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Blood Serum Proteome Correlates of Multiple Sclerosis Disease Progression as evaluated by Neuropsychological Test Outcomes: A 5-Year Longitudinal Study

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BACKGROUND

Patients with Multiple sclerosis (PwMS) progress through a complex, heterogeneous disease course spanning decades. Quantitative measurement of serum proteome biomarkers associated with Disease Progression (DP) could greatly enhance the care for MS patients. In addition to the Expanded Disability Status Scale (EDSS), several neuropsychological tests are used to assess cognitive and functional disability in MS patients.

OBJECTIVE

To identify serum proteins associated with neuropsychological test outcomes in MS.

METHODS

We recruited a total of 202 MS patients between 2009-2012 for a baseline (BL) visit. Subjects returned 6.0 ± 1.0 years later for a follow-up (FU) visit in 2014-2017 [1].

The inclusion criteria were: baseline age of 18-75 years old; diagnosed with either MS or clinically isolated syndrome (CIS), defined by the 2010-revised McDonald criteria; availability of either baseline or follow-up serum sample, MRI, clinical and neuropsychological assessments within 30 days of each other.

The exclusion criteria were: having clinical relapse or receiving intravenous corticosteroid therapy within 30 days before the MRI and serum sampling; not able to undergo any of the aforementioned study procedures.

Collected data consisted of:

- blood serum sample (201/142 patients at BL/FU);
- Expanded Disability Status Scale (EDSS) (186/196 patients at BL/FU);
- 25-Foot Walk Test (25FWT) (53/121 patients at BL/FU);
- 9-Hole Peg Test (9HPT) (51/126 patients at BL/FU);
- Symbol Digit Modalities Test (SDMT) (53/130 patients at BL/FU),
- Paced Auditory Serial Addition Test (PASAT) (52/122 patients at BL/FU).

Serum samples were analyzed using a custom immunoassay panel to measure the concentrations of 19 analytically validated protein biomarkers.

A patient was deemed a progressor if: (i) baseline EDSS ≤ 0.5 and follow-up EDSS of ≥ 2; or (ii) baseline 1 ≤ EDSS ≤ 5 and increase in EDSS ≥ 1 at follow-up; or (iii) baseline 5.5 ≤ EDSS and increase in EDSS ≥ 0.5 at follow-up.

Linear mixed-effects models with neuropsychological test outcome (25FWT, 9HPT, SDMT, or PASAT) as response, with fixed effects for protein concentration, age, sex, and BMI, and with patient ID as a random effect were utilized after removal of outliers using the non-parametric InterQuartile Range (IQR) method.

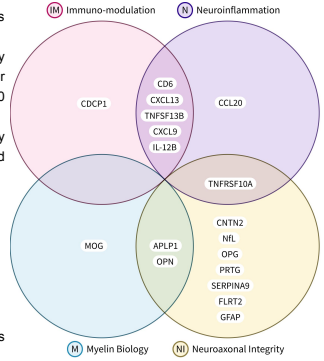

Figure 1. The Octave Bioscience Multiple Sclerosis Disease Activity (MSDA) test was developed using Proximity Extension Assay (PEA) methodology on the Olink™platform. It measures the concentrations of 18 proteins. In addition, the assay panel used to run the MSDA test also includes VCAN which was used in the proteomics analysis.

RESULTS

Progressors scored 26.9% (p=0.0248) 31.0% (p=0.0009), 18.1% (p=0.0004), 9.3% (p=0.6774) worse than non-progressors at the follow-up time point in the T25FWT, 9HPT, and SDMT, respectively.

Protein biomarkers that were statistically significant in predicting the test scores were CXCL9 for T25FWT (p=0.0093); NfL (p=0.0012), GFAP (p=0.0354), and CDCP1 (p=0.0261) for 9HPT; CCL20 (p=0.0134) and CDCP1 (p=0.0422) for SDMT; CCL20 (p=0.0287) and GFAP for PASAT (p=0.0160); NfL (p=0.0200) for EDSS.

Protein biomarkers that were nominally statistically significant in predicting impairment in the cognitive processing speed domain were IL-12B (p=0.0329) for a drop of 4 points in SDMT, IL-12B (p=0.0329) and SERPINA9 (p=0.0488, R2=0.226) for a drop of 8 points in SDMT, and CDCP1 (p=0.0479) at the follow-up visit for patients with SDMT z-scores less than -1.5 from a healthy population [2].

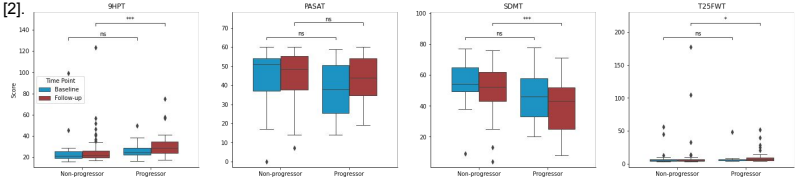

Figure 2. Changes in neuropsychological scores between baseline and over the follow-up period. ANalysis of COVAriance (ANCOVA) was used to compare log-transformed values between the two subgroups. P-value annotation legend: ns: 0.05 < p <= 1, *: 0.01 < p <= 0.05, **: 0.001 < p <= 0.01, *: 0.0001 < p <= 0.001.**

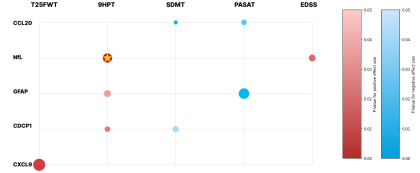

Figure 3. Biomarker concentration model parameters with adjustment for age, sex and bmi: The radius of each circle is proportional to the estimated standardized coefficient of the corresponding protein, red (blue) circles represent proteins with positive (negative) effects in estimating the second class label. The color of each circle represents the p-value. Biomarkers that survived the multiple hypothesis testing corrections are marked with a gold star (*).

CONCLUSIONS

In this cohort of patients, the 9HPT, SDMT and T25FWT were strongly associated with disease progression defined based on the EDSS. We found several protein candidates representing diverse biological pathways (neuroinflammation, immune modulation and neuroaxonal integrity) that were correlated with worsening of neuropsychological test outcomes; including CCL20, NfL, GFAP, CDCP1, and CXCL9. These findings require validation in an independent larger cohort and future analysis will include the evaluation of multi-protein models for a more accurate assessment of neuropsychological test outcomes.

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DISCLOSURES:

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