*SVOA Neurology*

ISSN: 2753-9180

ScienceVolks Open Access

Literature Review

# Role of Neurofilament Light Chain as A Biomarker in Neurological Disorders: A Literature Review

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DOI: https://doi.org/10.58624/SVOANE.2023.04.099

***Received:** June 15, 2023* ***Published:** July 10, 2023*

## Abstract

Neurofilament light chain (NfL) is a main element of neurons' structure which is exclusively confined to the neuroaxonal compartment, NfL therefore provides an advantage over other potential biomarkers since it's highly selective for neuronal cell injury and eventual neuronal cell death. Independent of etiology, NfL levels in CSF and blood increase above normal in response to neuronal damage and neurodegeneration, making it a suitable candidate as a biomarker in these circumstances. Biomarkers of neuronal injury and neurodegeneration have the potential to enhance diagnostic accuracy, disease monitoring, and prognosis.

***Keywords:** Neurofilament, NFL, biomarker, CSF, blood, Neurodegeneration, Neuronal injury.*

## Introduction

A biomarker is defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic or pathogenic processes, or pharmacological responses to a therapeutic intervention(1)."

The ideal biomarker should have the following characteristics(2): being reliable, precise, and can differentiate healthy controls from the patients, involved in the pathogenesis, and correlates with the disease activity and the degree of disability. Has high sensitivity and specificity, and is easily studied in a body fluid that is practical to obtain.

Neurofilaments (Nfs) are major structural elements of neurons that are exclusively confined to the neuroaxonal compartment (3, 4), so they are highly specific for neuronal cell damage and eventual neuronal cell death, offering an edge over other possible biomarkers(5). Nfs are heteropolymers compo sed of four subunits (fig.10): the triplet of the Nf light (NfL), medium (NfM), and heavy (NfH) chain, and either α-internexin in the central or peripherin in the peripheral nervous system(6, 7).

The precise functions of neurofilaments remain unknown, yet it is believed that they are essential for axon radial growth and stability, allowing for efficient, high-velocity conduction(8, 9).

Under normal conditions, Nfs are highly stable within axons and have a low turnover rate (7). They may leak from damaged neurons into the extracellular space, eventually reaching the CSF and blood, making it a specific marker capturing ongoing neuroaxonal degeneration and a sensitive biomarker of disease activity (10, 11).

## Main Text

### *NfL in ischemic stroke*

Ischemic stroke causes neuroaxonal damage following cerebral artery occlusion; therefore, sNfL may be a promising biomarker for predicting stroke severity and outcome (12). Multiple studies have reported that NfL level is associated with the severity of symptoms, and infarct size, and could predict the prognosis of acute ischemic stroke (13-16).

### *NfL in Amyotrophic Lateral Sclerosis*

Many studies have reported elevated serum and CSF levels of NfL in patients with ALS, and that it correlated with the disease severity and progression (17-20), but it may not be sufficient to distinguish ALS from other central nervous system diseases or peripheral neuropathy(21). Furthermore, increased sNfL levels were observed as early as 1 to 3.5 years before the development of symptoms (22).

The degree of upper motor neuron and lower motor neuron involvement in ALS is also correlated with CSF NfL levels (23).

### *NfL in Mild Cognitive Impairment and Alzheimer's Disease*

Mattsson and colleagues reported that Plasma NfL is significantly higher in patients with mild cognitive impairment and patients with Alzheimer's disease compared with healthy controls (24), a finding that was confirmed by other studies (25, 26). Higher levels of NfL in CSF were observed in Frontotemporal dementia when compared with other frequent causes of dementia such as Alzheimer's dementia, and dementia with Lewy bodies (27, 28).

### *NfL in Movement Disorders*

In Parkinsonian disorders, NfL levels were elevated only in patients with atypical parkinsonism (multiple system atrophy, progressive supranuclear palsy, and cortico-basal degeneration) while it was similar to healthy controls in patients with Parkinson's disease, which can be useful in early differentiation between those conditions (28, 29).

NfL levels were about three-fold higher in patients with Huntington's disease than in healthy controls (30). Increased CSF and plasma NfL appeared in young adult carriers of the Huntington's disease gene mutation about 24 years before the clinical onset of symptoms (31).

### *NfL in Traumatic Brain Injury*

Studies were conducted to assess the role of sNfL in its diagnosis with non-conclusive findings but showed promise as a prognostic factor for detecting complications, neuroimaging findings, and recovery (32).

### *NfL in Multiple Sclerosis*

Multiple studies have demonstrated the presence of neurofilaments, particularly NfL, in the CSF of MS patients and that it correlated with disability and disease activity(5, 33-37).

Treatment with any disease-modifying therapy in MS was found to be associated with significantly lower sNfL levels compared to untreated patients (38, 39), these findings confirm that CSF or serum/plasma NfL is a therapeutic response biomarker in MS. Higher levels of sNfL at baseline were associated with greater atrophy of the whole brain, gray matter, and deep gray matter nuclei in the long term(40).

sNfL has been established in recent years as a biomarker to quantify acute disease activity, monitor therapy response, and predict the course of disability (38, 41-45). sNfL was even found to be elevated in the presymptomatic phase before disease onset(46).

### *NfL in Prion Diseases*

Both sporadic and hereditary forms of Creutzfeldt-Jakob disease had much greater levels of CSF and blood NfL (approximately a 4-fold increase) than healthy individuals, which can appear as early as 2 years before clinical symptoms in the hereditary form(47-49).

## Conclusions

Even though Nfs are not disease-specific, they may have limited utility in differential diagnosis in some cases. They are showing great potential as a very useful quantifying tool in several neurological diseases with MS being at the top. They have the advantage of being non-invasive and they correlate directly with the degree of neuroaxonal damage. A few drawbacks need to be addressed including the absence of a normative database and a cut-off value for different diseases, and the more accurate detection technique (single molecule array) is relatively expensive.

## List of abbreviations

NfL: Neurofilament light chain; Nfs: Neurofilaments; MS: Multiple Sclerosis; ALS: Amyotrophic Lateral Sclerosis

## Acknowledgments

None

## Authors' contributions

MA and MN developed the idea, carried out the data gathering, prepared, and revised the final manuscript. IY, EH, and MMA revised the manuscript critically. All authors read and approved the final manuscript.

## Funding

None.

## Availability of data and materials

All data generated or analyzed during this study are included in this published article.

## Declarations

Ethics approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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**Citation:** Abd-ElHady ME, Yassine I, Hashish EA, Anani MM, Negm MI. Role of Neurofilament Light Chain as A Biomarker in Neurological Disorders: A Literature Review. *SVOA Neurology* 2023, 4:4, 98-102.