SEX DIFFERENCES IN PERIVASCULAR SPACE BURDEN IN ALZHIEMER'S DISEASE AND NORMAL ELDERLY

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BACKGROUND

Perivascular spaces (PVS):

- Fluid-filled spaces surrounding the brain's vasculature
- Play an important role in clearance of interstitial fluid and toxic metabolites[1]

Enlarged PVS (ePVS):

- May reflect some form of small vessel disease and are possibly associated with cognitive decline [2, 3]
- Males tend to have a greater ePVS burden, although no adequate explanation has been suggested for this difference

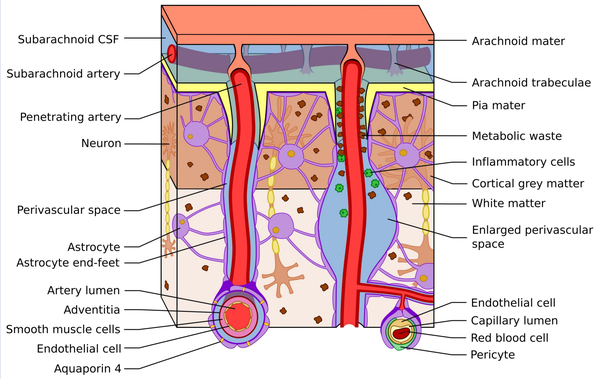

Figure 1: Schematic representation of enlarged and non-enlarged perivascular spaces. Illustration not to scale.

PURPOSE & HYPOTHESIS

Purpose: To examine ePVS volumes and counts for men and women with Alzheimer's disease (AD) and normal controls (NC)

Hypothesis: Based on previous research, we predict PVS volumes to be larger in males, with the possibility of diagnostic differentials

METHODS

Lesion Explorer (LE) [4,5] was used to automatically segment regions of cerebrospinal fluid (CSF) intensity within the WM and subcortical grey matter (GM) using T2 and T1-weighted MRI. A trained user then removed false positive non-VRS voxels (e.g. lacunes, subcortical hyperintensity (SH), and ventricular/sulcal CSF) from the mask.

The VRS segmentation was parcellated into BG and WM regions using SABRE [4]. Manual edits were performed to improve the basal ganglia delineation.

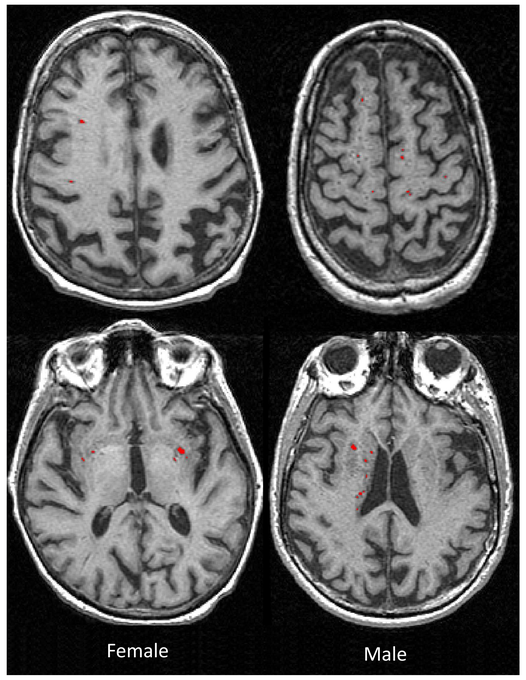

Figure 2: Semi-automatically segmented perivascular spaces (red) overlayed on a structural T1-weighted MRI of a female (left) and male (right) brain.

SUBJECTS

All subjects were taken from the Sunnybrook Dementia Study and provided informed consent to participate

AD (n=232)
- Males (n=102)
- Females (n=130)

NC (n=101)
- Males (n=41)
- Females (n=60)

ANALYSIS

Sex differences in ePVS measures were examined using MANCOVA and stratified by diagnosis

- **Adjusting for**: age, years of education (YOE), Mini-Mental State Examination (MMSE), total intracranial capacity (TIC), brain parenchymal fraction (BPF), and white matter hyperintensity (WMH) volume.

Non-normal variables were log transformed prior to analysis

RESULTS

Table 1. Bivariate test results comparing men and women

Alzheimer's Disease	Male (n=104)	Female (n=131)	Statistic	p
Age (years)	71.65 ± 9.03	72.46 ± 9.43	-.66	.51
YOE (years)	14.2 ± 4.23	13.35 ± 3.6	1.64	.10
MMSE †	24 ± 7	23 ± 5	5402.00	**.02**
TIC (cc)	1293.8 ± 108.5	1140.2 ± 109.0	10.750	**<.001**
BPF (%)	72.56 ± 4.72	73.06 ± 4.47	-0.820	0.41
WMH (cc) †	3.56 ± 7.79	5.05 ± 9.18	5859.00	.07
WM-ePVS (mm^3) †	15.51 ± 40.47	6.2 ± 19.5	5163.00	**.001**
BG-ePVS (mm^3) †	30.58 ± 46.01	23.93 ± 27.92	5403.00	**.006**
WM-ePVS (count) †	8 ± 13.75	5 ± 9	5185.00	**.002**
BG-ePVS (count) †	9.5 ± 9	8 ± 6	5711.00	.03
Normal Controls	**Male (n=42)**	**Female (n=63)**	**Statistic**	**p**
Age (years)	71.14 ± 8.14	68.87 ± 7.79	1.44	.15
YOE (years)	15.85 ± 3.13	15.55 ± 3.34	.47	.64
MMSE †	29 ± 1.25	29 ± 1	1049.00	.13
TIC (cc)	1296.2 ± 87.4	1151.4 ± 91.1	8.110	**<.001**
BPF (%)	78.01 ± 3.7	79.68 ± 3.74	-2.250	**.03**
WMH (cc) †	2.74 ± 8.11	1.97 ± 3.02	1008.00	**.039**
WM-ePVS (mm^3)†	19.13 ± 35.42	9.31 ± 13.15	864.50	**.003**
BG-ePVS (mm^3) †	31.02 ± 33.86	17.58 ± 26.22	949.00	.01
WM-ePVS (count) †	12.5 ± 12.5	5 ± 8	794.00	**<.001**
BG-ePVS (count) †	9 ± 6	6 ± 6	958.50	**.017**

Data presented in Mean ± SD and compared using independent t-tests unless otherwise specified

† Data presented in Median ± IQR and compared using Mann-Whitney U

Table 2. Multivariate test results comparing men and women after adjusting for age, YOE, MMSE, TIC, BPF, and WMH

Alzheimer's Disease	F	df	p	η^2
WM-ePVS (mm^3)	8.59	1	**.004**	.031
BG-ePVS (mm^3)	3.16	1	.077	-
WM-ePVS (count)	8.24	1	**.004**	.030
BG-ePVS (count)	2.56	1	.111	-
Normal Controls	**F**	**df**	**p**	**η^2**
WM-ePVS (mm^3)	.010	1	.909	-
BG-ePVS (mm^3)	.910	1	.342	-
WM-ePVS (count)	.280	1	.599	-
BG-ePVS (count)	.170	1	.684	-

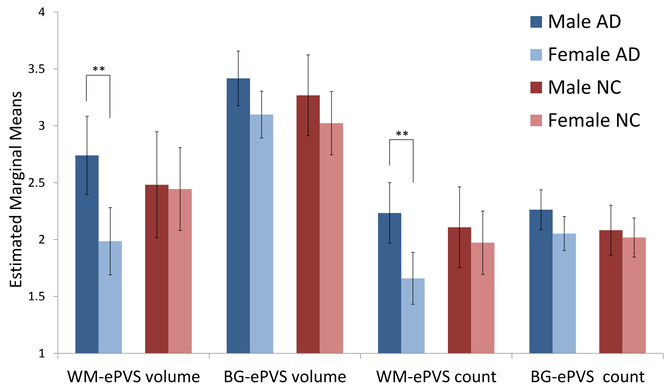

Figure 3: Estimated marginal means of ePVS measures derived from the MANCOVA. Error bars are presented as 95% CI.

DISCUSSION

Alzheimer's Disease:

Male sex is associated with a greater number and overall volume of ePVS in the WM, a possible marker of small vessel disease and amyloid angiopathy.

No sex difference in BG-ePVS burden was found after adjusting for covariates.

Normal Controls:

No sex difference in ePVS in volumes or counts were found after adjusting for covariates possibly indicating a mediation effect.

Further research is needed to understand why men with AD are at a higher risk for increased ePVS burden in the white matter.

The implications of these findings are limited due to uncertainty surrounding the mechanisms behind PVS enlargement; however, these findings advocate for the importance of gender stratification in future PVS research.

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