Venous collagenosis: a pathological correlate of white matter hyperintensities

Gayathiri Balasubramaniam[1], Sandra E. Black[2-6], Joel Ramirez[2,3], Fuqiang Gao[2,3], Alicia McNeely[2,3], Courtney Berezuk[2,3], Christopher Scott[2,3], Alex Kiss[4], Raza Noor[5], Kelvin Au[1], Julia Keith[1,6]

Department of Anatomic Pathology[1] , LC. Campbell Cognitive Neurology Research Unit[2], Heart and Stroke Foundation Canadian Partnership for Stroke Recovery[3], Hurvitz Brain Sciences Program, Sunnybrook Research Institute[4], Departments of Medicine (Neurology)[5], University of Toronto[6], Toronto, Ontario, Canada

BACKGROUND

Background

- White matter hyperintensities (WMH) are biomarkers for cerebral small vessel disease, which has a prominent role in stroke, dementia and aging[1]
- Pathological correlates of WMH include myelin loss, activated microglia and arteriolar disease[2,3]
- A few small studies describe collagenosis of the deep medullary veins as being involved WMH pathogenesis[4]
- As periventricular WMH become larger and confluent, periventricular infarcts (PVIs) may form

Purpose:

➢ To use an image-pathology correlative study to explore a potential relationship between WMH and venous collagenosis

METHODS

Participants:

WMH Cohort

- Autopsy confirmed AD patients (n=22)
- Controls (n=18) without neurodegenerative phenomena at autopsy

PVI Cohort

- Subjects (n=6) were part of the Sunnybrook Dementia Study
- All had a pathologic diagnosis of AD
- 12 PVIs were identified on imaging

Subject Characteristics		
Variable	AD	Non-AD
Age at death (years)	72.5 ± 10.3	76.3 ± 10.4
Sex (M)	59.1%	61.1%

Subject Characteristics	
Age at death (years)	78 ±3.9
Female/ Male	2/4

Tissue Pathology:

WMH Cohort

- Tissue blocks were obtained (Figure 1); 66 from the AD cases and 54 from Controls
- Blocks were embedded in paraffin, cut into 4µm thick sections, and stained with H&E/LFB and Masson's trichrome

PVI Cohort

- MRIs were used to localize PVIs in formalin-fixed coronally sectioned archived cadaveric brain tissue; 30 blocks were created from 12 PVIs
- Tissue blocks were embedded in paraffin, cut into 5 µm sections, and stained with:
  - H&E/LFB
  - Masson's trichrome
  - immunohistochemistry for GFAP, CD68 and neurofilament

Assessing Venous Collagenosis in the WMH and PVI cohort

- % stenosis of large veins (% lvs):
  - ➢ [external diameter- internal diameter]/external diameter X 100 on trichrome
- Venous collagenosis severity in medium and small calibre veins (0-3) was assessed[4]

WMH analysis on imaging:

- WMH severity was semi-qualitatively assessed using the Fazekas Scale on 3 levels (anterior, middle and posterior)

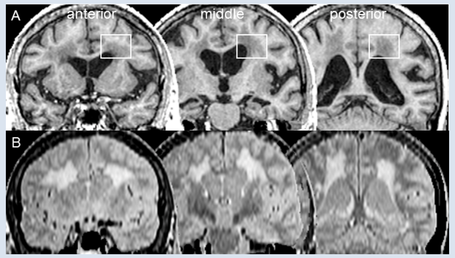

Fig 1. **A**. Coronal T1-weighted MR images demonstrating the areas of periventricular white matter sampled for histopathology (rectangles) **B.** Coronal PD-weighted MR images at levels corresponding A, which were used for the rating of WMH.

RESULTS

Vascular Pathology in the WMH cohort

- Venous collagenosis in both small and medium calibre veins was a common finding in both the AD and Control groups
- Average % lvs was 19.8% and was a frequent finding

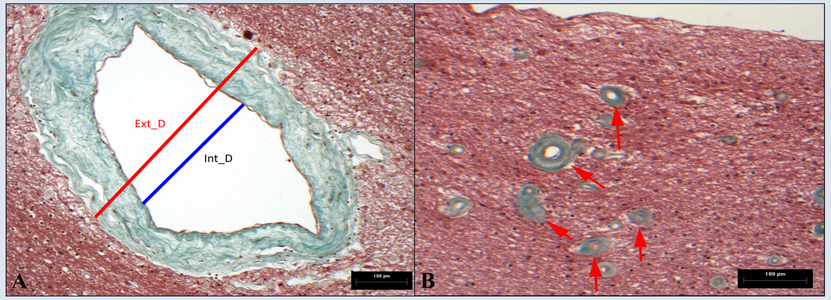

Fig 2. **A.** A large calibre vein with External and Internal diameters demarcated and used to calculate % lvs. **B**. Trichrome stained sections of periventricular white matter. Severe stenosis of small calibre veins (red arrow); grade 3.

WMH and Correlations

- WMH scores significantly correlated with:
  - ➢ periventricular white matter pallor (rs(116)=0.252, p=0.006)
  - ➢ collagenosis of small veins (rs(114)=0.268, p=0.004)
  - ➢ collagenosis of medium veins (rs(114)=0.266, p=0.004)
  - ➢ % lvs (rs(112)=0.377, p=0.000)
- % lvs is the strongest predictor of WMH(β=0.330, df=108, p=0.000)

ACKNOWLEDGEMENTS: We are grateful for support from Canadian Institute of Health Research MOP-13129, Alzheimer Society of Canada, Alzheimer's Association (USA), LC Campbell Foundation, and Heart and Stroke Foundation Canadian Partnership for Stroke Recovery

WMH Pathology in the PVI cohort

Vascular pathology

- 3 were histologically confirmed infarcts, 4 were dilated perivascular spaces and 5 were histologically undetectable
- For histologically confirmed infarcts, the average rating for small and medium veins was 3 and 1.33 respectively, and the average % lvs was >30%

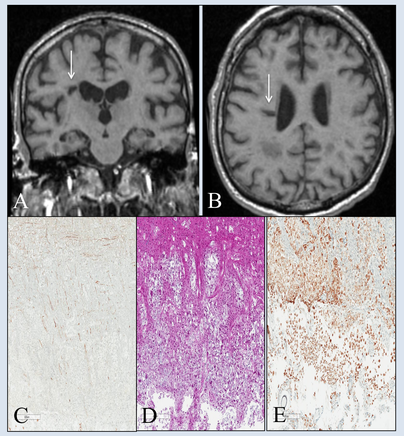

Fig 3. **PVIs. A &B** - coronal T1 MRI with PVI (white arrow). **C**- axonal loss on neurofilament; **D** - an influx of macrophages, confirmed on CD68 (**E**).

DISCUSSION

- Venous collagenosis is a frequent finding in individuals with WMH and may:
  - ➢ increase vascular resistance leading to decreased perfusion of deep white matter[4]
  - ➢ lead to edema in the deep white matter by shunting blood from the internal cerebral vein to the transmedullary veins[4]
  - ➢ impair interstitial fluid drainage[5] and facilitate the accumulation of certain toxins such as Beta-amyloid[2]
- Stenosis of both the small and large veins may be a possible mechanism underlying periventricular WMH with PVIs

CONCLUSION

- Venous collagenosis in periventricular veins of all calibre may underlie the pathogenesis of WMH and possibly lead to infarction
- Neuropathologists should attend to and document the presence of venous collagenosis in the standard neuropathological examination

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