The Correlation of Blood Neurofilament Light Chain with Brain Atrophy is Partly Independent from Inflammation

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Objective:
To assess if the correlation of blood neurofilament light chain (NfL) with brain volume loss (BVL) is independent of inflammatory activity (new/enlarging T2 lesions and relapses).

Background:
Blood NfL has recently been identified as a biomarker of neuroaxonal loss in MS. The aim of this analysis was to understand whether the association of NfL with BVL is mediated by its association with inflammation, or whether NfL levels have an additional independent correlation with BVL.

Design/Methods:
We included 215 patients (placebo:93, fingolimod 0.5 mg:122) enrolled in the FREEDOMS study with relapses, new/enlarging T2 lesions, BVL, and NfL level assessed at Month (M) 24. NfL levels were measured using SIMOA™ technology at M6, M12 and M24. The correlation of M24 NfL levels with BVL after adjusting for inflammatory activity was estimated. The proportion of treatment effect (PTE) on BVL explained by M24 NfL, active T2 lesions and relapses was estimated by a multivariate linear model.

Results: M24 BVL significantly correlated with active T2 lesions ($r=-0.36$, $p<0.001$), relapses ($r=-0.26$, $p<0.001$) and M24 NfL ($r=-0.46$, $p<0.001$). M24 NfL levels correlated with new/enlarging T2 lesions ($r=0.57$, $p<0.001$) and relapses ($r=0.35$, $p<0.001$). The correlation of NfL with BVL after adjusting for treatment, new/enlarging T2 lesions and relapses was $r=-0.30$ ($p<0.001$) indicating an impact of NfL on BVL not mediated by detectable inflammation. The PTE on BVL explained by new/enlarging T2 lesions was 89%, 33% by relapses and 97% by NfL levels.

Conclusions:
Blood NfL has an impact on BVL that is independent from inflammation; the PTE on BVL mediated by NfL was 97%, indicating that NfL outperforms inflammatory markers as a surrogate for BVL. This analysis further supports the role of NfL as a highly informative marker of the neurodegenerative aspects in MS.