH would be in keeping with leakage & edema rather than arteriolar ischemic damage.[7,8]
- Perivascular space/zone may serve as channels for ISF flow, representing a 'lymphatic' system analogue in the CNS.[4,5]
- Venous collagenosis could increase vascular resistance and blood-brain barrier leakage, and changing hemodynamics of perivascular fluid, and also interfering with drainage and removal of solutes (such as amyloid) in the ISF from the brain.[2-4]
- Amyloid angiopathy could also contribute to formation of focal WMH by interfering with perivascular fluid flow in the cortical arterioles.[6] (Fig 6).

V. CONCLUSION

- Focal WMH, a biomarker of small vessel disease, may relate to chronic perivascular chronic edema, arising from both venous and arteriolar disease in aging and AD.
- The visible focal WMH, like small silent lacunes, may represent a more widespread disorder which could be elucidated further by in vivo 7T and by correlative pathology studies

REFERENCES:

1. Pantoni, L. & Garcia, J.H. *Stroke* 1997;28, 652-659 .
2. Black, et al. *Stroke* 2009;40:S48-52.
3. Moody, et al. Radiology.1995;194:469-476.
4. Rennels ML et al. *Adv Neurol* 1990;52:431-439.
5. Iliff, et al. Transl Med 2012;147ra111.
6. Roher et al. Molecular Medicine 2003;9:112-122.
7. Ochi et al. Magn Reson Med Sci. 2009;8:139-42.
8. Yamada et al. AJNR 2010;31:1350-1352.

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