Body fluid biomarkers ideally allow for detection (i.e. yes/no?), quantification (i.e. how much?) and characterization (i.e. what cell type?) of pathological processes. In cardiology, elevated levels of troponins together with clinical and electrocardiogram (ECG) data have been used for many years to diagnose acute myocardial infarction.\(^1\) Neurological diseases in general, and multiple sclerosis (MS) in particular, are often characterized by subjective symptoms such as decreased sensibility, paraesthesias, pain or reduced visual acuity. An objective way of measuring tissue damage when presented with such symptoms is much needed. Likewise, quantification of tissue damage and monitoring response to treatment could aid in clinical decisions regarding initiation or escalation of therapy.

Neurofilaments constitute the major components of the axonal cytoskeleton in neurons and consist of three chains (neurofilament light (NFL), intermediate (NIF) and heavy (NFH)).\(^2\) The NFM chain has not been extensively studied in MS, and levels of the NFH chain has been shown to be of less importance compared with NFL in detecting tissue damage in MS.\(^2,3\) This proposal will therefore focus on NFL. The NFL chain is a 68 kDa protein which can be measured in the cerebrospinal fluid (CSF) by use of an ELISA.\(^4\) Increased levels of CSF NFL have been found in several neurological diseases including MS and other inflammatory conditions, vascular diseases and neurodegenerative diseases such as dementias and amyotrophic lateral sclerosis.\(^5\) In relapsing–remitting MS (RRMS), it seems that NFL increases sharply during a relapse, and then decreases gradually over time.\(^4\) Higher levels of NFL in the CSF in early MS (diagnostic lumbar puncture) predicted a higher multiple sclerosis severity score (MSSS) and a shorter time to conversion to secondary-progressive MS after a median of 14 years of follow-up, regardless of whether the lumbar puncture was performed during a relapse or not.\(^6\) After initiation of treatment with natalizumab in RRMS patients, both with and without a recent relapse, the levels of NFL decreased.\(^7\) The same was seen with mitoxantrone and rituximab treatment in patients with progressive MS.\(^8\) NFL levels also correlated with the presence and number of gadolinium enhanced (Gd+) lesions on magnetic resonance imaging (MRI).\(^8,9\) Importantly, in the study of progressive MS, treatment with immunosuppressive drugs reduced the levels of NFL, even in those patients without Gd+ lesions at baseline. This suggests that subclinical tissue damage, not readily detected by MRI, can be prevented by immunosuppressive treatment, and that this process may be monitored by measuring CSF NFL levels.\(^8\) Recently, a promising serum based assay for measuring NFL has been developed, and elevated serum NFL levels have been demonstrated in several neurodegenerative diseases.\(^10\) However, this method has not been studied extensively and needs further confirmation, especially in MS patients. Another advantage of performing a lumbar puncture is that it gives the opportunity to gather ancillary data such as cell counts, presence of oligoclonal bands and/or elevated IgG index and other CSF markers. It also allows for a more thorough work-up for diagnostic purposes, including differentiating against functional conditions by the use of NFL levels.

Based on the currently available evidence, the following conclusions can be drawn:

The levels of NFL in the CSF of patients with MS:

- Reflect on-going axonal damage;\(^2\)
- Increase during a relapse;\(^4\)
- Predict long term outcome;\(^6\)
- Correlate with another established surrogate marker of CNS inflammation, namely Gd+ lesions on MRI;\(^8,9\)
- Decrease during immunomodulatory treatment, both among RRMS and progressive MS patients;\(^7,8\)
- Decrease during immunomodulatory treatment in progressive MS patients without Gd+ lesions on baseline MRI.\(^9\)
I therefore propose that the only certain measure of the effectiveness of MS therapy is the CSF NfL level. Today we have access to a wide range of drugs for the treatment of MS. These drugs differ in efficacy and side effects, and in many instances escalation to a more effective regimen with a higher risk of serious side effects is warranted. We need to carefully select whom to treat aggressively, and serial measurements of the levels of CSF NfL can aid us in that selection process. We should not rest until our MS patients are relapse-free, have no MRI disease activity and normal levels of NfL in their CSF.

Conflict of interest
JS has received research grants from Neuro Sweden, has received lecture honoraria from Biogen Idec, Teva Pharmaceuticals, and Genzyme/Sanofi, and has received support to travel to scientific meetings from Biogen Idec.

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References