Serum Biomarkers of Brain Atrophy in Multiple Sclerosis

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BACKGROUND

- Disease progression in MS is a complex process that is currently understood in a qualitative way. To directly measure progression via its biochemical manifestation in serum is an important aim that may facilitate drug development.

OBJECTIVE

- To compare serum biomarkers of MS progression using well-characterized longitudinal cohorts of patients with and without severe progression. Here we aimed to identify blood-based biomarkers prognostic of gray and white matter atrophy. These findings complement previously reported findings for clinically-defined progression endpoints from the same cohort and analytes [1].

METHODS

- 37 MS patients from 2 phenotypically extreme MS groups followed yearly were available (Swiss MS Cohort Study, SMSC): (1) Worsening progressive MS (wPMS): Samples from 18 patients; median follow-up of 5.25 years between baseline visit and last MRI scan; median EDSS of 4.0 at baseline and 5.75 at last visit; no relapses during follow-up; (2) stable MS: Samples from 19 patients; 6.0 years median follow-up between baseline visit and last MRI scan; median EDSS from 3.0 at baseline visit to 2.5 at last visit. wPMS and stMS were matched by age, disease duration, EDSS and T2 lesion volume at baseline. See Table 1.
- Samples were analyzed with 3 assays: Olink Explore 3072, Target 48, and the Octave Custom Assay Panel. GFAP and NfL were also measured by Simoa assays.
- Brain MRI scans were performed annually in the SMSC. A standardized imaging protocol was applied across centers including a 3D MPRAGE and FLAIR sequence. T1w images were lesion-filled using FSL [2] and segmented by SPM12 [3] to compute gray (GMV) and white matter volume (GMV).
- Two linear mixed-effects models (see Figure 1) were run on the combined cohorts (1) and (2). The interaction between log of the baseline biomarker concentration and FU time was the contrast of interest.
- Significant proteins were ranked by effect size and compared to, $GFAP_{Simoa}$ for GMV and NfL_{Simoa} for WMV [4].

Table 1: Demographics

	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

Figure 1: Equation for linear mixed-effects models for white and gray matter volume. Baseline=date of serum collection. Follow-up time calculated from baseline serum collection date and MRI date. Bold= contrast of interest, *=random effects.

log(white_or_gray_matter_volume) ~ mri_tiv + age_at_baseline + sex + disease_duration_at_baseline + biomarker_value_at_baseline + followup_time_years + **biomarker_value_at_baseline x followup_time_years** + patient_id* + mri_scanner_change*

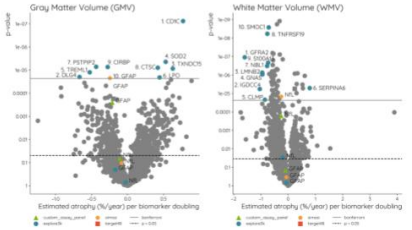
RESULTS

- Each doubling of baseline $GFAP_{Simoa}$ led to an additional loss of GMV (-0.25%/y [-0.36, -0.14], p<0.0001) but not WMV (-0.07% [-0.20, 0.07], p=0.35), while doubling of baseline NfL_{Simoa} resulted in additional loss of WMV (-0.25%/y [-0.36, -0.14], p<0.0001) but not GMV (-0.08%/y [-0.18, 0.02], p=0.10).
- For GMV, 9 proteins were statistically more significant than $GFAP_{Simoa}$ and passed Bonferroni significance. The top two proteins were CD1C, a dendritic cell marker, baseline doubling leading to (0.77%/y [0.50, 1.04], p=7.63e-08), and DLG4, a synaptic protein, baseline doubling leading to (-0.67%/y [-0.96, -0.37], p=1.99e-05). The top five effect-size proteins and GFAP are in Table 2.
- For WMV 52 proteins were statistically more significant than NfL_{Simoa} and passed Bonferroni significance. The top two proteins were GFRA2, a glial cell neurotrophic factor receptor, baseline doubling leading to (-1.59%/y [-2.15, -1.04], p=1.10e-07) and IGDCC4, an immunoglobulin superfamily member, baseline doubling leading to (-1.04%/y [-1.47, -0.61], p=5.74e-06). The top five effect-size proteins and NfL are in Table 2.
- See Figure 2 for a volcano plot of all Assay findings.

Table 2: Annualized percentage change per doubling of baseline biomarker

Assay (*=explore3k []=Simoa)	%/year change due to doubling (95% CI)	P-val
GMV		
CD1C*	0.77 (0.5, 1.04)	7.63E-08
DLG4*	-0.67 (-0.96, -0.37)	1.99E-05
TXNDC15*	0.63 (0.36, 0.9)	8.65E-06
SOD2*	0.53 (0.31, 0.75)	4.41E-06
TREML1*	-0.53 (-0.75, -0.3)	1.25E-05
[GFAP]	-0.25 (-0.36, -0.14)	2.23E-05
WMV		
GFRA2*	-1.59 (-2.15, -1.04)	1.10E-07
IGDCC4*	-1.04 (-1.47, -0.61)	5.74E-06
LMNB2*	-0.95 (-1.31, -0.59)	7.42E-07
GNAS*	-0.94 (-1.3, -0.58)	9.26E-07
CLMP*	-0.85 (-1.23, -0.47)	2.18E-05
[NfL]	-0.25 (-0.36, -0.14)	1.47E-05

Figure 2: Volcano plot of estimated atrophy (%/year) per biomarker doubling versus p-value.



CONCLUSIONS

- In our analysis of 2079 proteins, 61 proteins measured at baseline show prognostic potential to predict atrophy in the gray- or white- matter at least as significant as the Simoa benchmarks. The largest effects associated with additional atrophy are proteins primarily expressed in the central nervous system. Future work includes validation in independent cohorts, multivariable approaches to more accurately predict brain atrophy, and the incorporation of additional clinical and MRI metrics.

REFERENCES

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