THE DIAGNOSTIC AND PROGNOSTIC SIGNIFICANCE OF SERUM NEUROFILAMENT LIGHT CHAIN (NFL) LEVELS IN MULTIPLE SCLEROSIS

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https://doi.org/10.5281/zenodo.15611031

Relevance

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system, characterized by relapsing or progressive neurological deficits. Despite advances in imaging and immunological markers, early diagnosis and prognosis prediction remain a clinical challenge. Recently, serum neurofilament light chain (NfL) has emerged as a highly promising biomarker for neuroaxonal damage, reflecting disease activity and progression in MS. As a non-invasive, blood-based marker, NfL offers potential utility in both initial diagnosis and longitudinal monitoring. Multiple sclerosis (MS) is one of the most disabling chronic autoimmune disorders of the central nervous system (CNS), affecting over 2.8 million people globally. Characterized by demyelination, axonal injury, and neurodegeneration, MS leads to cumulative disability, cognitive decline, and impaired quality of life. While magnetic resonance imaging (MRI) remains the gold standard for diagnosis and monitoring, it has limitations in assessing the underlying neuroaxonal damage, particularly in the progressive phases of the disease.

There is an increasing need for minimally invasive, sensitive, and reliable biomarkers that can quantify disease activity, predict future disability, and evaluate therapeutic responses.

Neurofilament light chain (NfL), a cytoskeletal component of neurons released into the cerebrospinal fluid (CSF) and blood following axonal damage, has emerged as a potent candidate biomarker. Unlike conventional markers, serum NfL levels reflect ongoing neurodegeneration in real time and correlate well with radiologic and clinical parameters.

The potential of serum NfL to serve as a dynamic, cost-effective, and scalable tool for diagnosis, monitoring disease progression, and tailoring treatment decisions in MS warrants detailed exploration. Its incorporation into clinical practice could revolutionize personalized care for MS patients and reduce reliance on expensive and less accessible MRI scans.

Objective

To evaluate the role of serum NfL levels in diagnosing multiple sclerosis, assessing disease severity, and predicting clinical outcomes in both relapsing-remitting and progressive MS phenotypes.

The aim of this study is threefold:

1. To determine whether serum NfL levels differ significantly between patients with multiple sclerosis and healthy individuals, thereby validating its diagnostic relevance.

2. To investigate correlations between serum NfL levels and clinical-radiological parameters of disease activity and severity, such as relapse frequency, Expanded Disability Status Scale (EDSS) scores, and MRI lesion burden.

3. To assess the prognostic utility of baseline serum NfL levels in predicting long-term disability progression in both relapsing-remitting MS (RRMS) and progressive MS (PMS) phenotypes.

Materials and Methods

This was a prospective observational study involving 86 patients diagnosed with MS (62 relapsing-remitting, 24 progressive) and 40 healthy controls, aged 18–55 years. Serum NfL levels were quantified using ultra-sensitive Single Molecule Array (Simoa) technology at baseline, during relapse, and in remission phases. Expanded Disability Status Scale (EDSS) scores were used to correlate NfL levels with clinical severity. MRI scans with T1/T2-weighted and FLAIR sequences were assessed for lesion load and brain atrophy. Statistical analyses included Spearman correlation and logistic regression for prognostic value.

Results

Serum NfL concentrations were significantly elevated in MS patients compared to healthy controls ($p<0.001$), with the highest values observed during acute relapses. In relapsing-remitting MS, NfL levels correlated strongly with new gadolinium-enhancing lesions ($r=0.68$) and EDSS progression ($r=0.52$). In progressive MS, persistently elevated NfL levels were associated with accelerated brain atrophy and higher disability scores. Patients with NfL levels above 24 pg/mL at baseline had a 3.5-fold increased risk of reaching EDSS ≥ 4.0 within two years. Our analysis involved 86 MS patients (62 with RRMS, 24 with PMS) and 40 age- and sex-matched healthy controls. Serum NfL levels were measured using ultra-sensitive Simoa (Single Molecule Array) assays.

Key findings include:

- Serum NfL levels were significantly higher in MS patients (mean: 22.4 ± 5.8 pg/mL) compared to controls (mean: 9.1 ± 2.4 pg/mL; $p<0.001$), confirming its diagnostic relevance.
- In RRMS patients, NfL levels peaked during relapses, with an average increase of 35% compared to remission phases.
- Strong correlations were observed between elevated serum NfL levels and:
- New gadolinium-enhancing MRI lesions ($r=0.68$, $p<0.01$),
- Increased T2 lesion volume ($r=0.59$),
- EDSS score progression over 12 months ($r=0.52$).
- In PMS patients, NfL levels remained persistently high and were significantly associated with:
- Brain parenchymal fraction reduction indicating cerebral atrophy,
- Faster EDSS score deterioration (≥1.5 point increase within one year),
- Poor treatment response in those receiving first-line immunomodulatory therapies.
- Notably, patients with baseline NfL >24 pg/mL had a 3.5-fold greater risk of reaching an EDSS score of 4.0 or higher within two years ($p=0.004$, OR=3.54, 95% CI: 1.49–8.33).
- These results underscore that serum NfL levels not only reflect present disease activity but also have predictive value for future disability, especially when interpreted alongside clinical and MRI data.

Conclusion

Serum NfL is a reliable and sensitive biomarker of neuroaxonal injury in multiple sclerosis, with significant diagnostic and prognostic utility. Elevated NfL levels not only reflect current disease activity but also predict long-term disability and radiological progression. Routine integration of NfL testing in clinical practice could enhance early diagnosis, guide treatment escalation, and enable personalized disease monitoring in MS patients. Serum neurofilament light chain (NfL) has emerged as a highly informative and accessible biomarker for the diagnosis and monitoring of multiple sclerosis. Its ability to mirror active neuroaxonal injury provides clinicians with an objective tool to assess real-time disease activity, distinguish relapse from remission, and evaluate response to disease-modifying therapies (DMTs).

Beyond diagnosis, elevated baseline NfL levels serve as an early warning signal of future clinical progression, even in the absence of new MRI lesions, particularly in patients transitioning from relapsing to secondary progressive MS.

The use of serum NfL could help:

a. Identify high-risk patients for early aggressive therapy,
b. Minimize unnecessary treatment escalation in stable individuals,
c. Reduce healthcare costs by decreasing MRI dependence.

In conclusion, integrating NfL measurements into routine clinical workflows could represent a paradigm shift in precision neurology, facilitating individualized care and improving long-term outcomes for patients with MS. Future multicenter studies and standardization of assay platforms will be critical for broad implementation.

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