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Editorial

Neurofilament light in blood – What more is needed for clinical implementation in multiple sclerosis?

Cerebrospinal fluid (CSF) neurofilament light (NfL) is the best established fluid biomarker for neuroaxonal injury, irrespective of the underlying cause [3]. It has been studied as a disease intensity marker in both relapsing-remitting and progressive multiple sclerosis (MS), and its concentration often normalises in response to successful disease-modifying treatment [5]. Novel ultrasensitive analytical technologies have allowed for the reliable measurement of NfL concentration in blood [4]; virtually all findings for CSF NfL have been replicated in blood, and CSF and blood NfL concentrations show similar dynamics over time in response to acute injury and may thus be used inter-changeably [1].

In the current issue of *EBioMedicine*, Bittner et al. provide additional evidence on the clinical usefulness of serum NfL in a large multicentre cohort of newly diagnosed MS patients [2]. They show that a serum NfL concentration at the time point for the MS diagnosis not only increased the sensitivity of the diagnostic criteria, but also predicted disease course. Furthermore, there were interesting differences between MS patients with high versus low serum NfL concentration at baseline in regards to what drugs they were prescribed and how they responded to the selected treatment. Altogether, these results support the use of blood NfL as a biomarker in MS clinics, but a number of questions of relevance to the diagnostic algorithms and the practical work need to be addressed.

If CSF and blood NfL are so highly correlated and give the same information, is there really a need for CSF analysis in the diagnostic work-up of patients with suspected MS? The answer remains yes. CSF will still be needed to assess the neuroinflammatory component of the disease (CSF cell counts and oligoclonal bands); identifying reliable blood biomarkers for neuroinflammation has not yet been successful. The importance of blood NfL in an MS context may instead be to monitor disease activity and optimise the treatment (both drug selection and dose-finding). To that end, a baseline result will be important.

Could blood NfL replace repeated magnetic resonance imaging following initiation of disease-modifying treatment in MS? This is not yet known and needs to be carefully examined in future clinical studies.

What sample type is preferred (serum or plasma)? Here, most data suggest that serum and EDTA plasma give similar results [6], but for other sample types additional studies are needed. Overall, blood NfL seems to be a stable biomarker for which the pre-analytical sample handling is not that critical.

Are there commercially available blood NfL assays fit for use in clinical laboratory practice? Yes, there are, but most remain research grade according to the label by the manufacturer. The challenge for the clinical laboratories will now be to validate the currently available blood NfL assays for use in clinical laboratory practice. In the absence of certified reference materials and methods for the analyte, it will be important for laboratories to establish their own reference and decision limits in collaboration with the clinicians, and then make sure to maintain longitudinal stability in the measurements by careful lot-to-lot-bridging and an ambitious internal quality control programme. It is also advisable to collect and store multiple aliquots of reference samples that could be used to re-calibrate the assay, if longitudinal stability in the measurements is lost. Once certified reference materials and methods for blood NfL are available (work on this is ongoing in the International Federation of Clinical Chemistry and Laboratory Medicine network, as well as in other international consortia), an in house reference sample collection will be less important.

Gathering all information available on blood NfL across neurological diseases, it looks like we soon may start to use it in clinical neurology, much like hepatologists use liver enzymes and cardiologists use troponins to gauge organ injury in their respective areas of expertise.

Declaration of Competing Interest

HZ has served at scientific advisory boards for Denali, Roche Diagnostics, Wave, Samumed and CogRx, has given lectures in symposia sponsored by Fujirebio, Alzecure and Biogen, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (all outside submitted work).

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