Neurofilaments in disease: what do we know?

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Abstract

Neurofilaments are proteins selectively expressed in the cytoskeleton of neurons, and increased levels are a marker of damage. Elevated neurofilament levels can serve as a marker of ongoing disease activity as well as a tool to measure response to therapeutic intervention. The potential utility of neurofilaments has drastically increased as recent advances have made it possible to measure levels in both the cerebrospinal fluid and blood. There is mounting evidence that neurofilament light chain (NfL) and phosphorylated neurofilament heavy chain (NfH) are abnormal in a host of neurodegenerative diseases. In this review we examine how both of these proteins behave across diseases and what we know about how these biomarkers relate to *in vivo* white matter pathology and each other.

Keywords

neurodegeneration; NFL; NFH; NFM; white matter

Introduction

Neurodegenerative disease such as Alzheimer disease (AD), stroke, traumatic brain injury, and multiple sclerosis (MS) are common causes of disability and mortality. These diseases have a social and financial cost to the affected individuals and society more broadly. Biomarkers aid diagnosis and impact treatment, in turn improving the quality of life for patients and caregivers. No one biomarker fully characterizes a disorder, and new measures are constantly introduced to improve our understanding of disease.

Neurofilaments are type IV intermediate filaments sharing structural elements with nestin, peripherin, and α-internexin [1-3]. Neurofilaments fall into three categories, separated by their molecular weights of 68, 150, and 190-210 kilodaltons into light (NfL), medium (NfM), and heavy (NfH) chains [1,2,4]. Neurofilaments are heteropolymers; NfL forms the

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core of the structure and dimerizes with NfH or NfM to form tetramers, protofilaments, and finally ~10 nm fibers [1,2,4-6]. Neurofilaments are specifically expressed in neurons and are a major cytoskeleton protein[1,7]. Their gene expression [8] and phosphorylation levels [9] directly affect axonal diameter, myelination, and conduction velocity [9-13]. When neurons are damaged neurofilaments are released into the interstitial fluid then diffuse into the cerebrospinal fluid (CSF) and then the blood [2,4]. Antibodies have been successfully developed to measure NfL and phosphorylated NfH. These proteins may be good markers of acute disease activity, monitors of therapeutic intervention, and predictors of future disease trajectories.

Measuring Neurofilaments

CSF NfL was first measured using enzyme-linked immunosorbent assays (ELISAs) [14-16]. These anti-bodies have been adapted for electrochemiluminescence (ECL) assays [17], and subsequently for the ultra-sensitive single molecule array (SIMOA) platform. The SIMOA system is more sensitive than either ELISAs and ECL at measuring the low concentrations of neurofilaments present in the blood [18,19]. Work directly comparing CSF and either serum or plasma levels of NfL have generally found a high concordance (Pearson r or Spearman ρ =0.7-0.9, [20-28]) although other analyses have found only moderate (~ 0.5-0.69) associations [29-33]. There has been no obvious evidence that either plasma or serum provide better measurements, and NfL levels in the two are highly corelated [34]. Phosphorylated levels of NfH in both CSF and blood are commonly measured using ELISAs [35,36]or ECL [37,38] approaches, although translation of antibodies to SIMOA is possible [19]. Correlations between blood and CSF levels of NfH are lower than that observed for NfL [39,40], and this lower correlation may be due to sensitivity limits of ELISA and ECL [19]. There is some evidence that blood based levels of neurofilaments may partially be influenced by body size and blood volume in the brain [41], which may introduce discrepancies between CSF and blood levels.

Neurofilaments in Neurodegenerative Disease

As neurofilament levels reflect nonspecific damage to axons, they have been examined across many neurological disorders. NfL levels are elevated in most conditions relative to healthy controls, but the degree of elevation varies considerably between disorders [14,16,23,34,42-50]. Prion diseases have some of the highest levels [43,46,51], with frontotemporal dementia (FTD) [20,43-45,48,49,51,52] and amyotrophic lateral sclerosis (ALS) [44,53,54] also typically high relative to other diseases. Vascular dementia (VAD), multiple systems atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD) are moderately elevated [23,34,43,45,47,49,55]. Alzheimer disease (AD), mild cognitive impairment (MCI), Parkinson disease (PD), and dementia with Lewy bodies (DLB) are only modestly elevated over controls [34,43-45,47-49,54] (See meta-analysis of CSF NfL by Bridel et al., 2019). Cross-disease comparisons of NfH are limited, but show that NfH levels are generally increases across neurodegenerative conditions [37,50,56-58].

Multiple Sclerosis (MS)

MS is chronic neurodegenerative disease where an immune-mediated process causes inflammation that damages myelin. White matter lesions can be seen as hyperintensities on fluid-attenuated inversion recovery (FLAIR) scans while gadolinium-enhancing lesions can identify areas of inflammation. CSF and blood-based measures of NfL are consistently elevated in MS patients [16,59-65], tied to relapses [29,60,64], and elevated in clinically isolated syndrome (CIS) patients that later convert to MS [64,66,67]. Higher levels of NfL in both CSF and blood have consistently been related to T2-weighted hyperintensity and gadolinium-enhancing lesions [61,62,66-71]. Perhaps the most intriguing finding is that patients on disease modifying treatments show significant reductions in NfL levels relative to placebo [33,61,63,70,72-74]. Work examining NfH is consistent with those of NfL, levels are elevated in MS patients [37,38,64,68,72,75] and increases in those that relapse [38,64]. In CIS NfH has been found to be both elevated [64,76] and no different from controls [66]. There have been mixed results relating NfH to gadolinium enhancing lesions, with both significant [69] and no [64] associations observed.

Amyotrophic Lateral Sclerosis (ALS)

ALS is a rapidly progressing disorder that affects motor neurons. NfL levels in both the CSF and blood [14,16,22,24,44,50,54,77-82] are highly elevated in ALS patients relative to controls, particularly for upper motor dominant ALS. NfL values discriminate ALS from mimics [22,77,82,83], indicating a utility identifying the 7% of diagnoses that turn out to be other diseases [50]. NfL levels are strongly tied to symptomology, and elevated values predict shorter survival times and greater progression rates [22,24,80]. There is also evidence that elevated NfL is associated with altered white matter integrity in descending motor tracts [78,81]. Whereas MS researchers have been a driving force exploring NfL, much of what we know about NfH comes from ALS research. As with NfL, both CSF and blood levels of NfH are dramatically increases in ALS patients relative to controls [37,39,50,56,82-89], levels discriminate ALS patients from mimics [50,77,82,83,88,89], values increase near the onset of clinical symptoms [88], and higher levels predict faster decline [56,82-84,88,90] and shorter survival times [39,84,87,89].

Frontotemporal Dementia (FTD)

FTD is an umbrella term for heterogeneous disorders that affect the frontal and temporal lobes, commonly occur in individuals in their 50's and 60's, and prominently manifest in changes in behavior, language, or movement. FTD can be grouped into disorders that involve tau or TDP43 protein and there are genetic links between FTD and ALS [91]. NfL is consistently elevated in FTD, with patients having some of the highest levels seen across disorders [20,42-46,48,49,52,53,92-98]. In genetic forms of FTD, levels of NfL are not elevated in asymptomatic individuals but increase with the onset of impairment [98,99]. There is some evidence that NfH levels are elevated in FTD [93,100], but such effects are modest and have not always been found when excluding FTD patients with motor involvement [39,84].

Alzheimer Disease (AD)

AD is the leading cause of dementia and its hallmark pathologies are extracellular beta-amyloid plaques (Aβ) and intracellular tau tangles. There is an extensive literature examining CSF, neuroimaging, and blood-based biomarkers of these pathologies. Still, there is a desire to develop new biomarkers to better understand neurodegeneration occurring in AD. In autosomal dominant cohorts NfL levels are elevated in mutation carriers relative to controls [28,101,102] and show highly significant relationships with levels of Aβ [28,103], cognition [28,101,103], and atrophy [28,101]. In sporadic, late onset AD, the predictive value of NfL is less clear. Levels are elevated in impaired individuals [31,34,44,46,49,51,92,96,104-110] relative to controls, although this is not always found [100,111], and AD is one of the least elevated neurodegenerative disorders [34,43,45,47-49]. NfL has been significantly tied to abnormal Aβ levels [28,32,107,112], although no association is also commonly found [31,34,106,112,113]. NfH is typically not elevated in AD [37,56,93,111] when age is considered, although positive results exist [57]

The most consistent finding is that higher levels of NfL are associated with worse cross-sectional and longitudinal cognition [28,31,44,101,106,110,112-114]. However the influence of NfL on cognition is often found to be similar between those with or without abnormal Aβ levels [114] or is independent of Aβ [106,113], and the relationship with cognition may be driven by the high correlations of neurofilaments with age [28,38,45,104,110,115,116]. Neurofilaments in AD appear highly similar to MRI volumetries; they can be abnormal due to disease pathophysiology, levels are associated with cognition, but other comorbidities such as cerebrovascular disease and diabetes could be contributing factors. Still, as clinical trials shift to include anti-tau therapies, neurofilaments are a cost-effective marker of neurodegeneration not directly engaged by the drugs. Neurofilaments could also serve as a compliment to blood measures of Aβ [117] and tau [118] to screen participants to increase the efficiency of clinical trials, or serve as biomarker endpoints themselves.

Parkinson Disease (PD)

PD is common degenerative disease characterized by a loss of dopaminergic neurons leading to motor difficulties as well as cognitive symptoms. CSF NfL levels are generally low in PD, often not different than controls [34,47,55,92]. The low levels in PD distinguish it from the high levels seen in multiple system atrophy (MSA) [34,47,55,119,120] and progressive supranuclear palsy (PSP) [120] which have overlapping symptomology. NfL levels are increased in PD patients additionally suffering from dementia (PDD) [44,49,55,121]. NfH mirrors NfL, being elevated in MSA and PSP relative to Parkinson's disease [58,119] and controls [58].

Creutzfeldt–Jakob disease (CJD)

CJD is a rapidly progressive neurodegenerative condition caused by prions. NfL levels are elevated in those with CJD [27,43,46,122,123], with higher levels of being associated with more aggressive diseases courses and shorter survival time [27,46]. CSF NfH levels are also elevated in both sporadic and genetic forms of CJD, with levels increasing before the onset of symptoms [123,124]. The utility of neurofilaments in CJD is unclear, as CSF total tau has been shown to be a better predictor of disease severity [27].

Traumatic Brain Injury (TBI)

TBI represents a "silent epidemic" with as many as sixty-nine million individuals affected annually [125]. Blood levels of NfL are consistently increased in individuals with TBI [26,118,126,127]. Competitive athletes provide unique cohorts to study TBI. Blood-based levels of NfL are elevated in active but not retired boxers [128], increase after a bout [26], and levels negatively correlate with brain volumes measured with MRI [128]. In hockey players, serum NfL levels increase after a concussion, and levels were related to how long it took to return to play [118]. In football players serum NfL levels are higher in starters relative to non-starters, and the difference between groups gradually increases over the course of the season [129]. A similar pattern emerges for NfH; NfH is increased in animal models of TBI [130]. CSF levels increase after a bout in boxers [131], and serum levels are elevated in TBI and higher levels predict poorer outcomes [132]. Given that they can be measured in blood and correlate with meaningful outcomes, neurofilaments have a high utility in assessing and monitoring TBI.

Cardiovascular Disease

Impaired vascular systems can manifest as both chronic and acute neurological insults. CSF NfL and NfH are elevated in vascular dementia (VAD) [16,43,45,49,57], and these elevations may contribute to the mixed findings in the AD literature. Levels of NfL and NfH are increased after stroke [37,40,133-138], and increased levels of NfL are related to greater infarct size [133,135,138], as well as white matter changes [133], although this is not always the case [134]. With cardiac arrest blood NfL and NfH are elevated, and levels predict long-term neurological outcomes [139-141]. These results suggest that neurofilaments could aid neurological prognosis.

Other Neurodegenerative Conditions

The number and topical breadth of publications examining neurofilaments has drastically increased over the last few years. This trend will only increase given the relative low cost of neurofilament assays, and the ubiquity proved by blood-based measurements. Neurofilaments are examined in diverse diseases, representing both chronic and acute conditions. NfL levels are elevated in PSP [23,34,47,55,142,143], DLB [34,44,46,47], CBD [34,47], primary progressive aphasia (PPA) [144], Huntington disease [25,145], drug naïve subjects with HIV [146,147], psychiatric disorders such as bipolar disorder, depression, schizophrenia, and anorexia [94,148,149], spinal cord injuries [150], and postoperative delirium [151]. NfH has been shown to be a sensitive marker in DLB [100], PPA [144], PSP [58], VAD [57] spinal muscular atrophy [152], seizures [153], optic neuritis [154], and Guillain-Barré syndrome [37]. While promising, these results generally represent small samples and only a handful of publications.

Linking neurofilaments to pathology

Neurofilaments levels are interpreted as a marker of axonal damage across diverse diseases with demyelination, neuropathy, dendritic loss, frank cell death, and chronic inflammation. The most common link with white matter *in vivo* has been relating NfL levels to white matter hyperintensity (WMH) lesions in MS patients [61,62,66-71]. Diffusion tensor

imaging (DTI) is a MRI technique that is sensitive to the movement of water in the brain and is considered a measure of fiber integrity [155]. NfL has been related to altered DTI metrics in stroke patients [133], TBI [126], and ALS [78,81]. However, cross-sectional and longitudinal studies in older adult cohorts are an inconsistent, with a mixture of significant and null findings [32,156-158]. There is a dearth of research relating neurofilament levels to white matter health, particularly for NfH. While neurofilament levels are clearly meaningful, a greater understanding of what damage they represent is needed.

The relationships between NfL and NfH

Due to their interrelated nature, it is unclear if light, medium, and heavy chains would be expected to have divergent diagnostic utility. Still, the proteins are not identical, NfL forms the backbone of neurofilaments, with NfM and NfH forming the side arms [1,2,4-6], and different phosphorylation rates and molecular weights could impact solubility, diffusion, and proteolysis. NfL and NfH generally have similar overarching patterns; both are increased in neurodegenerative conditions, and the more rapidly a disease progresses the higher the neurofilament levels. When examined concurrently in the CSF, NfL and NfH have been reasonably correlated (~0.4-0.6) [40,64,66,68,77] but less so in serum [69]. The results relating NfL to outcomes in disease are more robust, but NfL is more commonly examined as NfH has primarily been embraced by researchers studying motor neuron disease. The exact cause of this differential adoption is unclear but may be driven by differential availability and promotion of commercial assays, greater heterogeneity of NfH antibody utilized in assays, as well as the fact that there has been minimal adoption of NfH antibodies to the SIMOA system.

Conclusions

Neurofilaments have been widely implemented in research, and it is a matter of time before they are routinely adopted in clinical settings. While neurofilament levels are significantly elevated in patient populations, measures overlap between diseases and with healthy control populations. Neurofilaments are unlikely to have diagnostic utility except when values drastically differ between conditions with similar clinical presentations (e.g. ALS and mimics). Instead, levels are best interpreted as an individual difference marker of neuronal damage that can aid prognosis and therapeutic monitoring in combination with clinical judgment. Longitudinal clinical, cognitive, and biomarker data collected in parallel with neurofilaments are crucial to this endeavor and something that has been done in only a handful of published studies. The gaps in our understanding of how neurofilament levels relate to in vivo white matter, as well as the relationships between NfL, NfM, and NfH, are further questions that also need to be addressed before neurofilaments become biomarkers included by default to study neurodegenerative diseases. Finally, although excellent preclinical animal work has been done [34], research is overwhelmingly in human populations. This is a missed opportunity, as animal work provides an unsurpassed ability to directly manipulate biological properties to ask questions that simply cannot be asked in human studies. Neurofilaments are a promising biomarker of neuronal damage that may greatly aid disease prognosis and therapeutic intervention.

Acknowledgements

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· of special interest

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Highlights

- Neurofilament levels are elevated in most neurodegenerative conditions

- Levels predict cross-sectional and longitudinal cognitive and clinical outcomes

- There is minimal work relating neurofilaments to *in vivo* white matter damage

- It is unclear how neurofilament light and heavy chains relate to one another

- Neurofilaments are promising biomarkers, but more work needs to be done
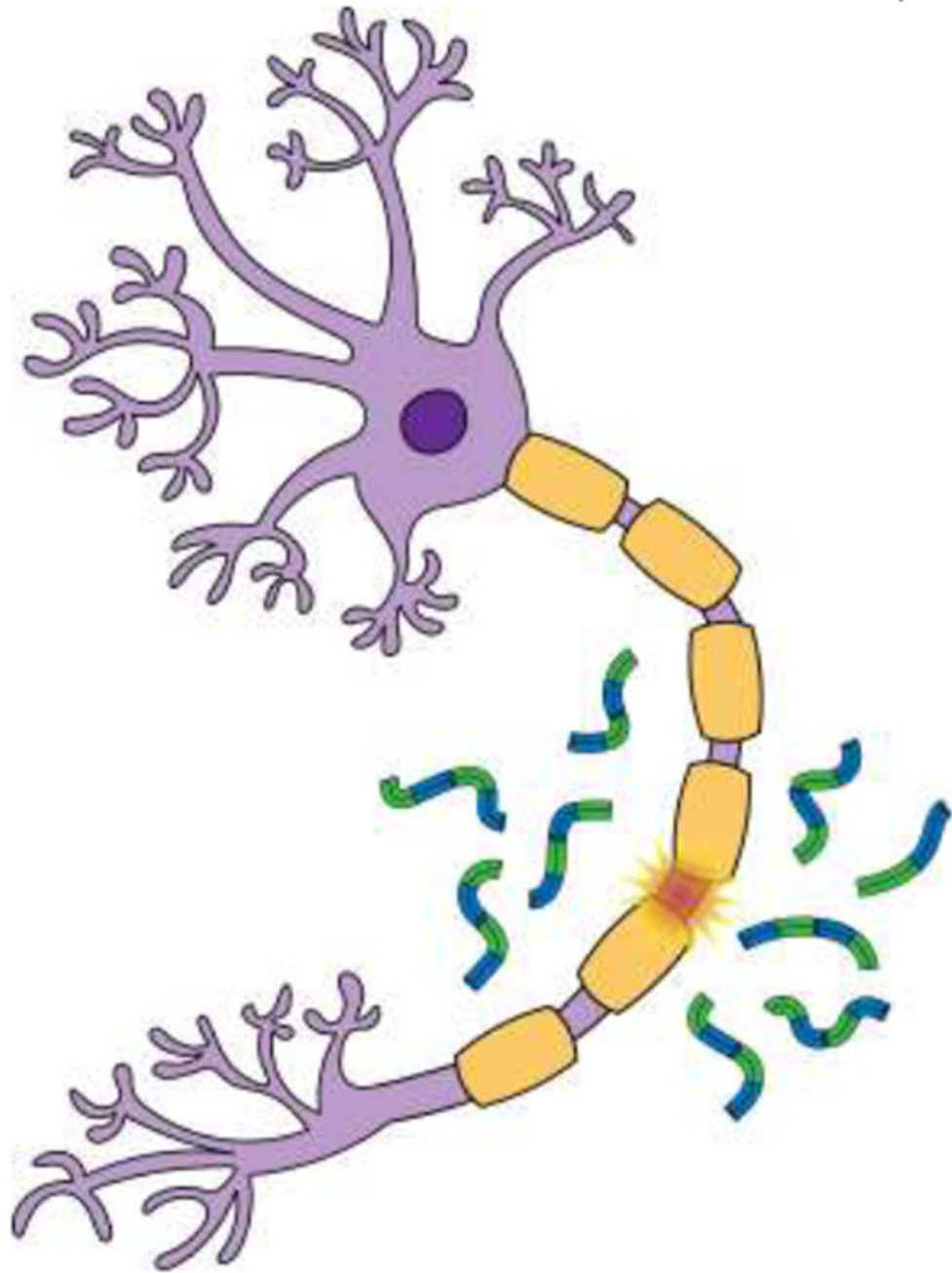
Figure 1:
When neurons are damaged neurofilaments are released into the interstitial fluid, before moving into the cerebrospinal fluid and blood.

Table 1:

Key Findings in Neurodegenerative Disorders

Disease	NfL Key Publications	NfH Key Publications	Finding Overview
Multiple Sclerosis (MS)	Lycke et al., 1998 [59] Malmeström et al. 2003 [60] Gunnarsson et al., 2011 [73] Kuhle et al. 2015 [74] Disanto et al., 2017 [29]	Teunissen et al. 2009 [64] Kuhle et al. 2010 [37] Kuhle et al. 2011 [38] Kuhle et al. 2013 [72] Kuhle et al. 2017 [69]	• Neurofilament levels are elevated in MS patients and clinically isolated syndrome patients that convert to MIS • Higher levels tied to relapses and MRI lesions • Neurofilament levels fall with disease modifying treatment
Amyotrophic Lateral Sclerosis (ALS)	Rosengren et al. 1996 [14] Lu et al 2015 [24] Menke et al. 2015 [81] Steinacker et al. 2016 [50] * Poesen et al. 2017 [82] *	Brettschneider et al. 2006 [56] Kuhle et al. 2010 [37] Ganesalingam et al. 2011 [39] Boylan et al. 2013 [90] Gendron et al. 2017 [84]	• Discriminates ALS from mimics • Levels are related to survival times and progression rates • Elevations are tied to altered DTI metrics • NfH has a history of use in ALS research
Frontotemporal Dementia (FTD)	Sjögren et al. 2000 [52] Landqvist et al. 2013 [42] Scherling et al. 2015 [48] Rohrer et al. 2016 [95]	De Jong et al. 2007 [100] Pijnenburg et al. 2007 [93] * Ganesalingam et al. 2011 [39]	• Neurofilaments are elevated relative to controls • Levels are even higher with overlapping ALS and FTD symptomology • It is unknown how neurofilaments vary by FTD subtypes
Alzheimer Disease (AD)	Bacioglu et al 2016 [34] Zetterberg et al. 2016 [106] Mattsson et al. 2016 [107] Mattsson et al. 2017 [31] Preische et al. 2019 [28]	Brettschneider et al. 2006 [56] Brettschneider et al. 2006 [57] Pijnenburg et al. 2007 [93] Kuhle et al. 2010 [37]	• Levels are modestly elevated above controls • Less diagnostic utility than established AD biomarkers • Unclear relationship with AD pathology • Higher values predict worse cognitive outcomes • May hold particularly utility for clinical trials
Parkinson Disease (PD)	Holmberg et al. 1998 [121] Abdo et al. 2007 [120] Hall et al. 2012 [47] Hall et al. 2018 [55]	Brettschneider et al. 2006 [58] Abdo et al. 2007 [120]	• Very low levels in PD • Elevated levels discriminate Parkinson Disease Dementia and Multiple Systems Atrophy from PD
Creutzfeldt-Jakob Disease (CJD)	Staffaroni et al. 2019 [27] Abu-Rumeileh et al. 2018 [46]	Van Eijk et al. 2010 [125] * Steinacker et al. 2016 [124] *	• Neurofilaments are greatly elevated in CJD • Total tau likely better predictor of disease activity
Traumatic Brain Injury (TBI)	Oliver et al. 2016 [130] Shahim et al. 2017 [26] Shahim et al. 2018 [119]	Anderson et al. 2008 [131] Neselius et al. 2013 [132] Shibahaski et al. 2016 [133]	• Neurofilament levels increase with TBI including sports-related head injury • Elevations predict time to return to play

Disease	NfL Key Publications	NfH Key Publications	Finding Overview
			• High utility as a blood-based monitor of TBI
Stroke and Ischemia	Tiedt et al. 2018 [134] Pujol-Calderon et al. 2019 [40] Moseby-Knappe et al. 2018 [141]	Singh et al. 2011 [137] Rundgren et al. 2012 [142]	• Llevels are elevated with stroke and cardiac arrest • Blood levels could serve as highly useful prognostic marker

*examines both NfL and pNfH