

Lower arterial cerebral blood flow is associated with worse neuroinflammation and immunomodulation composite proteomic scores

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Introduction

- Brain hypoperfusion has been linked with worse physical, cognitive and MRI outcomes in multiple sclerosis (MS).
- Understanding the proteomic signatures related to hypoperfusion could provide insights into the pathophysiological mechanism.

Aim

- To determine the relationship between cerebral arterial blood flow (CABF) and multivariate proteomic characteristics in people with MS (pwMS).

Methods

- 140 pwMS (86 clinically isolated syndrome (CIS)/relapsing-remitting (RRMS) and 54 progressive (PMS)) were included in the study
- CABF was determined using ultrasound Doppler measurement as the sum of the blood flow in the bilateral common carotid arteries and vertebral arteries.
- Proteomic analysis was performed using the Multiple Sclerosis Disease Activity (MSDA) with Proximity Extension Assay methodology on the OlinkTM platform.

Table 1. Demographic and clinical characteristics of the study population

Demographic and clinical characteristic of the study population	Total MS population (n=140)	CIS/RRMS (n=86)	PMS (n=54)	p-value CIS/RR vs. PMS
Female, n (%)	103 (73.6)	61 (70.9)	42 (77.8)	0.371 ^a
Age, mean (SD)	54.0 (10.9)	43.7 (10.3)	54.7 (8.2)	<0.001^b
BMI, median (IQR)	27.4 (24.1-31.1)	26.6 (24.2 – 29.3)	28.1 (22.6 – 31.1)	0.613 ^b
Obese, n (%)	36 (25.7)	19 (22.1)	17 (31.5)	0.216 ^a
Hypertension, n (%)	26 (18.6)	12 (14.0)	14 (25.9)	0.076 ^a
Hyperlipidemia, n (%)	31 (22.1)	19 (22.1)	12 (22.2)	0.986 ^a
Heart disease, n (%)	23 (16.4)	17 (20.0)	6 (11.1)	0.169 ^a
History of smoking, n (%)	60 (42.9)	36 (42.9)	24 (45.3)	0.78 ^a
Presence of diabetes, n (%)	6 (4.3)	3 (3.5)	3 (5.6)	0.557 ^a
CABF, mean (SD)	950.7 (256.5)	959.0 (249.9)	931.5 (278.7)	0.545 ^b
Disease duration, mean (SD)	20.6 (18.5)	16.6 (8.9)	27.0 (9.9)	<0.001^b
EDSS, median (IQR)	3.0 (1.6 – 6.0)	2.0 (1.5 – 3.0)	6.0 (4.0 – 6.5)	<0.001^c
MSSS, median (IQR)	2.3 (1.2 – 5.4)	1.5 (0.9 – 2.9)	5.6 (2.7 – 6.5)	<0.001^c
5-year relapse rate, mean (SD)	0.159 (0.361)	0.209 (0.4)	0.077 (0.24)	0.035^b
Use of DMT, n (%)				
IFN- β	45 (32.1)	30 (34.9)	15 (27.8)	0.778 ^a
Glatiramer acetate	35 (25.0)	20 (23.3)	15 (27.8)	
Natalizumab	8 (5.7)	6 (7.0)	2 (3.7)	
Off-label DMT	6 (4.3)	3 (3.5)	3 (5.6)	
Oral DMTs	15 (10.7)	10 (11.6)	5 (9.3)	
No therapy	31 (22.1)	17 (19.8)	14 (25.9)	

a – chi square test, b – Student's t-test, c - Mann Whitney U test. P-values lower than 0.05 was considered statistically significant and shown in bold.

- The MSDA score utilizes a stacked classifier logistic regression model of 18 age- and sex-adjusted protein concentrations and determines 4 disease pathway scores (immunomodulation, neuroinflammation, myelin biology, and neuroaxonal integrity) as well as an overall disease activity score (1 to 10).

Results

- There were no differences in CABF between CIS/RRMS vs. PMS groups.
- Lower CABF levels were correlated with the MSDA score ($r=-0.26$, $p=0.003$) and with neuroinflammation ($r=-0.29$, $p=0.001$), immunomodulation ($r=-0.26$, $p=0.003$) and neuroaxonal integrity ($r=-0.23$, $p=0.007$) pathway scores.
- After age and body-mass index (BMI)-adjustment, lower CABF remained associated with neuroinflammatory ($r=-0.23$, $p=0.011$) and immunomodulation ($r=-0.20$, $p=0.024$) pathway scores
- Individual analyses outlined neurofilament light chain, CCL-20 and TNFSF13B as contributors.

Conclusions

- Lower cerebral arterial perfusion in MS is associated with changes in multiple pathophysiological pathways and proteomic biomarkers.

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Table 2. Associations between proteomics-based score and total cerebral arterial blood flow in people with multiple sclerosis

Proteomics-based score all pwMS		CABF	Age-adjusted CABF	Age and BMI-adjusted CABF
MSDA score	r-value	-0.262	-0.275	-0.19
	p-value	0.003*	0.002*	0.033
Neuroinflammation score	r-value	-0.287	-0.312	-0.241
	p-value	0.001*	<0.001*	0.007*
Immunomodulation score	r-value	-0.256	-0.282	-0.214
	p-value	0.003*	0.001*	0.017*
Neuroaxonal integrity score	r-value	-0.234	-0.24	-0.165
	p-value	0.007*	0.006*	0.067
Myelin biology score	r-value	-0.058	-0.046	0.023
	p-value	0.51	0.605	0.799

Legend: Non-parametric Spearman's correlations and age-, BMI-adjusted correlations were performed. P-values lower than 0.05 was considered statistically significant and shown in bold. The multiple correlations were corrected for false discovery rate (FDR) using the Benjamini-Hochberg procedure. Significant correlations that survive the FDR correction are labeled with asterisks