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LETTER TO THE EDITOR

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Neurofilament Light Chain as a Potential Serum-Based Biomarker for Monitoring Disease Activity in Neuro-Behçet's Disease

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Dear Editor,

We have read with great interest the article by Zhan et al.(1) on biomarker candidates of neuro-Behçet's disease (NBD), which encompasses the central nervous system (CNS) manifestations of Behçet's disease (BD). Neuro-Behçet's disease may present with parenchymal or vascular involvement of the CNS and may lead to remarkable accumulation of disability in a relatively short period of time (2,3). However, biomarkers monitoring the clinical evolution and disease activity of NBD have been vastly understudied. As indicated by Zhan et al., the vast majority of NBD biomarker candidates (e.g. IL-6, neutrophil, IgA, BAFF etc.) have been described in the cerebrospinal fluid (CSF) (1) and thus are not suitable for longitudinal monitoring of disease activity through serial measurements over time. Neurofilament light chain (NFL) is a neuro-axonal cytoplasmic protein, which is intimately associated with neuronal degeneration, as well as inflammation and cognitive dysfunction in autoimmune disorders of the CNS such as multiple sclerosis (MS) (4). While the biomarker value of serum and/or CSF NFL has been vastly studied in a wide range of neurological disorders (5), as neatly indicated by Zhan et al., there is only a single article on the predictive role of CSF NFL levels in development of somatic and cognitive disability in NBD. In this study, only NBD patients with relatively higher CSF NFL levels (>1000 ng/L) were reported to develop cognitive impairment interfering with daily life activities (6).

Recently, we measured serum NFL levels of healthy controls and NBD patients during remission period, using the Siemens Healthineers Atellica Analyzer (Siemens Healthcare Diagnostics, Tarrytown, NY, USA), as per the manufacturer's instructions (7) and sought for potential correlations between serum NFL levels and somatic/cognitive disability measures of NBD. Twenty-four parenchymal NBD patients fulfilling the diagnostic criteria for BD (8) and 20 age-gender matched healthy controls were enrolled (Table 1). Sera of all patients were obtained during the remission period ≥5 months after the last exacerbation. All patients were under azathioprine or mycophenolate mofetil treatment and none of the patients were under steroid treatment during blood sampling. The number of patients with brainstem, diencephalon and spinal cord lesions on cranial MRI were 23, 15 and 4, respectively. Neuro-Behçet's

Table 1. Comparison of demographic and cognitive features of patients with neuro-Behçet's disease (NBD) and healthy controls (HC)

	NBD (n=24)	HC (n=20)	p value
Age	46.3±9.6	45.1±10.5	0.385
Gender (men)	15	10	0.515
Duration of NBD (years)	11.4±4.9	NA	NA
mRS	1.1±0.9	NA	NA
EDSS score	2.0±1.3	NA	NA
9 HPT (dominant hand, seconds)	18.4±8.0	15.2±2.5	0.034
Timed-25 Foot Walk Test (seconds)	12.4±7.0	8.2±1.3	0.004
MMSE	25.5±3.9	28.1±2.1	0.004
ACE-R, total	77.4±12.6	88.3±7.3	<0.001
ACE-R, attention/orientation	15.8±3.1	17.1±1.1	0.030
ACE-R, memory	16.3±4.5	20.8±3.6	<0.001
ACE-R, fluency	10.8±1.9	12.1±1.8	0.020
ACE-R, language	20.8±4.0	24.1±3.0	0.002
ACE-R, visuospatial	13.8±2.0	15.3±1.0	0.001
WCST, total errors	31.6±23.1	17.5±14.7	0.010
WCST, categories completed	4.7±1.9	5.7±0.7	0.011
WCST, perseverative errors	18.3±15.3	9.9±7.7	0.012
Stroop interference	60.4±22.4	44.9±16.2	0.007
Stroop spontaneous corrections	3.8±3.4	1.3±1.1	0.001
Stroop, errors	4.1±6.0	0.3±0.7	0.004
Serum NFL (pg/ml)	14.1±6.5	5.6±1.6	<0.001

All parametric variables are denoted as mean ± standard deviation; significant p values are denoted with bold characters; mRS: modified Rankin score; EDSS: expanded disability status scale; MMSE: mini-mental state examination; ACE-R: Addenbrooke's cognitive examination revised; 9 HPT: nine hole peg test; WCST: Wisconsin card sorting test; NA: not applicable; NFL: neurofilament light chain.

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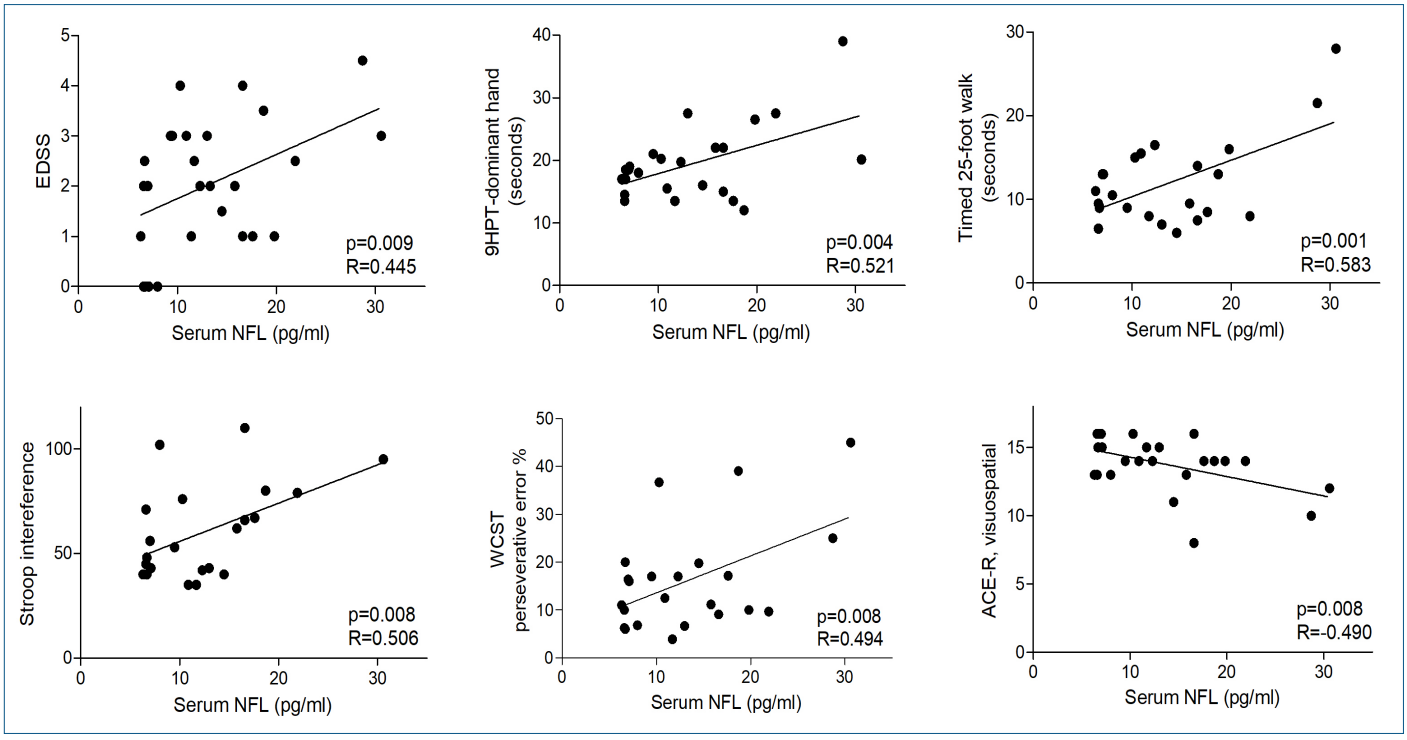

Figure 1. Significant correlations between serum neurofilament light chain (NFL) levels versus somatic and cognitive dysfunction measures of neuro-Behçet's disease patients (EDSS: expanded disability status scale; ACE-R: Addenbrooke's cognitive examination revised; 9HPT: nine hole peg test; WCST: Wisconsin card sorting test).

disease patients with other coexisting disorders and acute infections were excluded. Somatic disability was assessed by modified Rankin score (mRS), expanded disability status scale (EDSS), nine-hole peg test (9 HPT) and timed-25 foot walk test, whereas cognitive disability was assessed with mini-mental state examination (MMSE), Addenbrooke's Cognitive Examination Revised (ACE-R) test, Wisconsin Card Sorting Test (WCST) and Stroop test. The study was approved by the Institutional Review Board and informed consent was received from each participant. Categorical variables were compared among NBD patients and healthy controls by chi-square test, whereas parametric variables were compared by Student`s t- or Mann-Whitney U test, as required. Correlation analysis was done by Spearman`s test due to the uneven distribution of most parametric variables. $p<0.05$ was considered as statistically significant.

Neuro-Behçet's disease patients showed significantly higher serum NFL levels than healthy controls, and significantly impaired scores in all measures of somatic and cognitive functions (Table 1), as reported previously (9–11). Among somatic disability measures, EDSS, 9 HPT and timed-25 foot walk test results were significantly correlated with serum NFL levels (Figure 1), whereas mRS scores did not show significant correlation (p=0.091; R=0.343). Among cognitive disability measures, serum NFL levels significantly correlated with Stroop interference, WCST perseverative error percentage and visuospatial domain of ACE-R (Figure 1). Notably, although NBD patients showed worse scores than healthy controls in MMSE and all domains of ACE-R, no significant correlation was found between serum NFL versus MMSE scores (p=0.527; R=-0.135) and total scores (p=0.332; R=-0.207), attention/orientation (p=0.669; R=-0.091), memory (p=0.271; R=-0.234), fluency (p=0.821; R=-0.048) and language (p=0.975; R=-0.006) domain scores of ACE-R. The Spearman analysis displayed trend-level correlations between serum NFL versus variables of WCST total errors (p=0.062; R=0.395), WCST completed categories (p=0.096; R=-0.355), Stroop spontaneous corrections (p=0.098; R=0.344) and Stroop errors (p=0.060; R=0.406). There was no significant correlation between serum NFL levels and cognitive test scores of healthy controls.

Our results provide additional evidence for the ongoing neuroaxonal degeneration in NBD and indicate that serum NFL correlates with both cognitive and somatic disability in NBD. Furthermore, EDSS and ACE-R scores appear to reflect neuroaxonal degeneration more effectively than mRS and MMSE scores.

Notably, although all ACE-R cognitive domains showed significant deterioration in our cohort, NFL levels only correlated with the visuospatial domain putatively implying that this domain is more effectively afflicted by neuroaxonal degeneration, while non-degenerative processes might be in play in deterioration of other cognitive domains. Stroop test and WCST scores, which also showed significant or trend-level correlation with NFL, mostly reflect executive functions, which are processed by the anterior cingulate and dorsolateral prefrontal cortex (12). Characteristic lesion sites in NBD are brainstem, thalamus, spinal cord and basal ganglia (3). Similar to the parietal cortex involved in processing of visuospatial functions (13), brain regions involved in executive functions do not typically exhibit lesions in cranial MRI of NBD patients. Thus, our results also lend support to the notion that part of the somatic and cognitive disability of BD patients might be emerging through MRI-negative lesion activity occurring in normal-appearing brain regions (14).

Highlights

- **Serum NFL levels are elevated in neuro-Behçet's disease (NBD)**
- **Serum NFL level correlates with cognitive and somatic disability in NBD**
- **Neuroaxonal degeneration might occur in normal appearing brain regions**
- **Serum NFL may serve as a minimally invasive biomarker of NBD activity**

In conclusion, our results suggest that serum NFL is a promising biomarker candidate for disability progression in NBD and, different from previously proposed CSF markers, it is a minimally-invasive marker. Assessment of serum NFL levels in serially obtained sera might provide a more informative profile for the biomarker action of NFL in NBD.

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