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Neurofilament Blood Testing in Multiple Sclerosis:

From Measurement to Clinical Decision Making

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system manifesting primarily through clinical relapses. Along with this relapse activity, clinically silent—i.e., asymptomatic or minimally symptomatic—damaging neuroaxonal mechanisms also play a significant role. Accordingly, magnetic resonance imaging (MRI) has traditionally been of great importance in diagnosis and follow-up, as it can help visualize the typical inflammatory lesions in the white matter, sometimes even before the clinical onset of the disease (often as an incidental finding/radiologically isolated syndrome (RIS)). At the same time, however, MRI imaging also has its limitations: repeated MRIs are not always easily available in daily practice, spinal disease may be overlooked without targeted imaging and thus usually complex studies, and standard MRI parameters do not capture all MS-related disease progression. Brain atrophy measurements and BrainAGE (Brain Age Gap Estimate) procedures are technically challenging and often not standardized in routine care. All of this underpins the search for more sensitive and easily accessible biomarkers that reliably reflect the activity and neurological disease activity and progression at an early stage.

In recent years, measuring the neurofilament light chain (NfL) level in cerebrospinal fluid (CSF) and blood has proven particularly promising. NfL is a structural protein of the axonal cytoskeleton from the intermediate filament family. In axonal damage, neurons release NfL—first into the CSF and, to a lesser extent, across the blood–brain barrier into the bloodstream. Elevated NfL levels therefore reflect axonal damage, whether in MS or any other neurological disease.

NfL as a stable and meaningful biomarker

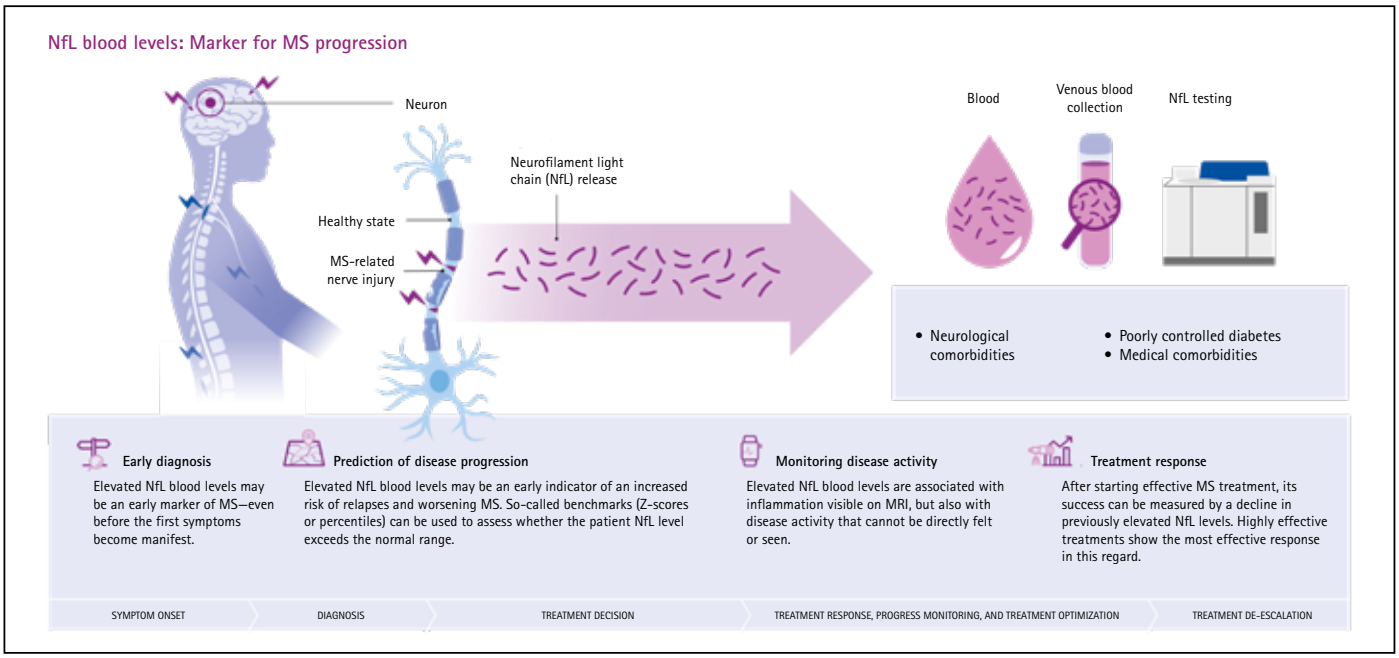
As early as the late 1990s, it was demonstrated that NfL levels in CSF are elevated in active MS. This sparked widespread interest in systematically establishing NfL as a marker of disease activity and studying its significance in different stages of the disease. However, repeated spinal taps burden patients and are not practical in routine practice.

Shortly thereafter, studies demonstrated a strong correlation between CSF and serum levels. This represented a key step toward noninvasive blood testing—ultimately representing a major milestone for a new MS biomarker.

But transitioning the testing from CSF to blood required significantly more sensitive analysis, as NfL serum levels are orders of magnitude lower than in CSF. Traditional antibody-based detection assays (ELISA) were inadequate for this purpose. The initial sensitive electrochemiluminescence techniques were replaced later by ultrasensitive digital immunoassays capable of detecting single molecules in a sandwich format. Subsequently, fully automated high-throughput platforms were developed for routine diagnostics.

NfL is robust in preanalytical terms: the marker remains highly stable at room temperature, over multiple freeze-thaw cycles, and under standardized shipping conditions. Both serum and EDTA plasma are suitable, but may yield different absolute values—which is another reason why consistent use of the same medium is recommended for monitoring the corresponding values.

At the same time, age- and body mass index (BMI)-adjusted reference models with Z-scores and percentiles have been established, significantly improving interpretation compared to raw values. NfL blood levels rise with increasing age and lower BMI, which complicates interpretation of



absolute values. Taken together, these advances in methodology have allowed the transition from diagnostic CSF to blood testing, paving the way for minimally invasive repeat monitoring in routine MS care.

Most NfL assays correlate very well but yield different absolute values. This is partly due to different antibody pairs and lack of a fully harmonized reference cohort for some of the available tests. Follow-up testing should therefore be performed on the same platform and with an identical sample matrix wherever possible, and the test used should always be charted.

Different assays can be compared using conversion models. Regardless, values should always be age- and BMI-adjusted (Z-score or percentile). This standardization improves the assessability of individual values. It should be noted that the underlying reference databases depend on specific assays—unavoidable platform switching therefore calls for extra caution, new baseline determination, and a transition phase with close monitoring. The reference app from the Basel University Medical Center facilitates interpretation and harmonization between the various assays (https://shiny.dkfbasel.ch/baselnfl-reference).

Neurofilament light chain levels in multiple sclerosis

In the future, NfL testing could become a versatile, clinically useful marker throughout the entire MS disease continuum, whereby current testing still relies on group level interpretation. Even in preclinical stages such as RIS, elevated NfL levels are associated with a higher risk of conversion to definite MS and may help redefine patient risk assessment about initiating potential disease-modifying immunotherapy. With the recently revised MS diagnostic criteria—allowing diagnosis even without a clinical episode such as a relapse—the baseline NfL level will also play a role. In case of elevated blood levels, this would indicate acute neuroaxonal injury.

In classic MS diagnosis after an initial demyelinating event, NfL is used more for prognosis and monitoring: High NfL levels often reflect the presence of inflammation-driven axonal injury, correlating with clinical relapse activity, gadolinium-enhancing lesions and new T2 lesions on MRI studies, and the degree of disability in MS. However, this also means that NfL is typically elevated at MS onset. Thus, repeat baseline testing after 3–6 months is recommended. Under immunotherapy, levels usually decline—faster and pronounced with highly effective immunotherapies such as natalizumab and B-cell-depleting modalities such as ocrelizumab, and more moderately with platform therapies. NfL determination can therefore support treatment decisions, for example, treatment escalation in elevated levels despite immunotherapy, or de-escalation when levels remain low and stable over time, particularly in older patients and those with comorbidities requiring treatment modification.

Caution in comorbidities

Various non-MS specific factors can also elevate NfL levels and should thus be considered when assessing NfL blood levels. These include acute and chronic cerebrovascular events, e.g., ischemic stroke and progressive microangiopathy, traumatic brain injury, and encephalopathy of various origins. Neurodegenerative diseases such as dementia syndromes and motor neuron disorders are also associated with axonal injury and can significantly elevate NfL blood levels.

Spinal and peripheral nervous system disorders such as myelopathy of various causes, clinically pertinent spinal canal stenosis, and polyneuropathies may also affect NfL levels. Traumatic nerve lesions and postoperative conditions following neurosurgical and orthopedic procedures may also cause temporary NfL level elevations. This also applies to some systemic factors: Impaired kidney function presumably reduces clearance and is associated with elevated NfL blood levels. Poorly controlled diabetes may also elevate NfL levels via peripheral nerve injury.

In practical terms, unexpected elevations in NfL levels should first be validated analytically and time-wise (same matrix and assay over time, plausible collection time, possibly repeat testing after 3–6 months). If elevated NfL blood levels persist without new comorbidities, imaging is strongly recommended in order to assess the current MS activity. Whether treatment should be intensified in the future in case of persistently elevated NfL blood levels alone is currently a topic of international discussion. Above all, however, this requires broader application in everyday clinical practice and, of course, more appropriate study data providing evidence-based proof that treatment escalation is also associated with a decline in NfL levels. The latter will become increasingly relevant in the future if, despite highly effective immunotherapies, elevated NfL levels continue to be detected in the blood and neuroprotective translational approaches may need to be supplemented.

Outlook

Given that MS is characterized not only by relapse activity but also by insidious neuroinflammatory and neurodegenerative processes resulting in progression independent of relapse in some of those affected, the question arises as to what extent NfL blood levels can reflect or predict this development. More studies are needed to clarify the Z-score and time period at which such risk constellations can be reliably assumed.

Practical conclusions

In recent years, NfL blood testing has progressed from a mere research tool into a promising biomarker for routine MS care. This non-invasive diagnostic allows repeated, minimally invasive monitoring of disease activity and treatment effects, thereby providing important information supplementing MRI and clinical assessment. Possible comorbidities should always be taken into account, and the values should be interpreted as Z-scores adjusted for age and BMI. In the future, NfL testing may not only support treatment decisions, but also contribute to the early identification of patients at risk of progression independent of relapse.

Literature available from the author

NfL: Potential applications in multiple sclerosis

Application scenario	Frequency/Action	Interpretation (Z-score/percentile)	Possible consequence
Baseline in confirmed MS and RIS	Baseline testing in stable condition. Before DMT start, redo baseline.	Patient reference value for future comparisons.	Basis for progress assessment and risk stratification.
Monitoring under DMT without clinical/MRI dynamics	Regularly every 3–6 months.	Decline to normal range, ideally < 80. Percentile → good response. Persistently elevated → inadequate response to DMT	Intensify treatment and/or monitoring, e.g., early MRI.
Acute relapse or suspected relapse symptoms	Repeat testing. Note the kinetics.	Delayed elevation, peak after approx. 2–3 weeks, slow decline. Not every relapse is associated with high NfL levels.	Differentiate between progression and pseudoprogression; schedule follow-up visit.
Therapy decision over the course of treatment (escalation/ de-escalation)	Monitoring every 3–6 months	Low/stable → maintain. Rising/ persistently high → warning signal.	Intensify at high activity. De-escalate only if levels remain low and clinical/MRI findings are stable.
Planned break from treatment	Before discontinuation and then every 3–6 months.	Normal range (< 80th percentile) and stable → break is more acceptable.	Break with close NfL monitoring. Re-evaluation and possibly resumption in case of elevation.
Suspected PIRA	Integrate into routine monitoring.	Elevation may indicate progression independent of relapse activity (PIRA).	Possible adjustment of treatment.

Abbreviations: DMT, disease-modifying therapy; Gd+, gadolinium-enhancing (contrast-enhancing) lesion(s) on MRI; MS, multiple sclerosis; MRI, magnetic resonance imaging; NfL, neurofilament light chain; PIRA, progression independent of relapse activity; Z-score, standardized score relative to age/ BMI-adjusted reference

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