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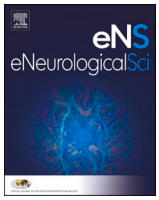

Review article

The role of Neurofilament light (NfL) and glial fibrillary acidic protein (GFAP) in MS and AQP4-NMOSD: Advancing clinical applications.

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ABSTRACT

Fluid biomarkers such as Glial Fibrillary Acidic Protein (GFAP) and Neurofilament Light (NfL) play important roles in the diagnosis, monitoring, and evaluation of therapeutic responses in conditions such as Multiple Sclerosis (MS) and Aquaporin-4 Neuromyelitis Optica Spectrum Disorder (AQP4-NMOSD). These biomarkers offer key insights into the underlying pathophysiological mechanisms of these diseases, enabling effective follow-up and personalized treatment approaches, which are essential for improving patient outcomes. Herein, we synthesize the structural attributes, functional roles, and clinical significance of GFAP and NfL in the context of MS and AQP4-NMOSD. We explore the critical implications of these biomarkers in disease manifestation and progression, emphasizing the necessity to develop standardized methodologies and multicentric studies to confirm their clinical applicability.

1. Introduction

Fluid biomarkers are integral to the management of neurological disorders [1,2], serving as indicators of diagnosis, prognostication, and therapeutic monitoring [3]. These molecular markers are particularly valuable in conditions such as Multiple Sclerosis (MS) and Aquaporin-4 Neuromyelitis Optica Spectrum Disorder (AQP4-NMOSD) [4].

MS is a complex, chronic inflammatory and degenerative demyelinating disease of the central nervous system (CNS), influenced by both genetic and environmental factors. It manifests with symptoms that vary based on the location of lesions and is a major cause of neurological disability among young adults [5]. The diagnosis of MS has evolved with newer criteria, combining clinical evaluations with advanced magnetic resonance imaging (MRI) techniques and other supportive diagnostic tools. Despite these advances, there remains a pressing need for reliable and accessible biomarkers that accurately reflect disease severity, progression, and treatment response [6]. A suitable blood biomarker for MS should correlate with clinical severity, disease activity, increasing disability, and treatment efficacy, which would significantly enhance clinical management and therapeutic strategies [7,8].

Similarly, AQP4-NMOSD is an autoimmune inflammatory disorder targeting astrocytes, primarily characterized by the presence of Aquaporin-4 antibodies that lead to astrocytic damage and subsequent neuroaxonal deterioration [9]. AQP4-NMOSD presents unique diagnostic and prognostic challenges. Although anti-Aquaporin-4 antibodies serve as a critical diagnostic biomarker for AQP4-NMOSD, their ability to reflect ongoing disease activity and predict outcomes is limited [10,11]. This limitation underscores a significant deficiency in the current approach and emphasizes the urgent need to develop and incorporate more effective biomarkers to better manage the complexities of AQP4-NMOSD.

In the context of MS and AQP4-NMOSD, two proteins, glial fibrillary acidic protein (GFAP) and neurofilament light chain (NfL) have been identified as key biomarkers [12,13]. GFAP is a marker of astrocytic damage and is particularly useful in AQP4-NMOSD, a condition marked by severe astrocyte involvement due to autoimmunity against AQP4 water channels on astrocytes [9]. Elevated levels of GFAP in AQP4-NMOSD indicate a high degree of astrocytic destruction and gliosis,

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which are hallmarks of the acute phase of the disease. Conversely, NfL is indicative of neuronal and axonal damage and is valuable in both MS and AQP4-NMOSD [14]. Increases in NfL levels in the cerebrospinal fluid (CSF), or blood, correlate with disease activity and progression. High NfL levels during relapses or in the progressive stages of these diseases signal active neurodegeneration, helping clinicians adjust therapeutic interventions accordingly [15–18]. This review explores the structural characteristics and clinical applications of the biomarkers GFAP and NfL in MS and AQP4-NMOSD.

2. Structure

2.1. Neurofilament light chain protein (NfL)

Intermediate filaments (IFs) are essential components of the cellular cytoskeleton, characterized by their intermediate diameter (~10 nm) compared to microfilaments (actin filaments, ~7 nm) and microtubules (~25 nm). They belong to a large and diverse family of over 70 human proteins, divided into six major classes: Class I and II keratins in epithelial cells; Class III proteins, including vimentin, peripherin, desmin, and GFAP, found in mesenchymal and glial cells; Class IV neurofilaments such as NfL, Neurofilament Medium (NfM), and Neurofilament Heavy (NfH), predominantly expressed in neurons; Class V nuclear lamins, which form a meshwork beneath the inner nuclear membrane; and Class VI proteins like nestin [19].

Neurofilaments, a type of intermediate filament, consist of five primary isoforms: NfL, NfM, NfH, α-internexin, and peripherin. These proteins are crucial as they form obligate heteropolymers essential for neuronal structure and function. Mutations in neurofilament genes have been linked to various neurological disorders, such as Amyotrophic Lateral Sclerosis (ALS), Charcot-Marie-Tooth disease, and spinal muscular atrophy [20].

NfL, also known as neurofilament light polypeptide (abbreviated as NF-L or NFL), has a structure defined by several key domains. The N-terminal or head domain regulates filament assembly and diameter and includes phosphorylation sites that modulate interactions with other cytoskeletal components. The rod domain, composed of coiled-coil alpha-helices, facilitates dimerization and further polymerization into stable filaments. The staggered arrangement of this domain within filaments is crucial for their flexibility and strength. The C-terminal, or tail, domain is involved in cross-bridging with other neurofilaments and, interacting with other proteins, plays a vital role in the dynamics of the neuronal cytoskeleton [20,21].

In terms of functional role and assembly, NfL partners with other neurofilament subunits—NfM, NfH, and α-internexin—to form heteropolymers. These heteropolymers assemble into 10 nm neurofilaments that are integral for maintaining neuronal shape and internal organization. Neurofilaments are particularly abundant in large-caliber axons, where they are essential for maintaining axonal diameter, which in turn influences nerve conduction velocity. This structural and functional setup underscores the critical role of NfL in neuron architecture and function [20,22].

The primary structure of NfL is a linear sequence of amino acids with a high concentration of acidic and basic residues, vital for its functional roles. Its secondary structure primarily features alpha-helices within the central rod domain, crucial for forming coiled-coil dimers with other neurofilament subunits. The tertiary structure consists of these alpha helices coiling into a more compact form, facilitating the formation of stable, elongated dimers that enhance filament integrity. At the quaternary level, NfL interacts with other neurofilament proteins (NfM, NfH, and α-internexin), forming heteropolymeric filaments that are essential to maintaining the structural integrity and functionality of neurons, particularly influencing axon diameter and nerve impulse conductivity [23].

These neurofilament proteins undergo various post-translational modifications such as phosphorylation, which is the most extensive and affects neurofilament spacing and axonal transport. Hyperphosphorylation of neurofilament proteins can lead to the formation of pathological aggregates, a feature common in diseases such as Alzheimer's disease (AD), and ALS. These aggregates, further stabilized by amyloidogenic elements, become remarkably resistant to decay. Other modifications include citrullination, glycosylation, and glycation, each playing roles in neurodegeneration and autoimmune pathology [24].

2.2. Glial fibrillary acidic protein (GFAP)

GFAP, the signature intermediate filament of astrocytes, plays a crucial role within the CNS. As a type-III intermediate filament, it is part of a class that also includes vimentin, desmin, and peripherin, all essential to the structure and function of the cell's cytoskeleton. GFAP, encoded by gene on chromosome 17q21, consists of 432 amino acids. While this class is primarily associated with cells of mesenchymal origin, GFAP is specifically expressed in astrocytes within the CNS. It is prominently expressed in mature astrocytes located in various regions such as the gray and white matter, cerebellum, subventricular and subgranular zones, and Müller cells in the retina. Beyond the CNS, GFAP is also expressed in peripheral locations, including hepatic stellate cells, enteric glial cells, and other non-neural cells, underscoring its widespread relevance in both central and peripheral cellular structures [25–27].

The structure of GFAP, a type III intermediate filament, comprises three key domains: head, rod, and tail. The central rod domain is crucial, as it coils around another filament, aligning the N-terminal and C-terminal ends in parallel to form a dimer. GFAP can form both homodimers and heterodimers with other type III proteins but does not interact with type I and II keratins, leading to separate intermediate filament networks in cells expressing both types. These filaments begin as GFAP dimers that link to create staggered tetramers, the basic building blocks of the filament. Filament formation relies on both the rod domain and the non-helical head and tail domains, which provide structural variability and essential sites for assembly, including two conserved arginines and an aromatic residue in the head domain required for proper filament assembly [28].

The primary structure of GFAP includes a sequence of amino acids featuring specific motifs typical of intermediate filament proteins, such as stutter interruptions which are crucial for the protein's assembly and alignment [29]. The secondary structure is dominated by alpha-helical regions within its rod domain, essential for forming coiled-coil dimer interactions. The tertiary structure of GFAP involves these helical rod domains flanked by non-helical head and tail domains, allowing both parallel and antiparallel alignments crucial for overall filament architecture. At the quaternary level, GFAP can form both homopolymeric filaments from GFAP alone and heteropolymeric filaments with other type III intermediate filaments like vimentin. This dimer and tetramer formation flexibility is key to GFAP's role in maintaining cellular architecture and mechanical stability, especially within astrocytes [30].

3. Function

3.1. Neurofilament light chain protein (NfL)

NfL's primary function is to support the structural framework of the neuron by integrating into the neurofilament network. This network is essential for maintaining the axon's diameter, which directly influences the speed and efficiency of nerve signal conduction. NfL also has a significant role in axonal transport, which involves the bidirectional movement of molecular cargos such as nutrients, organelles, and signaling molecules between the neuronal soma and synaptic terminals. This function is critical for neuronal survival and functionality [31,32].

In terms of clinical significance, elevated levels of NfL in the CSF and blood are associated with neurodegeneration, making it a valuable biomarker for various neurological diseases such as MS, AD, and ALS. The increase in NfL levels typically reflects the extent of neuronal

damage and can be used to monitor disease progression and response to therapy [33].

Furthermore, the stoichiometry of neurofilament proteins shifts in disease states, typically showing an increase in NfL relative to decreases in NfM and NfH. This alteration may represent an adaptive mechanism to conserve energy in neurons during progressive neurodegeneration, explaining why NfL is particularly promising as a biomarker. The release of stable, pathology-specific NfL cleavage products into body fluids enhances its effectiveness as a clinical biomarker, improving the sensitivity of measurements due to its abundance [23].

Neurofilament proteins and their cleavage products are released from neurons in response to axonal damage, with *in vitro* studies confirming a direct correlation between the number of degenerating neurons and neurofilament levels [34]. These proteins have been detected in CSF, blood, amniotic fluid, and ocular fluids, providing vital tools for the diagnosis and monitoring of neurological conditions [35]. The kinetics of NfL, governed by both release from injured neural tissue and clearance from the blood, exhibit an extended peak time and a decay rate that mirrors ongoing pathology, making NfL a valuable indicator of disease state and progression [20,36].

Advancements in detection technologies, such as the ultra-sensitive Single Molecule Array (SIMOA) technique, have significantly improved the ability to measure NfL levels in blood, offering over 25 times higher sensitivity compared to traditional assays like enzyme-linked immunosorbent assay (ELISA) and electrochemiluminescence (ECL). NfL's inherent stability further enhances the robustness of these detection methods [37,38].

3.2. Glial fibrillary acidic protein (GFAP)

GFAP provides mechanical strength and structural support to astrocytes, forming the main component of the intermediate filament network within these cells. This network is critical for maintaining the shape and mechanical integrity of astrocytes, particularly during the CNS development and repair processes. GFAP expression significantly increases in response to CNS injuries and diseases, a phenomenon known as reactive gliosis. During this process, astrocytes proliferate and become hypertrophic, with GFAP playing a significant role in the formation of a glial scar. This scar is essential for containing wounds and preventing further damage to CNS tissue [39].

GFAP influences synaptic function by modulating the ability of the astrocyte to regulate neurotransmitter levels within the synaptic cleft. Through its involvement in the intermediate filament network, GFAP indirectly contributes to the uptake and release of neurotransmitters, thus affecting neuronal excitability and synaptic plasticity [40].

With elevated levels in the CSF or blood indicating astrocytic damage, GFAP is a valuable biomarker for CNS disorders. Conditions such as traumatic brain injury, stroke, and neurodegenerative diseases show increased GFAP levels, which can be crucial for assessing the extent of glial injury and neuroinflammation, thus providing valuable insights into disease severity and progression [41].

Indeed, the role of GFAP extends to various diagnostic applications, where sensitive detection methods like ELISA, ECL, and fluorescence-based assays are used to measure its levels in body fluids such as CSF, vitreous fluid, and amniotic fluid. The development of SIMOA has enabled the detection of GFAP even in the blood of healthy individuals and those with neurological diseases, substantially improving diagnostic capabilities [40].

Furthermore, the mechanisms underlying the drainage of GFAP and its breakdown products into the blood under pathological conditions involve a combination of bulk flow through arachnoid villi, the glymphatic system, and continuous fluid exchange at the CNS barriers. These pathways highlight the complex nature of GFAP dynamics in health and disease [42].

4. Clinical application

4.1. Neurofilament light chain protein (NfL)

Neurofilament proteins, specifically NfL and NfH, are emerging as important biomarkers across a range of neurological diseases, reflecting disease activity, progression, and therapeutic responses [43,44] (Table 1). Elevated NfL levels in CSF and blood correlate with cognitive decline and brain atrophy in AD and frontotemporal dementia (FTD), aiding early diagnosis and monitoring [45–47]. In stroke and traumatic brain injury, increased neurofilaments signify acute neuroaxonal damage and help assess injury extent, essential for clinical decisions like safe return to sports [48]. In ALS, high neurofilament levels are linked to disease progression and prognosis, facilitating tracking and therapy evaluation [49]. Elevated neurofilament levels have also been observed in atypical parkinsonian disorders such as progressive supranuclear palsy and multiple system atrophy, as well as in Huntington's disease. Their potential utility is also being investigated in conditions like epilepsy, encephalitis, and bipolar disorder, though their clinical relevance in these areas remains less well-established. [50,51].

NfL is increasingly recognized as a vital biomarker in MS, indicative of active inflammation and ongoing neuroaxonal damage associated with greater disability, heightened disease activity, and increased relapse risk [52–61]. Elevated NfL levels in CSF and blood effectively distinguish MS patients from healthy individuals, although they do not differentiate between MS subtypes. As a nonspecific biomarker, NfL levels are also elevated in other neurological conditions as previously mentioned, limiting its diagnostic specificity for MS except in cases requiring differentiation from other disorders [23,62]. In MS clinical practice, NfL serves primarily as a prognostic indicator, with high serum NfL levels predicting future relapse risk, disability progression, and the development of new MRI lesions, including gadolinium-enhancing and T2 lesions [61,63–72]. Longitudinal studies have demonstrated that baseline and changes in NfL levels correlate with disease progression, brain atrophy, and cognitive decline, reinforcing its utility in monitoring disease trajectory [64,65,73–75]. In clinical trials, disease-modifying therapies (DMTs) consistently reduce NfL levels, reflecting decreased neuroaxonal degeneration and improved treatment efficacy [76–83]. For example, the RADIANCE trial demonstrated that Ozanimod significantly lowered MRI lesion activity and NfL levels over 24 weeks by sequestering lymphocytes, thereby reducing neuroinflammation [84]. Similarly, Evobrutinib, a Bruton tyrosine kinase (BTK) inhibitor, markedly decreased NfL levels over 2.5 years compared to placebo, highlighting its therapeutic potential [85]. Additionally, Ofatumumab, an anti-CD20 monoclonal antibody, has shown superior efficacy in reducing relapse rates, MRI lesions, and NfL concentrations compared to teriflunomide, with early initiation linked to better long-term outcomes [86–90]. These findings underscore NfL's potential in monitoring MS progression and assessing therapeutic responses [63].

Standard ELISA assays are used to measure NfL in CSF, while the SIMOA Quanterix NF-Light assay is preferred for blood measurements; both CSF and serum NfL are valuable, with CSF preferred for initial diagnosis and serum ideal for ongoing monitoring, and factors such as age, body mass index (BMI), renal function, diabetes, and neurotoxic treatments can influence NfL levels and should be accounted for during interpretation [63]. Overall, neurofilaments hold significant potential as biomarkers for a broad range of neurological conditions, aiding in diagnosis, monitoring disease progression, and evaluating therapeutic efficacy. As such, the ongoing development of sensitive immunoassays for their detection in blood is likely to expand their clinical application [91], making them integral to the proper management of neurodegenerative and neuroinflammatory diseases.

4.2. Glial fibrillary acidic protein (GFAP)

GFAP is a vital biomarker for various CNS disorders, reflecting

Table 1
Key Points on Neurofilament Biomarkers in Multiple Sclerosis.

- ➢ NfL is the primary biomarker for MS, indicating neuronal degeneration and disease activity, while NfM and NfH require further investigation.
- ➢ Elevated NfL levels in CSF and blood signal both inflammation and neurodegeneration, making it useful prognosis but limited for diagnosis due to its non-specificity. NfL is a nonspecific marker elevated in various neuronal damage conditions, limiting its diagnostic specificity for MS but useful in differentiating it from other diseases in specific cases.
- ➢ Elevated NfL levels in serum, which peak during relapses, predict greater disease progression including more lesions, relapses, disability, brain atrophy, and cognitive decline when measured at baseline and longitudinally.
- ➢ Disease-modifying therapies (DMTs) consistently reduce NfL levels, indicating decreased neuroaxonal damage and improved clinical outcomes.
- ➢ Standard ELISA assays are used for measuring NfL in CSF, and the Single-Molecule Array (SIMOA) Quanterix NF-Light assay is preferred for blood measurements. Both CSF and serum NfL measurements are valuable, with CSF preferred for initial diagnosis and serum ideal for ongoing monitoring, following specific resampling guidelines.
- ➢ Age, BMI, renal function, diabetes, and neurotoxic treatments can influence NfL levels and should be accounted for during interpretation.

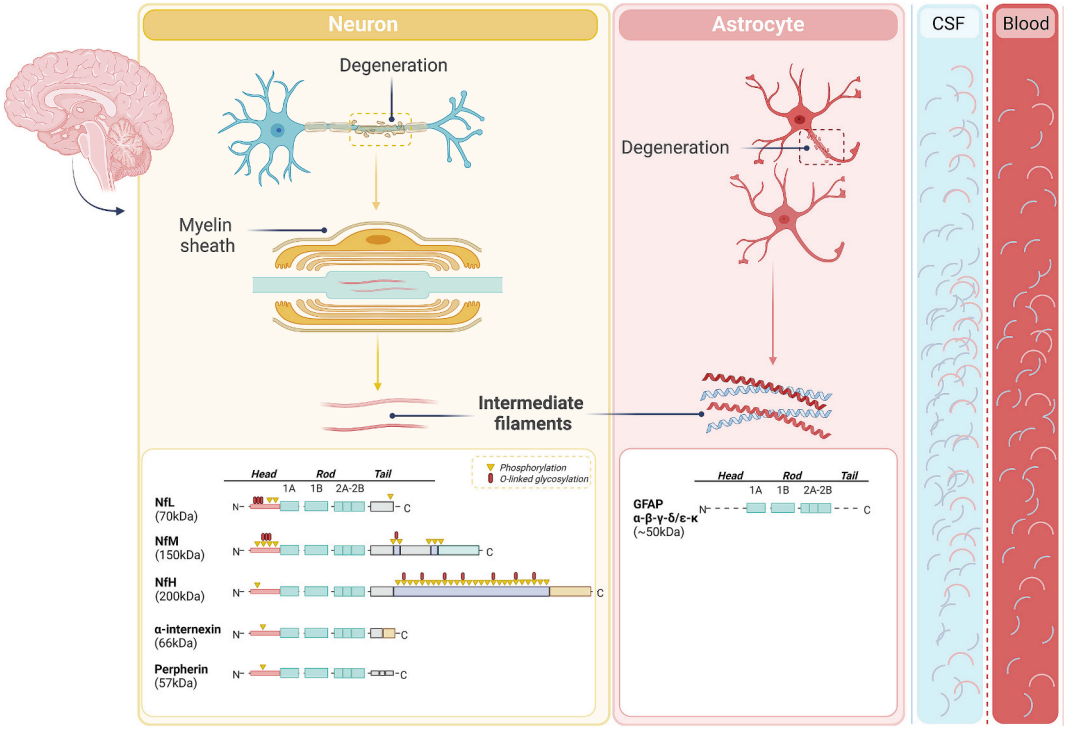

Fig. 1. Neurofilament Structure and Degeneration in Neurons and Astrocytes. In neurons, neurofilaments (NfL, NfM, NfH, α-internexin, peripherin) are crucial for maintaining structure and function. In astrocytes, GFAP, with its head, rod, and tail domains essential for structural integrity, plays a similar role. Neurofilament subunits are depicted with conserved α-helical rod domains and variable head and tail domains, showing phosphorylation and O-linked glycosylation, especially in the tails of NfM and NfH. Neurofilament assembly begins with monomers forming coiled-coil heterodimers, which align into tetramers and then assemble into mature filaments (~10 nm in diameter). GFAP in astrocytes similarly contributes to cellular structure with its distinct domains. Upon axonal and astrocytic damage, neurofilament and GFAP proteins are released into the extracellular space, cerebrospinal fluid (CSF), and blood. These cleavage products can be detected by highly sensitive immunoassays, making them valuable biomarkers for diagnosing neurological disorders.

neuronal damage and disease activity. In traumatic brain injury and spinal cord injuries, elevated GFAP levels assess injury severity and guide clinical decisions, leading to FDA-approved blood tests that reduce unnecessary CT scans [25,92–94]. In neurodegenerative diseases such as AD and FTD, increased GFAP correlates with disease progression and astrocytic damage, serving as both diagnostic and prognostic tools, while in Alexander disease, GFAP levels align with disease severity and inform therapeutic approaches [95]. In oncology, GFAP levels in glioblastoma and other brain tumors correlate with tumor volume and postoperative outcomes, though diagnostic accuracy requires further research [96–98]. Additionally, GFAP indicates disease presence and severity in conditions such as epilepsy, delirium, sepsis-related encephalopathy, and infections such as COVID-19 and West Nile virus [26,99]. This broad applicability makes GFAP a versatile biomarker in neurology, enhancing differential diagnosis precision, aiding management decisions, and tracking disease progression across diverse neurological contexts [100].

In MS and AQP4-NMOSD, GFAP serves as a critical biomarker reflecting astrocytic activation and neuroinflammation. Elevated GFAP levels are significantly higher in MS and AQP4-NMOSD patients compared to healthy controls, with primary progressive MS patients exhibiting higher GFAP levels than those with relapsing-remitting MS, indicating more severe disease states [26,41,101–107]. Additionally, studies have shown higher GFAP levels in NMOSD compared to MS, aiding in differential diagnosis. This is particularly relevant in the presence of AQP4 autoantibodies, which contribute to astrocyte destruction during acute relapses—an essential factor for guiding distinct treatment protocols [108].

GFAP levels correlate with various clinical characteristics, serological biomarkers, disability measures like Expanded Disability Status Scale (EDSS), disease duration, NfL levels, and imaging measures such as T2 lesion volume, underscoring its role in disease progression and severity [30,103,104,106,107,109–116]. The correlation of GFAPs with brain atrophy and cognitive decline further supports the role of the protein in monitoring disease progression and therapeutic efficacy [117].

While initial ELISA and ECL assays did not find significant differences in GFAP levels between MS and non-inflammatory disorders,

sensitive SIMOA assays have detected higher serum GFAP in MS, particularly in progressive MS [103,118–120].

Autoimmune GFAP astrocytopathy is another condition where GFAP plays a central role. This steroid-responsive central nervous system disease can present as a monophasic or relapsing condition, characterized by symptoms and signs of meningoencephalomyelitis or its limited forms. The diagnosis is supported by the detection of GFAP-IgG in CSF along with paraclinical findings such as inflammatory CSF or characteristic T1 postgadolinium imaging features. Approximately 25 % of patients have an associated neoplasm, most commonly ovarian teratoma, while others develop the condition for unknown reasons. Recently, autoimmune GFAP astrocytopathy has been increasingly differentiated from other autoimmune CNS disorders, further highlighting the importance of accurate diagnostic markers such as GFAP-IgG and associated clinical and imaging features to guide appropriate treatment and management strategies [121,122].

Overall, GFAP's ability to differentiate CNS conditions, its association with disease severity, and its responsiveness to treatments make it an invaluable biomarker in neurology. However, further research is needed to refine its clinical application and fully integrate it into patient care strategies.

5. Conclusion and future perspectives

In summary, the clinical application of GFAP and neurofilament protein measurements holds transformative promise for enhancing the management of neurological disorders by providing a sensitive and minimally invasive measure of neuroaxonal damage. These biomarkers are poised to revolutionize our approach to diagnosing and monitoring diseases, such as MS, AQP4-NMOSD, and others. The ability to assess brain tissue damage with a simple blood sample marks a significant advancement in both research and clinical practice, facilitating early detection, more informed therapeutic decisions and improved patient outcomes.

However, several challenges must be addressed for widespread clinical adoption. For GFAP, further research is needed to understand its release mechanisms, effects of protein aggregation on analytical accuracy, and physiological dynamics, including protein binding and metabolism. The specificity of assays for different GFAP isoforms and the contributions of distinct astrocyte subclasses to circulating GFAP levels require clarification. For NfL, the establishment of normative data across all age groups, the impact of comorbidities, and the standardization of measurement techniques are critical. Additionally, defining disease-specific cutoff values and correlating NfL changes with clinical outcomes will enhance its clinical utility, particularly in MS [20,123,124].

Efforts should focus on developing robust, disease-specific databases for both GFAP and NfL to provide precise cutoff values and reference ranges. These resources, combined with multicenter trials and retrospective analyses of existing data, will validate the clinical use of these biomarkers and refine their role in monitoring disease progression, therapeutic efficacy, and patient outcomes.

As research advances, integrating GFAP and NfL into routine clinical practice has the potential to transform neurological care. By enabling more accurate diagnoses, better monitoring of disease activity, and tailored therapeutic strategies, these biomarkers could significantly improve patient outcomes and contribute to the development of new treatments.

CRediT authorship contribution statement

Sara Samadzadeh: Writing – original draft. **Roy D. Sleator:** Writing – review & editing, Supervision.

Declaration of competing interest

None.

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