NFL as a Biomarker for Neurodegenerative Disorders

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Neurofilament light chain (NFL) is a promising new biomarker for neurodegeneration which can be measured both in the brain cerebrospinal fluid (CSF), and in the peripheral blood.

Neurofilaments are proteins that provide structural support for neurons and play a number of important roles in intracellular transport of proteins within the neurons. In a healthy central nervous system, NFL levels measured in both CSF and in the blood are low, indicating low levels of neuronal loss.

However, when nerve cells are damaged, NFL is released into the CSF and also leaks to the blood. Thus, NFL protein in both the blood and CSF can serve as an indicator of neuronal loss and the rate of disease progression in neurological disorders. The higher the steady state level of NFL is, the faster the disease progresses.1,2

Moreover, NFL has been shown to precede clinical disease symptoms by 1-2 years in many diseases and this may allow the identification and treatment of pre-symptomatic subjects.1,2

Finally, effective therapeutics were shown to reduce the level of NFL in correlation with their efficacy allowing NFL to be used as a surrogate biomarker for drug effect.3-5

Higher than normal levels of NFL in either the blood or CSF were shown to be an indicator of brain damage in multiple chronic and acute neurodegenerative diseases including:

- Alzheimer’s disease (AD), both sporadic and familial;
- Amyotrophic lateral sclerosis (ALS);
- Corticobasal degeneration (CBD);
- Creutzfeldt-Jakob disease (CJD);
- Dementia with Lewy bodies (DLB);
- Frontotemporal dementia (FTD);
- HIV-associated dementia (HID);
- Traumatic brain injury (TBI);
- Multiple sclerosis (MS, it includes clinically isolated syndrome, relapsing-remitting multiple sclerosis, primary progressive multiple sclerosis and secondary progressive multiple sclerosis);
- Multiple system atrophy (MSA);
- Normal pressure hydrocephalus (NPH);
- Parkinson’s disease (PD) and Parkinson’s disease dementia (PDD);
- Spinal muscular atrophy;
- Guillain-Barre syndrome;
- Huntington disease (HD);
- HIV positive with cognitive impairment (HAD);
• Progressive supranuclear palsy (PSP);
• Other disorders, such as bipolar disorder, noninflammatory neurological disorders, optic neuritis, progressive supranuclear palsy (PSP), vascular dementia and stroke.

![Figure 1](image1.png)

**Figure 1:** Increase of cerebrospinal fluid (CSF) neurofilament light chain (NfL) with respect to healthy controls (HC) in a variety of central nervous system diseases. Columns represent mean fold increases and SEM of CSF NfL in neurological diseases versus HCs. Red columns: increase of CSF NfL ≥10, blue increase in NfL 2–10 fold, grey columns increase in NfL <2.

1) Alzheimer’s disease (AD)

In AD patients, plasma NfL is correlated with the severity of neurofibrillary tangle pathology, cognition deficits, neuroimaging measures of disease severity, Braak staging and degree of neurodegeneration\(^1,2,7,8\) (Figures 2, 3).

![Figure 2](image2.png)

**Figure 2:** Plasma NfL concentrations in healthy controls (CTL) versus Alzheimer’s disease (AD) patients \(p < 0.001\). The horizontal dashes indicate median (long) and quartiles (short).
2) **Frontotemporal dementia (FTD)**

CSF NfL levels are 3-5 times higher in sporadic FTD patients than in controls\(^9,10\), while they are 8 times higher in genetic FTD patients than in controls\(^11\). CSF NfL levels in FTD patients correlate with disease severity and with neuropsychological test (Figure 4A).

In serum, NfL levels in genetic FTD patients were more than 8 times higher than in controls and serum NfL levels showed a high correlation with CSF NfL levels\(^11\).

Rojas et al. (2019, poster presentation at AAIC) observed elevated plasma Nfl concentration levels (Quanterix SIMOA) in a cohort of 290 subjects from the LEFFTDS consortium, comprising 187 C9orf72, GRN or MAPT mutation carriers and 103 non-carriers.

Furthermore, both plasma and CSF Nfl is correlated with neuropsychological test scores, global cognitive scales, language impairment, parahippocampal atrophy and volumes of several brain regions, including the frontal lobes and the white matter underlying these lobes\(^12\) (Figure 4).

Alector uses Quanterix immunoassays and their Single Molecular Array (SIMOA) technology, to measure NfL in plasma and in CSF. The sensitivity of these assays is high enough to permit quantitation of low baseline plasma NfL found in healthy controls.
Figure 4: (A) NfL levels are normal in presymptomatic mutation carriers but increases in symptomatic FTD-GRN patients compared to controls. (B) Correlation of serum NfL with frontotemporal lobar degeneration Clinical Dementia Rating Scale Sum of Boxes (FTLD-CDR) score for FTD (left y axis, red) and with Mini-Mental State Examination (MMSE) for AD (right y axis, blue). (C) Increased serum NfL correlates with decreased brain volume in bvFTD patients (red).

3) Amyotrophic lateral sclerosis (ALS)

Serum NfL is elevated in ALS patients vs controls and elevated NfL levels positively correlate with rate of decline and patient death $^{13}$ (Figure 5).

Figure 5: Reduced survival in ALS patients with serum NfL levels above 71.5 pg/ml.
4) **Parkinson’s disease (PD)**

NfL levels correlate with the rate of motor and cognitive decline in PD patients\(^{12}\) (Figure 6).

![Figure 6](image)

**Figure 6:** Graphs showing outcomes for (A) motor progression and (B) cognitive progression in patients with Parkinson disease (PD) who had baseline NfL concentrations above or below the cutoff levels.

5) **Multiple sclerosis**

Blood NfL levels are associated with clinical and MRI-related measures of disease activity and nerve cell damage and have prognostic value in multiple sclerosis \(^{3,14-16}\) (Figure 7).

![Figure 7](image)

**Figure 7:** Blood NfL levels at baseline relative to the number of lesions. The dotted line represents plasma NfL (pg/mL, median) concentrations in healthy controls. Gd\(^+\) = gadolinium-enhancing.
6) Huntington disease (HD)

Mean concentrations of NfL in plasma at baseline were significantly higher in Huntingtin mutation carriers (HTT) than in controls and the difference increased from one disease stage to the next. At any given timepoint, NfL concentrations in plasma correlated with clinical and MRI findings and also correlated significantly with subsequent decline in cognition\textsuperscript{17,18} (Figures 8-11).

**Figure 8:** Baseline Nfl concentrations in plasma by disease stage

**Figure 9:** Associations between Nfl concentration in plasma, age and CAG repeat count (disease severity), in 201 HTT mutation carriers and 97 controls.

**Figure 10:** Nfl concentration in plasma at baseline by disease progression status at 3 years.
Figure 11: Concentrations in CSF (A) and plasma (B) in HTT mutation carriers and controls. CSF and plasma NfL show a similar disease associated increase.

7) *Traumatic brain injury*

Patients with incomplete recovery from Traumatic Brain Injury had significantly higher plasma Nfl levels compared to patients who completely recovered [19] (Figure 12).

Figure 12: Nfl levels in traumatic brain injury patients with complete vs. incomplete recovery.
NFL correlates with treatment response

1) Spinal muscular atrophy treatment response

NFL levels are reduced upon treatment of Spinal muscular atrophy with Nusinersen\(^2,3\) (Figure 13).

![Figure 13: Course of neurofilaments (NFL and pNfH- Phospho neurofilament heavy chain) in a spinal muscular atrophy (SMA) type 1 infant under treatment with nusinersen (A). The NFL decrease mirrors clinical improvement as measured by CHOP-Intend, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (B); CSF, cerebrospinal fluid.](image)

2) Multiple sclerosis treatment response\(^3,16\) (Figure 14)

![Figure 14: Fingolimod significantly reduces blood NFL levels compared to placebo. Dotted line represents plasma NFL (pg/mL, geometric mean) concentrations in healthy controls. ***p < 0.0001. n = number of patients.](image)
BIBLIOGRAPHY

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