CSF neurofilament light
A universal risk biomarker in multiple sclerosis?

Axonal loss from relapses and neurodegeneration is a main element of multiple sclerosis (MS) pathology, so an objective biomarker to detect and quantify it should be of great value. Neurofilaments belong to the intermediate filament family of proteins and are the major components of the cytoskeleton of neurons. They consist of 3 isotypes: a neurofilament light (NFL) chain of 68 kDa, a neurofilament intermediate (NIF) chain of 150 kDa, and a neurofilament heavy (NHF) chain of 190 to 210 kDa.1 During the process of axonal injury, intracellular components, including neurofilaments, are released into the extracellular fluid and subsequently into the CSF. Thus, analysis of neurofilament levels in the CSF may reliably capture the extent of axonal damage and neurodegeneration in the CNS, regardless of the underlying cause.1 Evidence for increased CSF neurofilament levels in MS mainly exists for NFL and NFH, whereas NIF has not been extensively studied so far.1 Several test systems exist to determine NFH and NFL, and a commercially available ELISA to detect NFL is advantageous in discriminating patients with MS from controls.2

Elevated levels of CSF NFL occur in all stages of MS, including the clinically isolated syndrome (CIS), and higher levels have been associated with relapses and MRI-based measures of disease activity.1,3,4 Of note, CSF NFL at the diagnostic lumbar puncture could prognosticate physical disability in patients with MS 11 years later.1 Patients with CSF NFL levels above the median at baseline had a 5-fold increased risk of higher disability scores and a 2-fold increased risk of conversion to secondary progressive MS at follow-up.3 CSF NFL is a reliable marker to capture treatment effect in patients receiving natalizumab,5 mitoxantrone, rituximab,6 or fingolimod.3,7

Along these lines, some studies on CSF NFL investigated whether this marker would be capable of predicting conversion from CIS to MS, but initial positive findings could not be replicated.8,9 It has not been clear whether or not CSF NFL levels determined at the stage of CIS would be associated with disability progression and MRI changes in the long run. In this issue of *Neurology®,* Arrambide et al.10 present a well-designed study using a 2-step approach to determine the prognostic value of CSF biomarkers, including NFL, neurofascin, semaphorin 3A, fetuin A, and glial fibrillary acidic protein in CIS for conversion to MS. In the screening phase, only NFL was increased in 35 patients with CIS who converted to clinically definite MS during a mean follow-up time of 78.8 (SD 33.4) months, compared with 33 CIS nonconverters with mean follow-up time of 57.9 (SD 35.2) months. CSF NFL correlated with changes in brain parenchymal fraction (r = −0.892) and percentage brain volume change (r = −0.842) at 5 years, but did not correlate with disability. In the replication phase, CSF NFL was investigated in a second cohort of 155 patients with CIS obtained from 2 different centers with a mean follow-up time of 3.7 (SD 2.3) years. For every 100-ng/L increase of CSF NFL, the authors observed an increased risk of conversion to clinically definite MS (hazard ratio = 1.009, 95% confidence interval 1.005–1.014) and 2010 McDonald MS (hazard ratio = 1.009, 95% confidence interval 1.005–1.013). The results are encouraging and strengthen the role of CSF NFL as reliable biomarker in MS.

Bringing the results of Arrambide et al.10 into context with previously published studies, the question arises whether CSF NFL can serve as an “omnipotent” body fluid biomarker in order to predict conversion from CIS, prognosticate disability progression,7 and monitor treatment response5,7 in MS. Although in the present investigation CSF NFL levels were predictive for conversion from CIS to MS, the predictive values of oligoclonal bands and number of T2 lesions were higher. However, as concluded by Arrambide et al., CSF NFL levels may be more relevant to predict medium- to long-term brain volume changes. Further research is needed to clarify these issues, to determine which biomarker(s) is best for each outcome measure, and to pinpoint the role of NFL in clinical practice.

Furthermore, assay variations need to be considered when performing ELISAs for NFL measurements. In a recent multicenter study, poor interlaboratory

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From the Department of Neurology (M.K.), Medical University of Graz, Austria; and Department of Neurology (J.S.), Umeå University Hospital, Sweden.

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agreement was attributed to variations in the preparation of protein standards. The following questions also remain unanswered: (1) What is the optimal cutoff level to indicate abnormal CSF NfL concentrations? (2) What is the longitudinal age-related variation of NfL? and (3) What degree of CSF NfL decrease indicates a good treatment response during immunomodulatory or immunosuppressive therapy?

Once answers to these questions have been found, NfL could be included as an outcome measure in clinical trials. The potential value of including body fluid biomarkers in clinical trials has just recently been demonstrated, where insufficient disease inhibition by intrathecal rituximab in progressive MS was indicated by the lack of a reduction of markers for CNS inflammation and neurodegeneration, including NfL, which in the end supported an early termination of the trial. A drawback of using CSF biomarkers as outcome measures is the requirement to perform repeated lumbar punctures. Recently, a sensitive electrochemiluminescence immunoassay has been developed, showing increased serum NfL levels in patients with CIS. These findings are promising but need to be replicated. Because this assay allows determination of NfL in serum, it would certainly facilitate repeated follow-up measurements and make it much easier to incorporate this important biomarker into the toolbox of instruments to monitor disease activity in MS.

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REFERENCES