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Is CSF neurofilament light chain measurement relevant for MS?

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MS is a chronic inflammatory demyelinating disease of the CNS in which an autoimmune etiology targeting CNS myelin is implicated. Tremendous efforts to search for biomarkers that potentially reflect the inflammatory process in the CNS have been made, although MRI was the only reliable clinical method for that purpose until recent findings showing the usefulness of the measurement of neurofilaments. Neurofilament release is assumed to be a consequence of axonal damage, with some components appearing in the CSF and then in blood at extremely low concentrations.[1] An ELISA for CSF neurofilament light chain protein (NfL) has shown to give consistent results as a marker for MS disease activity, suggesting it may be useful as a measure of MS treatment response.[1]

NfL levels in the CSF can predict a sustained status of no evidence of disease activity 3, namely, no clinical relapse, brain MRI activity, or progression in the Expanded Disability Status Scale (EDSS).[2] Another study showed that this CSF marker not only identified patients with clinically isolated syndrome who later developed MS[3] but also patients with relapsing-remitting MS (RRMS) who showed progression in the EDSS or converted to secondary progressive MS at 5-year follow-up.[4] It has also been reported that the potent disease-modifying drug (DMD) natalizumab markedly reduced axonal damage when assessed using CSF NfL levels.[5] Furthermore, measurement of CSF NfL levels may serve as an effective tool for monitoring the treatment effects of fingolimod.[6] Therefore, NfL in the CSF has been established as a biomarker for the assessment of prognosis and treatment efficacy in patients with MS. However, it is still unclear whether CSF NfL levels can be used for decision-making regarding MS treatment.

In this issue of *Neurology® Neuroimmunology & Neuroinflammation*, Reyes et al.[7] attempted to address some of the above-mentioned issues. These authors enrolled 203 patients with MS (RRMS 58%, progressive MS 42%), of whom 169 (83%) were not treated with any DMD at the time of enrollment (baseline). Study participants were assessed for disease activity in terms of occurrence of relapse and/or sustained disability progression, MRI findings, and NfL level in the CSF. However, although CSF NfL levels were determined, no specific algorithm for treatment selection according to NfL results was used, and thus, the treatment decision-making process was primarily dependent on clinical and/or MRI findings under the discretion of MS consultants. Thus, the effect of CSF NfL measurements on treatment choice was only modest. The investigators classified final treatment decisions into 2 categories: "no treatment/no escalation," which included patients not started with a DMD (n = 36) or those who remained with their previous DMD (n = 26), and "treatment/escalation," which included treatment-naive patients for whom medication with any DMD was begun (n = 129) and patients whose DMD at study enrollment was changed to a more potent treatment (n = 12). The EDSS was assessed at baseline and at least 1 year after the treatment decision. The relevance of high or low levels of CSF NfL in the decision-making process was retrospectively analyzed by comparing median values obtained among subgroups in the 2 categories. The "no treatment" and "no escalation" subgroups showed low median values (264.5 and 269 pg/mL, respectively), whereas the "escalation" subgroup showed the highest median value (696 pg/mL) and the "treatment" subgroup had the intermediate values (above or below 400 pg/mL). However, the median EDSS score at baseline did not change for at

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least 1 year within the 2 subgroups of each category: 2.5 vs 2.5 in the "no treatment/no escalation" group and 4 vs 4.75 in the "treatment/escalation" group, with the median EDSS score change of 0 in both. These findings suggest that results of NfL measurement in the CSF affected treatment choice, despite guidelines for its use were not available. In addition, those decisions seemed to be successful in 1-year follow-up results. This study demonstrates the potential utility of CSF NfL levels in individual patients with MS as a biomarker for treatment decision-making independent of clinical and MRI findings. Because CSF samples are routinely collected during the initial assessment or as part of the studies used in the differential diagnosis of MS, the availability of CSF for the measurement of NfL does not constitute a limitation.

Readers of this article may wonder about the need of NfL CSF studies considering the fact that determination of NfL levels in blood has been established as a feasible biomarker of MS treatment response, based on findings of a 2-year follow-up study[8] and another study showing its use for the prediction of 10-year MRI disease activity.[9] Thus, it is important to ask why NfL levels in the CSF should also be determined. Although the advantages of blood samples include easy collection and repeatability, blood NfL measurements only show potentially useful information when samples from a large number of patients are considered, the usefulness in individual cases is limited because of the narrow range of results assessed (10–100 pg/mL)[8–10] and a possible contribution of comorbidities affecting the peripheral nervous system.[1] Ethnic differences may also be a concern, although CSF and blood NfL measurements conducted in Japanese patients with MS showed comparable results with those of patients included in studies from western countries.[10]

In summary, measurement of NfL levels in the CSF still has an important role in MS clinics, and the value obtained from a 1-time lumbar puncture may provide guidance for initial treatment. The work by Reyes et al. is an important first step toward a well-designed follow-up study conducted with a large-scale cohort over at least a 5-year period to clarify the relevance of this unique biomarker.

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