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LETTER TO THE EDITOR

Serum neurofilament light chain and small fiber neuropathy: Every cloud has a silver lining

To the Editor,

It was with great interest that we read the study by Baka et al. [1]. These authors explored the significance of serum neurofilament light chain (NfL) as a possible biomarker of small fiber neuropathy (SFN) by testing the sera of 30 patients and comparing the results to those from a cohort of 19 healthy individuals. No difference was found with regard to serum NfL levels in the two groups. Although no correlation was detected with any of the parameters of small fiber impairment, the authors reported an interesting negative correlation between sural sensory nerve action potential (SNAP) and serum NfL in the patient group [1].

We largely concur with the content presented by Baka and colleagues in the discussion. However, we deem it essential to provide a comprehensive perspective by delving into certain aspects that, in our view, have been insufficiently addressed. Additionally, we propose some insights into potential future biomarkers applicable in the context of SNF.

Firstly, employing NfL as a biomarker for peripheral nerve diseases poses greater challenges compared to its application in central nervous system (CNS) diseases. This complexity arises from the fact that the majority of the NfL signal in blood originates from the CNS [2].

Neurofilament proteins play a crucial role in maintaining the structural integrity of neurons and are essential components of the neuronal cytoskeleton. Among these proteins, we list α-internexin, peripherin (PRPH), two splicing variants of neurofilament medium chain (NfM), two splicing variants of neurofilament heavy chain (NfH) and NfL [3].

Studies have revealed the importance of neurofilament proteins as biomarkers for various neurological and non-neurological conditions, generally reflecting neuronal damage and degeneration. Monitoring their levels in biological fluids can provide valuable insights into the progression of neurological diseases [3].

However, in the process of selecting an appropriate biomarker for the peripheral nervous system (PNS), it is imperative to consider their expression patterns. α-internexin exhibits expression primarily in the CNS, while PRPH is predominantly expressed in the PNS. On the other hand, the remaining isoforms, namely, NfH, NfM and NfL, lack specificity for either the PNS or CNS and can be employed as biomarkers in diseases of both systems [3]. Commonly utilized immunoassays at present measure levels of NfL and NfH. Nonetheless, encouraging outcomes emerge from the application of homebrew technology integrated with Simoa [4]. This approach has demonstrated exceptional sensitivity in quantifying PRPH levels in peripheral blood, paving the way for the identification of biomarkers specifically tailored for PNS diseases [4].

Finally, Baka et al. did not consider the body mass index (BMI) of patients and healthy subjects in the NfL analysis. Indeed, BMI represents a possible confounding factor influencing the levels of NfL in the serum and should always be taken into account as a covariate, together with age [5].

We propose therefore that, even if NfL levels may not represent a reliable diagnostic biomarker for SFN, their serum concentrations actually reflect the degree of axonal degeneration as suggested by the negative correlation of sural SNAP with serum NfL, and that PRPH may better perform as a biomarker in this condition.

AUTHOR CONTRIBUTIONS

Domenico Plantone: Conceptualization; formal analysis; writing – original draft; writing – review and editing. **Guido Primiano:** Conceptualization; methodology; writing – review and editing.

CONFLICT OF INTEREST STATEMENT

Both the authors have nothing to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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