

From neurofilament research to multiple sclerosis clinical practice

Where do we stand?

Benedetta Bodini, MD,
PhD
Peter Arthur Calabresi,
MD

Correspondence to
Dr. Bodini:
benedetta.bodini@icm-institute.
org

Neurology® 2017;88:1–2

Neuroaxonal degeneration is a major mechanism underlying clinical progression in multiple sclerosis (MS), but it is incompletely controlled by current therapies and remains challenging to monitor.¹ Neurofilaments (Nf), a major component of the axonal cytoskeleton, are released into body fluids (CSF and subsequently serum) when axonal damage occurs,² and therefore have been investigated as promising biomarkers of acute and chronic neuronal damage. In turn, Nf could be an indicator of neuroprotective treatment response in patients with MS.^{3,4} In particular, increased levels of both the light (NfL) and heavy (NfH) subunits in CSF and serum have been found in all stages of MS, with the highest levels reached during clinical and radiologic MRI activity. Previous studies have shown that NfL is associated with acute neuroaxonal damage, while NfH has been correlated with brain volume reduction and clinical disability accrual over time.^{5,6}

In this issue of *Neurology*®, Kuhle et al.⁷ have investigated the effect of riluzole on serum Nf as well as the relationship between clinical and MRI outcomes and serum Nf levels in patients with MS. The study cohort was composed of a group of patients with early relapsing-remitting MS who participated in a randomized double-blind trial comparing riluzole and placebo as an add-on therapy to weekly interferon- β (IFN- β)-1a IM. Twenty-two patients randomized to riluzole and 21 to placebo were followed-up for 24 months with serum Nf samples, MRI scans, and clinical and neuropsychological assessments. NfL and NfH levels were measured by ELISA and electrochemiluminescence immunoassay.

Patients on riluzole showed similar levels of both Nf subunits during the follow-up period compared with those on placebo. However, the lack of significance could be the result of a power issue related to the small sample size, and does not exclude a real effect of riluzole on Nf levels. When the 2 treatment groups were analyzed together, a significant decrease in NfL relative to baseline was detected at 12 months and confirmed at 24 months, which might reflect ongoing neuroaxonal damage. However, as suggested

by the authors, a regression to the mean effect, combined with a potential treatment effect of IFN- β , might also have contributed to the NfL decrease observed over the follow-up. Clarifying the real effect of immunomodulatory therapies on NfL levels would have required the inclusion of a placebo cohort and a healthy control comparator group. In this study, Kuhle et al. further observed that a longitudinal increase in NfL correlated with a worsening in clinical disability and cognitive impairment.

Beyond the analysis of the effect of riluzole on NfL, the main result found by Kuhle et al. was the correlation between higher levels of NfL at baseline and more rapid development of whole brain atrophy quantified on MRI scans.⁷ However, patients showing higher levels of NfL were also more radiologically active at baseline, and developed a greater number of gadolinium-enhancing lesions over the follow-up. The more rapid decline in brain volume observed in this subgroup of patients might therefore partly be the result of a greater pseudoatrophy effect related to anti-inflammatory therapies, either IFN- β or steroid treatments that may have been received during the follow-up.⁸

Overall, this study by Kuhle et al. adds a relevant contribution to the current debate on the use of Nf as biomarkers of neuroaxonal damage in MS clinical practice, but leaves important questions still open. While the decrease in serum NfL detected over the follow-up, as well as the correlation with brain atrophy and clinical scores, support the potential of Nf as a biomarker of disease progression and persistent neuroaxonal damage, a key question arises on the real superiority of this serum measure over MRI-derived metrics in reflecting neuronal-specific pathologic changes.⁹ In particular, the added value of Nf over MRI-derived volume measures sensitive to neuronal damage, such as cortical and deep gray matter volume changes, and more exploratory metrics such as axial diffusivity and MR spectroscopy *N*-acetylaspartate, is yet to be proven. Moreover, unlike MRI-derived metrics, Nf levels do not provide regional localization information, which can be

See page 826

From Sorbonne Universités (B.B.), UPMC Paris 06, Institut du Cerveau et de la Moelle Épineière, ICM, Pitié-Salpêtrière Hospital, Inserm UMR S 1127, CNRS UMR 7225, Paris, France; and Department of Neurology (P.A.C.), Johns Hopkins Hospital, Baltimore, MD.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the editorial.

essential in defining the pathologic course of the disease.

Prospective longitudinal studies including patients with all phenotypes of the disease and healthy controls, directly comparing Nf with MR-derived metrics over time, will be able to establish whether Nf, alone or combined with other imaging biomarkers, can have a place in MS clinical practice and therapeutic trials. Such studies could also inform on the evolution of Nf levels over a long time course, determining the rate and the timeframe in which Nf levels rise and fall in each individual.

Another major issue that needs to be addressed is reproducibility, which remains suboptimal.² This is particularly true for Nf quantified on serum samples, which even more than CSF samples are affected by the lack of reproducibility validation. Suboptimal sensitivity of serum assays is an additional issue that could limit detection of a treatment effect. In this study by Kuhle et al., as in the phase II lamotrigine trial in secondary progressive MS,¹⁰ no difference in reduction of Nf levels was observed between patients on treatment and patients on placebo. However, in the lamotrigine trial, a reduction in NfH was found in patients with adherence to lamotrigine, compared with those with a poor adherence to the treatment. Taken together, the results from these 2 trials do not exclude nor confirm a neuroprotective effect of these drugs on axonal degeneration.

At present, the measure of CNS and serum Nf levels is an interesting candidate to quantify neuroaxonal degeneration in MS, but remains for now a research tool. Further validation steps are essential before considering Nf biomarkers of neuroaxonal degeneration a reliable outcome measure for clinical trials of neuroprotective treatments.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosure forms.

REFERENCES

1. Correale J, Gaitán MI, Ysraelit MC, Fiol MP. Progressive multiple sclerosis: from pathogenic mechanisms to treatment. *Brain* Epub 2016 Oct 29.
2. Teunissen CE, Khalil M. Neurofilaments as biomarkers in multiple sclerosis. *Mult Scler* 2012;18:552–556.
3. Comabella M, Montalban X. Body fluid biomarkers in multiple sclerosis. *Lancet Neurol* 2014;13:113–126.
4. Salzer J. The only certain measure of the effectiveness of multiple sclerosis therapy is cerebrospinal neurofilament level: yes. *Mult Scler* 2015;21:1239–1240.
5. Malmstrom C, Haghighi S, Rosengren L, et al. Neurofilament light protein and glial fibrillary acidic protein as biological markers in MS. *Neurology* 2003; 61:1720–1725.
6. Kuhle J, Leppert D, Petzold A, et al. Neurofilament heavy chain in CSF correlates with relapses and disability in multiple sclerosis. *Neurology* 2011;76:1206–1213.
7. Kuhle J, Nourbakhsh B, Grant D, et al. Serum neurofilament is associated with progression of brain atrophy and disability in early MS. *Neurology* 2017;88:826–831.
8. Vidal-Jordana A, Sastre-Garriga J, Pérez-Miralles J, et al. Brain volume loss during the first year of interferon-beta treatment in multiple sclerosis: baseline inflammation and regional brain volume dynamics. *Neuroimaging* 2016;26: 532–538.
9. Arrambide G, Espejo C, Tintore M. The only certain measure of the effectiveness of multiple sclerosis therapy is cerebrospinal neurofilament level: no. *Mult Scler* 2015; 21:1240–1241.
10. Gnanapavan S, Grant D, Morant S, et al. Biomarker report from the phase II lamotrigine trial in secondary progressive MS: neurofilament as a surrogate of disease progression. *PLoS One* 2013;8:e70019.