# Cerebral microbleeds and posterior perivascular spaces in Alzheimer's disease patients from the Sunnybrook Dementia Study.

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## Background

The investigation of cerebral microbleeds and perivascular spaces visualized on MRI of Alzheimer's disease (AD) patients provides unique insight into the complex, comorbid small vessel disease that is commonly observed in AD [1].

## Objective

The purpose of this study was to examine cerebral microbleed burden in AD and its potential associations with MRI-visible posterior perivascular spaces (PVS) and global cognition.

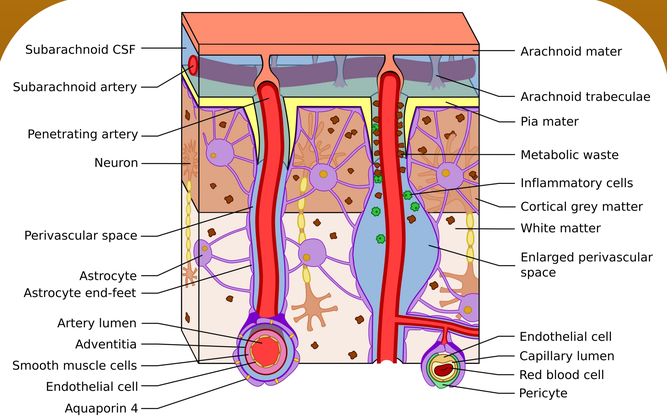


**Fig. 1** Schematic representation of the brain's perivascular Virchow-Robin space and surrounding tissues. The cortical perivascular space is bounded by the adventitia of the vessel and the astrocyte end-feet, and is filled with CSF from the subarachnoid space. Beta amyloid is thought to accumulate around the blood vessel possibly resulting in perivascular blockage and enlargement of the space, as shown on the right vessel [4].

## Discussion

These results suggest that multiple microbleeds on T2* MRI may be a macroscopic reflection of significant underlying CAA with AD pathology [5].

Moreover, these findings provide support for the theory that increased MRI-visible posterior PVS in AD patients with lobar microbleeds may indicate retrograde PVS enlargement in the posterior white matter [6].

Possibly reflecting impaired clearance of cerebral amyloid through the brain's posterior perivascular waste removal system.

## Methods

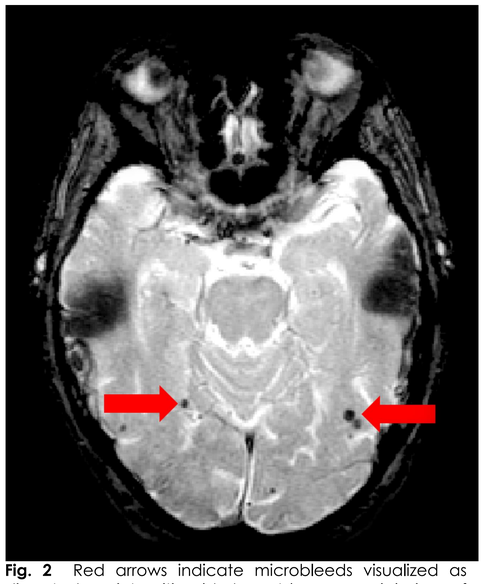

**Fig. 2** Red arrows indicate microbleeds visualized as discrete hypointensities (dark spots) on an axial view of iron sensitive T2*-weighted gradient-recalled echo (GRE) MRI of an AD patient.

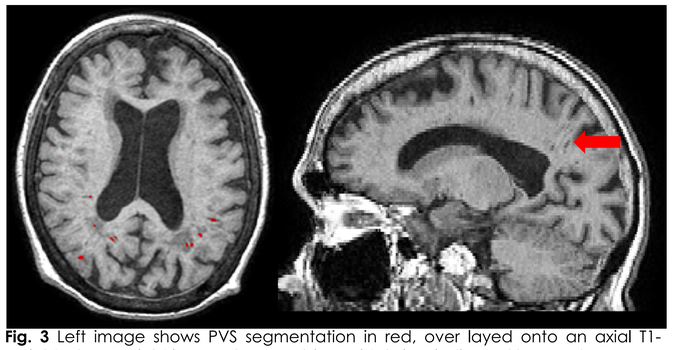

**Fig. 3** Left image shows PVS segmentation in red, over layed onto an axial T1-weighted MRI. Right image shows PVS in sagittal view indicated by a red arrow.

Cross-sectional analysis was performed on 160 probable/possible AD patients in the Sunnybrook Dementia Study. See Table 1. (ClinicalTrials.gov NCT01800214).

Microbleed burden was assessed on T2* MRI using the Microbleed Anatomical Rating Scale (MARS) [2] (Fig.2). Posterior (parieto-occipital) PVS volume and counts (Fig. 3), global atrophy, and white matter hyperintensities (WMH) were quantified using Lesion Explorer [3]. The Mini-Mental State Examination (MMSE) was used to assess global cognition. All analyses accounted for age, sex, and education.

## Results

**Table 1.** Summary of patient demographics and neuroimaging metrics.

| | Total Sample | Cerebral Microbleed Burden: Without Microbleeds | Cerebral Microbleed Burden: With Microbleeds | p |
|---|---|---|---|---|
| **Demographics** | | | | |
| Number (%) | 160 (100) | 121 (75.6) | 39 (24.4) | -- |
| Age (years) | 73.3 ± 9.5 | 73.3 ± 9.7 | 73.5 ± 8.7 | n.s. |
| Sex, male | 81 | 57 | 24 | n.s. |
| Education (years) | 13.7 ± 4.0 | 13.8 ± 3.9 | 13.5 ± 4.3 | n.s. |
| MMSE | 21.8 ± 6.9 | 22.3 ± 5.2 | 20.3 ± 10.6 | n.s. |
| **Neuroimaging** | | | | |
| BPF, % | 0.72 ± 0.05 | 0.73 ± 0.05 | 0.70 ± 0.05 | n.s. |
| Microbleeds | 1.1 ± 3.6 | 0.0 | 4.6 ± 6.1 | -- |
| Posterior PVS Volume, $mm^3$ | 18.7 ± 46.2 | 16.8 ± 44.0 | 23.1 ± 51.5 | n.s. |
| Posterior PVS Count | 7.7 ± 17.4 | 7.2 ± 16.0 | 8.9 ± 20.6 | n.s. |
| Posterior WMH, cc | 3.3 ± 5.5 | 3.5 ± 5.8 | 2.8 ± 4.8 | n.s. |

Data are presented as Mean ± SD
Raw volumes are presented for illustrative purposes, analyses were performed on normalized data
*p<0.05, **p<0.01, ***p<0.001

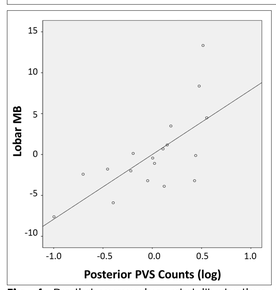


**Fig. 4.** Partial regression plot illustrating the relationship between posterior PVS counts and lobar MB (β=1.72, p=0.02).

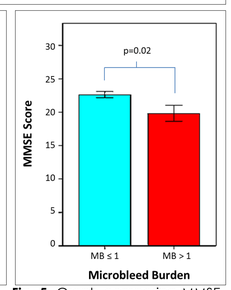


**Fig. 5.** Graph comparing MMSE between AD patients with multiple (MB>1) versus those with one or none (MB≤1).

Linear regression analysis revealed that lobar microbleeds were significantly associated with posterior PVS counts (β=1.72, p=0.02) in microbleed positive AD patients (Fig.4). A statistical trend approaching significance was also noted between lobar microbleeds and posterior PVS volume (β=1.37, p=0.06).

Microbleeds occurred in approx. 24.4% of AD patients, with 65% having >1 microbleed, and lobar pre-dominance in 97%. Additionally, patients with multiple microbleeds had lower MMSE (p=0.02) (Fig. 5).

Although a significant sex difference (men > women) was demonstrated (β=0.63, p=0.017), no statistically significant relationships were demonstrated with DRS score, age, WMH volume, education, or global atrophy.

**References**
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