I. BACKGROUND AND OBJECTIVES

The origin(s) of white matter hyperintensities (WMH) in aging and Alzheimer’s disease (AD) is not fully understood. Previous studies suggest that parenchymal cerebral vessels (e.g., arteries and veins) play a role not only in blood circulation but also in the pathogenesis of ischemic or inflammatory brain disease. Specifically, the perivascular space around vessels may serve as brain lymphatics. 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.

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 decided.

III. RESULTS

1. Focal WMH at the baseline (N=757)
1) Focal WMH overall
- 94% (715/757) were designated as perivascular and 6% (42/757) or not-perivascular, based on whether or not they overlapped with or were centered on intramedullary vessels. (Fig1)
- AD had more focal WMH centered on a vessel than the controls (94.9% vs 90.6%) ($\chi^2=5.29$, 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%) ($\chi^2=5.54$, p=0.018).

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%) ($\chi^2=7.36$, p=0.007).

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, which can be easily reproduced (see Fig 4).

V. CONCLUSION

- Focal WMH may signify dysfunction of peri-vascular edema, blood brain barrier leakage that likely represents regional venous hypertension (due to the venous collagenosis seen pathologically as a substrate of perivenicular 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 perivascular 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.

REFERENCES

ACKNOWLEDGMENTS
We gratefully acknowledge financial support from L. C. Campbell Foundation, Heart and Stroke Foundation Canadian Partnership for Stroke Recovery, Canadian Institute of Health Research, Alzheimer Society of Canada, and Alzheimer’s Association (USA)