Relationships between Myeloperoxidase and the Cognitive and Neuroimaging Correlates of Mild Vascular Cognitive Impairment

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Introduction

- People with mild vascular cognitive impairment (mVCI), the most prevalent form of vascular cognitive impairment (VCI) and a prodromal stage of vascular dementia, display a combined etiology of cognitive impairment and vascular comorbidities
- Currently, there are no treatments that successfully alter the disease progression of mVCI.
- Myeloperoxidase, and enzyme found in neutrophils, creates reactive oxygen and nitrogen species and has been implicated in the pathophysiology of vascular disorders and cognitive impairment.
- **The purpose of this study is to investigate the association between peripheral MPO and cognitive and neuroimaging correlates of mVCI. I hypothesize that higher peripheral MPO concentrations will be associated with lower verbal memory scores and higher white matter hyperintensity volumes in mVCI patients.**

Methods

- Patients will be recruited during intake from a cardiac rehabilitation program. Clinical history of vascular disease, and the core criteria for Subcortical Ischemic MCI including cognitive deficits and neuroimaging results will be used to make the diagnosis of mVCI
- Verbal memory will be assessed using Hopkins Verbal Learning test- Revised as a part of a 60-minute battery recommended by National Institute of Neurological Disease and Stroke-Canadian Stroke Network standards
- White matter hyperintensity (WMH) volumes will be acquired using 3 Tesla Prisma Siemens MR scanner and quantified using the Canadian Dementia Imaging Protocol for the semiautomatic and simultaneous quantification of WMH volumes
- Myeloperoxidase (MPO) will be measured form the plasma processed from a fasting blood draw using Abcam's MPO ELISA kit
- Pearson's correlations and multiple liner regression will be used to assess the relationships between MPO and verbal memory, and MPO and WMH volumes using SPSS version 26.
- Covariates were selected based on the current literature.

Results

- Patient demographics are displayed in Table 1.

Patient Characteristics (n=27)	Mean (SD) or n (%)
Age (years)	67.2 ± 7.4
Sex, males	20 (74%)
Education: Grade school High School College diploma Bachelor's degree Professional degree Post-graduate degree	1 (3.5%) 8 (30%) 4 (15%) 11 (41%) 1 (3.5%) 2 (7%)
BMI (kg/m2)	29.4 ± 5.3
Resting systolic blood pressure (mmHg)	127 ± 18

Outcome measures	Mean ± SD	Range
Verbal memory composite Z-score	-1.14 ± 1.04	-2.61 – 1.29
HVLT total recall Z-score	-1.06 ± 1.13	-2.75 – 2.05
HVLT delayed recall Z-score	-1.30 ± 1.08	-2.75 – 1.41
HVLT recognition discrimination index Z-score	-1.06 ± 1.26	-2.75 – 0.99
White Matter Hyperintensity Volumes (mm^3)	**Mean ± SD**	**Range**
Periventricular	4761.5 ± 5637.8	455 – 42959
Deep	573.6 ± 692.3	1 – 2755
Log base 10 Periventricular	3.48 ± 0.41	2.66 – 4.4
Log base 10 Deep	2.22 ± 0.93	0 – 3.44
Myeloperoxidase concentrations (ng/mL)	**Mean ± SD**	**Range**
MPO	5.12 ± 3.42	1.46 – 15.5
Log base 10 MPO	0.64 ± 0.23	0.17 – 1.19

- Pearson's correlations between MPO and verbal memory, and WMH volumes in Table 2.

Verbal memory outcomes	Log MPO (n=27)
Verbal memory composite Z-score	-0.106 (p= 0.599)
HVLT total recall Z-score	0.041 (p= 0.839)
HVLT delayed recall Z-score	-0.058 (p= 0.773)
HVLT recognition discrimination index Z-score	-0.249 (p= 0.211)
Neuroimaging markers	**Log MPO (n=27)**
Log base 10 Periventricular WMH volume	0.423 (**p= 0.028**)*
Log base 10 Deep WMH volume	0.169 (p= 0.400)
Log base 10 total WMH volume	0.393 (**p= 0.043**)*

- Multiple linear regressions between MPO and verbal memory, and WMH volumes in Table 3. (*p<0.05)

Dependent Variables (covariates: BMI, education)	Beta	P-value
Verbal memory composite Z-score	-2.284	**0.035***
HVLT-R total recall Z-score	-1.373	0.243
HVLT-R delayed recall Z-score	-1.966	0.086
HVLT-R recognition discrimination index	-3.510	**0.010***
Dependent Variables (covariates: age, RSBP)	**Beta**	**P-value**
Log base 10 Periventricular WMH volume	0.334	0.301
Log base 10 Deep WMH volume	-0.607	0.366
Log base 10 total WMH volume	0.241	0.451

Conclusions

- Cognitive decline is associated with a higher risk of hospitalization and mortality and contributes to a decline in activities of daily living and quality of life
- Findings suggest that MPO can have detrimental effects on cognition which may be mediated by changes in WMH volumes, in mVCI population
- Novel therapeutic target for preventing cognitive decline

References

- ROCKWOOD, K., WENTZEL, C., HACHINSKI, V., HOGAN, D. B., MACKNIGHT, C. & MCDOWELL, I. 2000. Prevalence and outcomes of vascular cognitive impairment. Vascular Cognitive Impairment Investigators of the Canadian Study of Health and Aging. Neurology, 54, 447-51.
- LAU, D. & BALDUS, S. 2006. Myeloperoxidase and its contributory role in inflammatory vascular disease. Pharmacol Ther, 111, 16-26.
- WU, C. Y., BAWA, K. K., OUK, M., LEUNG, N., YU, D., LANCTÔT, K. L., HERRMANN, N., PAKOSH, M. & SWARDFAGER, W. 2020. Neutrophil activation in Alzheimer's disease and mild cognitive impairment: A systematic review and meta-analysis of protein markers in blood and cerebrospinal fluid. Ageing Res Rev, 62, 101130.
- TAY, A., TAMAM, Y., YOKUS, B., USTUNDAG, M. & ORAK, M. 2015. Serum myeloperoxidase levels in predicting the severity of stroke and mortality in acute ischemic stroke patients. Eur Rev Med Pharmacol Sci, 19, 1983-8.

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