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Glial Fibrillary Acidic Protein Predicts Short-term Progression Independent of Relapse Activity in Primary Progressive Multiple Sclerosis

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Introduction:

Prediction of progression is a significant unmet need in people with progressive multiple sclerosis (PwPMS). Glial fibrillary acidic protein (GFAP) has been proposed to be a promising marker of progression in MS. Nevertheless, previous studies were either restricted to single-center studies with predominantly relapsing multiple sclerosis, or were based on solely EDSS progression, which limit its generalization to current state-of-the art clinical setting and clinical trials in PMS.

Objectives/Aims:

To evaluate whether assessment of GFAP can potentially contribute to better prediction of disability progression in PwPMS.

Methods:

EMerging blood BIOmarkers in PROgressive Multiple Sclerosis (EmBioProMS) investigated blood levels of GFAP and NfL (neurofilament light chain) in PwPMS with primary (PP-) or clinically defined secondary progressive MS (SPMS), who were prospectively recruited in eight MS clinics in Germany. 6-months Confirmed Disability Progression (CDP) was defined with using combined outcome parameter of EDSS, timed-25-foot walk test (T25FW) and nine-hole-peg-test (9HPT).

Results:

NfL and GFAP levels were available from 668/809 visits from 243 subjects with a median follow-up of 25.1

months [IQR 13.7 – 38.5]. NfL and GFAP levels were elevated compared to age- and sex-adjusted reference mean (i.e., Z score of 0, $p<0.001$ for both). In participants with sufficient FU to evaluate progression ($n= 338$ visits), 111 (32.8%) events of progression were documented. More than half of the progression events were evident through worsening of T25FW (58/111, 52.3%), followed by 9HPT (40/111, 36.0%), while EDSS progression was evident in 38/111 (34.2%). Particularly elevated GFAP (> 3) and high NfL (> 1.5) Z scores at baseline were associated with 2.9- and 2.6-fold higher risk for CDP in the PPMS participants ($n=101$, HR: 2.88 [1.21 – 6.84], and 2.55 [1.09 – 5.93], $p= 0.016$ and 0.030, respectively). The predictive potential of high GFAP was particularly evident in subjects with concomitant low NfL concentrations (i.e., Z score <= 1.0) (4.31 [1.53 – 12.1], $p = 0.006$). None of the HR for the selected cut-offs was significant in the SPMS population ($n= 68$).

Conclusion:

Blood GFAP levels may provide a tool to identify PwPPMS at high risk of progression in clinical setting, and potential candidates for clinical trials targeting disease progression. Participants with high GFAP and low NfL might constitute a distinct, non-active PPMS population with a particularly high risk for progression.

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