Neurofilament light chain

Neurofilament light chain (NfL) is a protein that is part of the neurofilament structure, which provides structural support to neurons in the central nervous system (CNS). Neurofilaments are a type of intermediate filament found in the cytoplasm of neurons, and they play a crucial role in maintaining neuronal integrity and axonal transport.

NfL is released into the cerebrospinal fluid (CSF) and bloodstream when neurons are damaged or degenerate. Therefore, elevated levels of NfL in CSF and blood are considered indicative of neuronal injury or damage. Because of this, NfL has gained significant attention as a potential biomarker for various neurological conditions, particularly those involving neurodegeneration, axonal injury, and central nervous system disorders.

NfL has been studied about a range of conditions, including:

Neurodegenerative Diseases: Elevated NfL levels have been observed in conditions such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), and frontotemporal dementia. Monitoring NfL levels can help track disease progression and response to treatments.

Traumatic Brain Injury (TBI): Following head trauma, NfL levels in blood and CSF can increase due to axonal damage and neuronal injury. Measuring NfL may aid in assessing the severity of the injury and monitoring recovery.

Multiple Sclerosis (MS): NfL levels can be used as a marker of axonal damage in MS patients. Higher NfL levels are associated with more active disease and worse prognosis.

ALS (Amyotrophic Lateral Sclerosis): NfL levels are often elevated in ALS patients and can correlate with disease progression and prognosis.

Huntington's Disease: Elevated NfL levels have been found in individuals with Huntington's disease and are associated with disease severity and neurodegeneration.

Neuromyelitis Optica (NMO): NfL levels can be used to monitor disease activity and treatment response in patients with NMO, an autoimmune disorder that primarily affects the optic nerves and spinal cord.

Cerebral Small Vessel Disease: NfL has been studied as a potential biomarker for white matter damage caused by cerebral small vessel disease.

The measurement of NfL levels has become more feasible with advancements in technology, particularly highly sensitive immunoassays. This has enabled researchers and clinicians to more accurately detect and quantify NfL in blood and CSF samples. The use of NfL as a biomarker is still an area of active research, and its potential clinical applications continue to expand as our understanding of its significance in various neurological conditions grows.

Neurofilaments (NF) are the 10 nanometer or intermediate filaments found in neurons. They are a major component of the neuronal cytoskeleton, and are believed to function primarily to provide structural support for the axon and to regulate axon diameter. Neurofilaments are composed of

polypeptide chains or subunits which belong to the same protein family as the intermediate filaments of other tissues such as keratin subunits, which make 10 nm filaments expressed specifically in epithelia. The family of proteins making intermediate filaments is divided into 5 major classes, the keratins forming the classes I and II. Class III contains the proteins vimentin, desmin, peripherin and glial fibrillary acidic protein (GFAP). The major neurofilament subunits occupy the class IV family of intermediate filaments, along with two other filament proteins of neurons, alpha-internexin and nestin.

The class IV intermediate filament genes all share two unique introns not found in other intermediate filament gene sequences, suggesting a common evolutionary origin from one primitive class IV gene. Finally, class V corresponds to intermediate filaments of the nuclear cytoskeleton, the nuclear lamins. The term neurofibril refers to a bundle of neurofilaments.

Neurofilaments as biomarkers

The quantification of neurofilament light chain (NfL) in blood and cerebrospinal fluid (CSF) has proved useful in many contexts, for the diagnosis and prognosis of various neurological disorders. There is, however, a diversity of practices between centers, essentially linked to the context of use (COU), analytical methods, consideration of comorbidities, determination of cut-points, or use of interpretation scales. Finally, for the same biochemical profile, the interpretation and reporting of results may differ from one center to another, raising the question of test commutability. To date, no consensus has been reached between the different laboratories involved to define the most appropriate conclusions/comments based on COU and cut points. This work is an essential step towards consensual harmonizing the clinical use of NfL after CSF and/or blood analysis in various neurological contexts, as advocated by the Alzheimer's Association “Biofluid Based Biomarkers PIA” working group.

Method: This international project involves 58 clinical laboratories in 16 countries specializing in the biochemical diagnosis of neurological disorders. We obtained a description of the COU, pre-analytical, and analytical (biological fluid and method used to quantify NfL) protocols of all the centers involved through a questionnaire.

Results: Of the centers, 42% quantified NfL in CSF, 29% in serum 28% in plasma, and 1% in dried blood spots. The COUs were as follows: Frontotemporal dementia (FTD, 17%), Alzheimer's disease (AD, 16%), multiple sclerosis (MS, 16%), amyotrophic lateral sclerosis (ALS, 11%), psychiatric syndrome (PS, 10%), Creutzfeldt-Jakob disease (CJD, 8%), Parkinson's disease (PD, 8%), peripheral neuropathy (PN, 7%) and traumatic brain injury (TBI, 7%). Most centers define pathological cut-points based on published literature and take age into account (50%).

The initial results highlight the state of the art regarding the clinical use of NfL analysis in CSF and blood in the context of different neurological diseases. They have now defined a coordinator for each COU subgroup and are organizing consensus meetings to harmonize the use and reporting of NfL measurements for the identified clinical applications. The results of these next steps will be presented [1)].

Neurofilament (NFL) has shown to be a promising biomarker of neuroaxonal injury in various neurological disorders but has not been investigated in Acute bacterial meningitis (ABM).

Grønhøj et al. aimed to obtain a temporal profile of NFL, neuron-specific enolase (NSE), and S100B in serum during ABM, and (ii) to evaluate their use as biomarkers of severity (Glasgow coma score) and prognosis (Glasgow Outcome Score, GOS and death) in severe ABM.

Fifteen adults with severe community-acquired ABM who were admitted to the intensive care unit (ICU) and fulfilled the inclusion criteria were included. Lumbar puncture and blood tests were performed on admission, and blood tests were performed three times daily during the ICU stay. GOS was obtained on day 30.

Serum NFL was significantly elevated in ABM patients compared to healthy controls, both at admission and throughout the observation period ($p < .01$). NFL increased significantly from day 1 up to day 3-6 ($p < .0001$), peaking day 6. NSE increased significantly from admission up to day 3 ($p < .01$). At day 5-6, the serum values were not significantly different from values at admission. The highest median serum value of S100B was observed at admission (0.10 µg/L, IQR 0.06-0.14), significantly decreasing day 4-6 ($p < .05$). None of the investigated biomarkers revealed significant correlation with severity and prognosis.

This study represents the first clinical observation of the temporal profile of NFL in serum, in severe ABM. No correlation with severity or prognosis [2].

Interest in neurofilaments has risen sharply in recent years with recognition of their potential as biomarkers of brain injury or neurodegeneration in CSF and blood. This is in the context of a growing appreciation for the complexity of the neurobiology of neurofilaments, new recognition of specialized roles for neurofilaments in synapses and a developing understanding of mechanisms responsible for their turnover.

Gafson et al. reviewed the neurobiology of neurofilament proteins, describing current understanding of their structure and function, including recently discovered evidence for their roles in synapses.

They explored the emerging understanding of the mechanisms of neurofilament degradation and clearance and review new methods for future elucidation of the kinetics of their turnover in humans. Primary roles of neurofilaments in the pathogenesis of human diseases will be described. With this background, they then will review critically evidence supporting use of neurofilament concentration measures as biomarkers of neuronal injury or degeneration. Finally, they will reflect on major challenges for studies of the neurobiology of intermediate filaments with specific attention to identifying what needs to be learned for more precise use and confident interpretation of neurofilament measures as biomarkers of neurodegeneration [3].

Khalil et al. in 2018 reviewed what is known about the structure and function of neurofilaments, discuss analytical aspects and knowledge of age-dependent normal ranges of neurofilaments and provide a comprehensive overview of studies on neurofilament light chain as a marker of axonal injury in different neurological disorders, including multiple sclerosis, neurodegenerative dementia, stroke, traumatic brain injury, amyotrophic lateral sclerosis and Parkinson's disease. They also consider work needed to explore the value of this axonal damage marker in managing neurological diseases in daily practice [4].

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