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Serum Biomarkers of Clinical and Radiographic Disease Progression in Multiple Sclerosis

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Introduction

Disease progression in MS is a complex process that is currently understood qualitatively. To directly measure progression via serum proteins may lead to new insights and better outcomes for patients.

Objectives

To identify blood biomarkers capturing i) EDSS progression (independent of relapse activity) and ii) gray and white matter brain atrophy using well-characterized longitudinal cohorts with and without severe disease progression [1].

Methods

Serum samples from 2 phenotypically extreme MS groups followed yearly were analyzed (Swiss MS Cohort Study): (1) Worsening progressive MS (wPMS): 184 samples from 18 patients; median follow-up of 6.5 years; median EDSS of 4.0 at baseline (BL) and 6.0 at last visit; no relapses during follow-up; (2) stable MS (stMS): 169 samples from 19 patients; 7.1 years median follow-up; median EDSS from 3.0 to 2.5. wPMS and stMS were matched by age, disease duration, EDSS and T2 lesion volume at BL. Samples were analyzed with 3 Olink assays: Explore 3072, Target 48, and the Octave Custom Assay Panel, and 2 Simoa assays for GFAP and NfL [2]. Brain MRI scans were performed annually using a standardized imaging protocol [3]. Single protein linear-mixed-effects models for each endpoint were run on the combined cohorts (1) and (2). Variables of interest and covariates, including patient demographics and clinical characteristics, were dependent on the model. Proteins were ranked by p-value and effect size.

	Stable MS	Worsening progressive MS	*P*-value
Samples (*n*)*	169	184	
Number of patients	19	18	
Baseline data			
Age (years)	44.2 [39.5-49.2]	43.8 [40.9-53.8]	0.784
Disease category at study entry (%)			0.018
RRMS	18 (94.7)	10 (55.6)	
PMS	1 (5.3)	8 (44.4)	
EDSS score	3.0 [2.5-3.8]	4.0 [3.1-4.4]	0.065
Follow-up data			
Number of samples per patient	9 [8, 10]	10 [9, 12.5]	0.097
FU time (years) (range)	7.1 [5.7-8.0] [4.1-9.0]	6.5 [5.2-7.7] [2.7-8.5]	0.395
EDSS score at last sampling	2.5 [2.0-3.8]	6.0 [5.6-6.9]	<0.001
Number of confirmed disease progression events (%)			<0.001
0	19 (100.0)	0 (0.0)	
1	0 (0.0)	6 (33.3)	
2	0 (0.0)	8 (44.4)	
3	0 (0.0)	4 (22.2)	

	stable MS	wPMS
Number of patients	19	18
Number of samples = MRIs	105	93
Median samples/patient	5.0	5.5
Baseline visit data		
Sex (Number women, %)	(12, 63.2)	(11, 61.1)
Median age (years)	44.19	43.82
Median BMI	27.54	25.29
Median EDSS	3	4
Median disease duration	9.37	13.7
DMT (Number, %)		
Platform	(4, 21.1)	(0, 0.0)
Untreated	(3, 15.8)	(6, 33.3)
Monoclonal antibodies	(4, 21.1)	(6, 33.3)
Orals	(8, 42.1)	(6, 33.3)
MRI total intracranial volume (TIV) (mL)	15.19	14.44
Follow-up data		
Median follow-up time at last MRI (years)	6.02	5.25
Median EDSS at last visit	2.5	5.75
Total Relapses	0	0

Table 1: Demographic Information for the full cohort (left) and the subset of the cohort with MRI (right)

The following formulas were used to model the relationship between progressor status (clinical model), gray matter, and white matter atrophy with protein concentration:

Clinical Model: log(protein concentration) ~ 1 + age at baseline + disease duration at baseline + BMI + sex + DMT category [Orals, Platform, Monoclonal, None] + EDSS + **progressor status** + followup time + **progressor status : followup time** + *patient id**

MRI Models: log(white or gray matter volume) ~ 1 + MRI TIV + age at baseline + sex + disease duration at baseline + protein concentration at baseline + follow up time + **protein concentration at baseline : follow up time** + *patientid* + MRI scanner change**

** = random effect*
Bold text = coefficient of interest

Results

- Serum protein differences were found between wPMS and stMS, with several detected at higher significance than GFAP or NfL.
- IL15, a proinflammatory cytokine, was the strongest differentiator at the group level and was increased by 32% [15, 51] (p=1.17e-04) in wPMS.
- ARHGEF1, a nucleotide exchange factor, showed the largest change over time and decreased by 13%/y [18, 8] (p=1.32e-05) in wPMS.
- CD1C, a dendritic cell marker, was the top protein for gray matter volume loss with baseline doubling leading to 0.77%/y [0.50, 1.04] (p=7.63e-08).
- GFRA2, a glial cell neurotrophic factor receptor, was the top protein for white matter volume loss with baseline doubling leading to -1.59%/y [-2.15, -1.04] (p=1.10e-07).

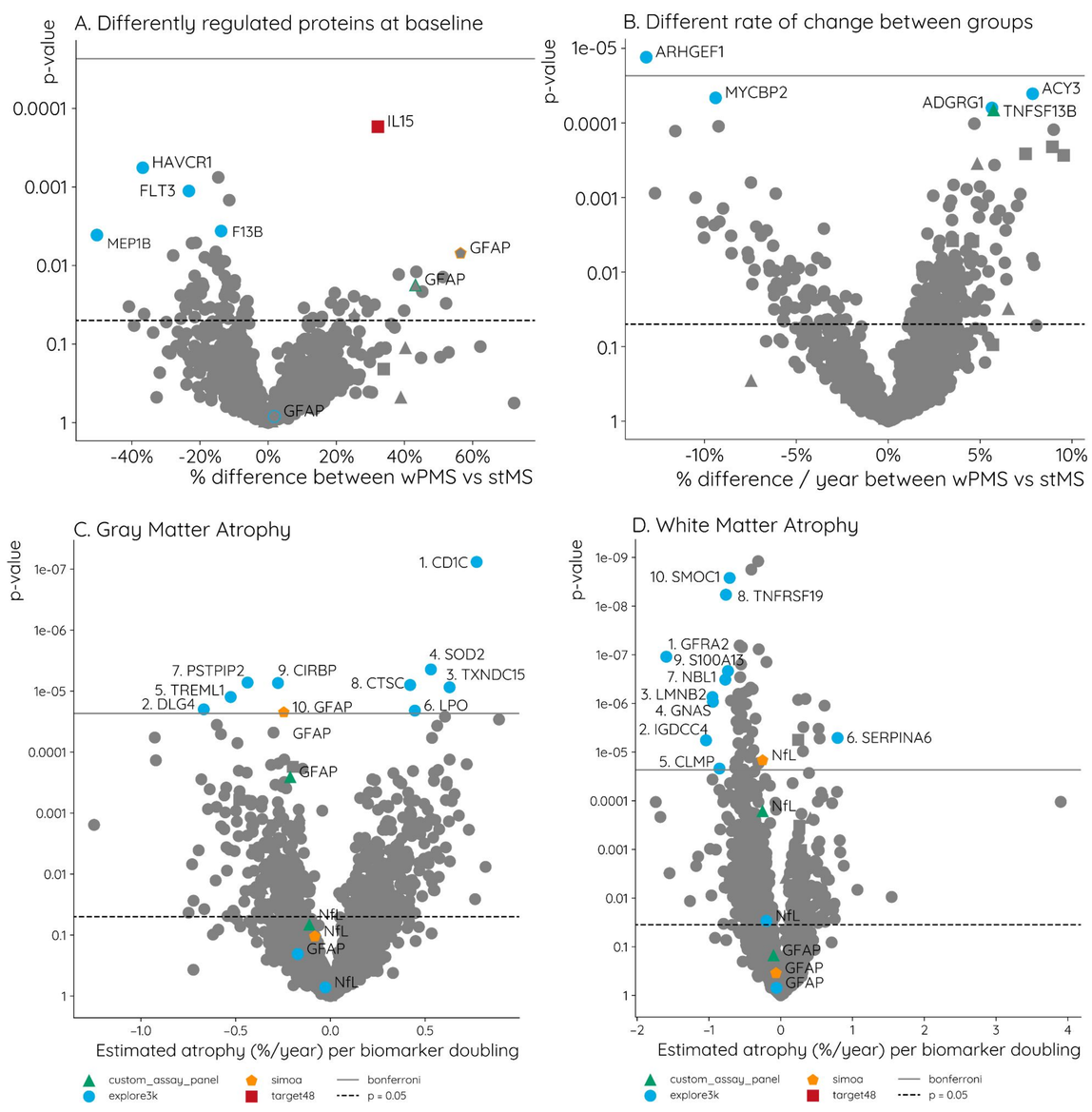

Figure 1: Volcano plots of A) Percent Difference Between wPMS vs StMS versus p-value B) Percent Difference per year between wPMS vs stMS versus p-value C) Estimated Gray Matter atrophy (%/year) per biomarker doubling versus p-value D) estimated White Matter atrophy (%/year) per biomarker doubling versus p-value.

Conclusions

In our analysis of over 2000 biomarkers, several proteins show potential to predict clinical and radiographic endpoints of progression at higher significance than either GFAP or NfL. Future work includes validation in independent cohorts, and multi-protein approaches to more accurately predict EDSS progression (independent of relapse activity) and brain atrophy.

Disclosures: This study was funded by Octave Bioscience. Ferhan Qureshi, Anisha Keshavan, Shannon McCurdy and Ati Ghoreyshi are employees of Octave Bioscience.

References: [1] Meier S, Willemse E, Schaedelin S, et al. Serum Glial Fibrillary Acidic Protein Compared With Neurofilament Light Chain as a Biomarker for Disease Progression in Multiple Sclerosis. JAMA Neurology. Feb 2023. https://doi:10.1001/jamaneurol.2022.5250 [2] Oechtering J, Maceski A, Keshavan A, et al. Serum biomarkers of progression by proteomic search in extreme MS phenotypes. Oral Presentation. ECTRIMS 2022. [3] Keshavan A, Oechtering J, Maceski A, et al. Serum Biomarkers of Brain Atrophy in Multiple Sclerosis. Poster# P039. ACTRIMS 2023.