*Editorial, Sellebjerg F, Börnsen L, Ammitzbøll C, Nielsen JE, Vinther-Jensen T, Hjermind LE, von Essen M, Ratzer RL, Soelberg Sørensen P, Romme Christensen J. Defining active progressive multiple sclerosis.Mult Scler. 2017 Aug 1:1352458517726592.*

**Fluid biomarkers for disease activity in multiple sclerosis**

Henrik Zetterberg, MD, PhD[1,2,3,4], Charlotte Teunissen, PhD[5]

[1]*Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden*

*2Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden*

[3]*Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London, UK*

[4]*UK Dementia Research Institute, London, UK*

[5]*Neurochemistry Laboratory and Biobank, Department of Clinical Chemistry, Amsterdam Neuroscience, VU University Medical Center Amsterdam the Netherlands*

**Correspondence:**

Henrik Zetterberg

Clinical Neurochemistry Laboratory

Sahlgrenska University Hospital/Mölndal

S-431 80 Mölndal, Sweden

Tel: +46 31 3430025

Fax: +46 31 419289

E-mail: henrik.zetterberg@gu.se

Multiple sclerosis (MS) is an inflammatory and degenerative central nervous system disease. There is accumulating evidence that the inflammatory activity is responsible for nervous tissue degeneration and disability development, especially during the early phases of MS. The rate of inflammation or disease activity is reflected in relapses and lesion formation on magnetic resonance imaging (MRI) and subsequently in residual disability and atrophy development. Experience from two decades of therapeutic interventions in relapsing-remitting (RR) MS shows that immunomodulatory and immunosuppressive drugs reduce disease activity and there seems to be an effect also on the rate of disease progression. Thus, disease-modifying therapies (DMTs) reduce CNS inflammation and change the clinical course and prognosis of MS. Currently, patient assessment for treatment decisions in clinical practice is based almost entirely on clinical and MRI measures. However, to predict disability development, degeneration and therapeutic response, the development of biomarkers that reflect disease activity, meaning inflammatory activity and the intensity of the axonal injury process, is essential.

In the current issue of *Multiple Sclerosis Journal*, Sellebjerg *et al*. publish a paper in which they examine the ability of cerebrospinal fluid (CSF) biomarkers that either reflect neuroaxonal injury (neurofilament light, NfL), demyelination (myelin basic protein, MBP) or immune activation (matrix metalloproteinase 9 [MMP-9] and C-X-C motif chemokine ligand 13 [CXCL13]) to detect disease activity in primary (n=26) and secondary (n=26) progressive MS.[1] The results were compared to those obtained in 24 healthy controls. The authors show that both MS groups had increased concentrations of most biomarkers, and that there was no difference in marker levels between the primary and secondary progressive MS subtypes, suggesting similarities in underlying disease mechanisms, in line with a similar clinical progression rate in these patient groups. Moreover, they showed that increased CSF MMP-9

and CXCL13 identified a subset of patients who would have been defined as inactive by clinical and/or MRI consensus criteria, but showed a significantly higher CSF NfL concentration and IgG-index. On the basis of the data, the authors hypothesise that these CSF biomarkers are more sensitive than clinical and MRI criteria to low-grade disease activity in MS. Including CSF biomarkers in the criteria would thus help identifying patients with such ongoing neurodegenerative and neuroinflammatory disease activity.

Earlier studies have shown that CSF NfL concentration decreases in response to successful treatment, both in relapsing remitting[2] and primary progressive[3] disease. Similar results have been published for CXCL13,[2] whereas CSF MMP-9 and MBP changes in response to DMT remain unknown. A drawback with CSF examination as a read-out to evaluate treatment response, *i.e.*, reduced disease activity, is that it necessitates repeated lumbar punctures, which some patients (and clinicians) find challenging. Recent large-scale studies, however, identified risk factors for post-lumbar puncture complications,[4] and international consensus criteria to optimise the procedure and minimise complication risks have been developed.[5] These standard operating procedures make repeated CSF examination feasible, also in clinical practice. Nevertheless, recent developments in ultrasensitive measurement techniques have made it possible to monitor the levels of some biomarkers for MS disease activity in blood.

A general challenge with blood-based measurements, however, is that the biomarker concentration may reflect release from extra-cerebral sources rather than changes in the brain. In MS, it has proven very hard to detect an inflammatory profile in the blood that reliably reflects the inflammatory process in the brain due to release of the biomarkers from immune cells in the blood;[6] more sensitive assays are unlikely to solve this problem. However, CNS-enriched proteins, such as NfL, may be detected in the blood at very low concentrations. Now,

an ultrasensitive assay for NfL based on Single molecule array technology is available. The assay allows for quantification of NfL down to subfemtomolar concentrations,[7] is 25-fold as sensitive as an earlier electrochemiluminescence-based method for NfL,[8] and provides results that correlate closely with CSF concentrations.[7,8] MS patients have increased serum or plasma concentrations of NfL in active disease and the concentrations are normalised in response to effective treatment.[9,10] These results support the value of serum NfL as a sensitive and clinically meaningful blood biomarker to monitor disease activity and the effects of therapies in MS. In regards to CXCL13 and MMP-9, biomarker release from extra-cerebral sources is likely to surpass any concentration change in plasma of relevance to the brain. However, in clinical practice one could envision that patients with MS may undergo a detailed examination in a specialist centre with thorough clinical, imaging and CSF examinations so that their specific stage or subtype of MS can be diagnosed and the optimal treatment selected. They could then undergo follow-up with repeated blood tests for disease activity (NfL may be the most promising biomarker for this purpose at present) to make sure that the treatment is the right one and that it is dosed until disease activity is no longer detectable. This may open a new era for monitoring treatment efficacy and disease activity in MS.

## Declaration of Conflicting Interests

Dr. Zetterberg is one of the founders of Brain Biomarker Solutions in Gothenburg AB, a GU Ventures-based platform company at the University of Gothenburg, has received travel support from Teva and has served at advisory boards for Roche Diagnostics and Eli Lilly. Dr. Teunissen received grants from the European Commission, the Dutch Research Council (ZonMW), Association of Frontotemporal Dementia/Alzheimer's Drug Discovery Foundation, Alzheimer Netherlands. She participates in advisory boards of Fujirebio and Roche, received non-financial support from research consumables from ADxNeurosciences, performed contract research or received grants from Janssen prevention center, Boehringer, Brainsonline, AxonNeurosciences, EIP farma, Roche and Probiodrug, which are all unrelated to the present work.

**Funding**

The authors received no financial support for the research, authorship, and/or publication of this article.

**References**

**1.** Sellebjerg F, Börnsen L, Ammitzbøll C, et al. Defining active progressive multiple sclerosis. *Mult Scler.* 2017;In press.
**2.** Novakova L, Axelsson M, Khademi M, et al. Cerebrospinal fluid biomarkers as a measure of disease activity and treatment efficacy in relapsing-remitting multiple sclerosis. *J Neurochem.* Apr 2017;141(2):296-304.
**3.** Axelsson M, Malmestrom C, Gunnarsson M, et al. Immunosuppressive therapy reduces axonal damage in progressive multiple sclerosis. *Mult Scler.* Jan 2014;20(1):43-50.
**4.** Duits FH, Martinez-Lage P, Paquet C, et al. Performance and complications of lumbar puncture in memory clinics: Results of the multicenter lumbar puncture feasibility study. *Alzheimers Dement.* Feb 2016;12(2):154-163.
**5.** Engelborghs S, Niemantsverdriet E, Struyfs H, et al. Consensus guidelines for lumbar puncture in patients with neurological diseases. *Alzheimers Dement (Amst).* 2017;8:111-126.
**6.** Teunissen CE, Malekzadeh A, Leurs C, Bridel C, Killestein J. Body fluid biomarkers for multiple sclerosis--the long road to clinical application. *Nat Rev Neurol.* Oct 2015;11(10):585-596.
**7.** Gisslen M, Price RW, Andreasson U, et al. Plasma Concentration of the Neurofilament Light Protein (NFL) is a Biomarker of CNS Injury in HIV Infection: A Cross-Sectional Study. *EBioMedicine.* Jan 2016;3:135-140.
**8.** Kuhle J, Barro C, Andreasson U, et al. Comparison of three analytical platforms for quantification of the neurofilament light chain in blood samples: ELISA, electrochemiluminescence immunoassay and Simoa. *Clin Chem Lab Med.* Apr 12 2016.
**9.** Piehl F, Kockum I, Khademi M, et al. Plasma neurofilament light chain levels in patients with MS switching from injectable therapies to fingolimod. *Mult Scler.* Jun 01 2017:1352458517715132.
**10.** Disanto G, Barro C, Benkert P, et al. Serum Neurofilament light: A biomarker of neuronal damage in multiple sclerosis. *Ann Neurol.* Jun 2017;81(6):857-870.