Glial cell injury and MRI measures of chronic multiple sclerosis inflammation

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Introduction

- In multiple sclerosis (MS), severe chronic lesional activity could lead to complete tissue destruction that is replaced by the cerebrospinal fluid (CSF).
- Atrophied lesion volume (aLV), is an exploratory imaging marker in MS reflecting the volume of lesions subsumed into cerebrospinal fluid (CSF) that predicts disability progression and transition into progressive MS phenotype.[1]
- Moreover, meningeal infiltrates imaged as leptomeningeal contrast enhancement (LMCE) are linked with greater cortical

Objective

- To determine the relationship between multivariate, serum-derived proteomic data with future development of aLV and LMCE in a heterogeneous group of persons with MS (pwMS).

Methods

- Serum-based proteomic and MRI data for 202 pwMS (148 clinically isolated syndrome/relapsing-remitting; CIS/RRMS and 54 progressive MS; PMS) was acquired both at baseline and at 5.4-years follow-up visit.
- The concentrations of 21 proteins related to multiple pathways of MS pathophysiology were derived using a custom developed and validated Proximity Extension Assay on the Olink™ platform.

Methods (continued)

- The accrual of aLV was determined by combining fluid attenuated inversion recovery (FLAIR)-based lesion masks from both timepoints and the follow-up CSF map. (Figure 1)
- LMCE were defined as signal intensity within the subarachnoid space greater than intensity of brain parenchyma on postcontrast scans.
- Regression models and age-adjusted analysis of covariance (ANCOVA) were used.

Results

- Baseline factors such as older age (standardized beta=0.176, p=0.022), higher levels of glial fibrillary acidic protein (GFAP) (standardized beta=0.312, p=0.001) and lower levels of myelin oligodendrocyte glycoprotein (MOG) (standardized beta=-0.271, p=0.002) were associated with greater accrual of aLV over the follow-up. (Table 1)

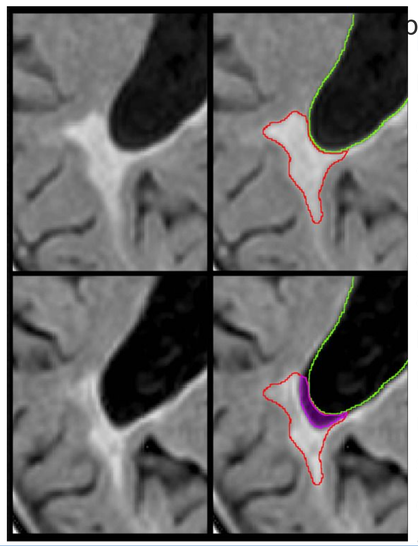

Figure 1. Representative example of an atrophied lesion. Magenta region showing the area that was lesion at baseline but has now been subsumed into cerebrospinal fluid (atrophied lesion).

Table 1. Regression model using blood-based biomarkers for predicting chronic inflammation as aLV

Absolute atrophied T2-LV in pwMS (n=202)	Standardized Beta Coefficient	t-statistics	p-value	Tolerance	VIF	R^2
Sex	-0.006	-0.080	0.937	0.958	1.044	
Age at baseline	0.176	2.308	**0.022**	0.860	1.162	0.067
BMI	-0.103	-1.388	0.167	0.912	1.097	
GFAP	0.312	3.382	**0.001**	0.588	1.699	0.088
MOG	-0.271	-3.142	**0.002**	0.673	1.486	0.138
Absolute atrophied T2-LV in pwPMS (n=54)	Standardized Beta Coefficient	t-statistics	p-value	Tolerance	VIF	R^2
Sex	0.078	0.616	0.541	0.966	1.035	
Age at baseline	0.510	3.562	**0.001**	0.745	1.342	0.106
BMI	0.074	0.558	0.580	0.876	1.141	
MOG	-0.493	-3.406	**0.002**	0.729	1.371	0.203
GFAP	0.394	2.864	**0.007**	0.809	1.236	0.331
FLRT2	-0.296	-2.182	**0.035**	0.833	1.2	0.404

- The presence of LMCE at the follow-up visit was not predicted by any baseline proteomic biomarker nor cross-sectionally associated with any follow-up proteomic concentrations.

Conclusion

- Higher baseline GFAP levels and lower MOG levels are associated with greater aLV development over 5-year follow-up in pwMS.
- There are no proteomic differences between pwMS with and without presence of LMCE.
- Proteomic markers of glial activation are associated with chronic lesional pathology and may be specific to the progressive MS phenotype.

References

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Disclosures

- Ferhan Qureshi, Anisha Keshavan, Kelly Leyden and Ati Ghoreyshi are employees of Octave Bioscience.
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