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Neurofilament Light Chain as a Biomarker for Cognitive Decline in Parkinson Disease

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Abstract

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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Background: Neurofilament light chain protein (NfL) is a promising biomarker of neurodegeneration.

Objectives: To determine whether plasma and CSF NfL (1) associate with motor or cognitive status in Parkinson's disease (PD) and (2) predict future motor or cognitive decline in PD.

Methods: Six hundred and fifteen participants with neurodegenerative diseases, including 152 PD and 200 healthy control participants, provided a plasma and/or cerebrospinal fluid (CSF) NfL sample. Diagnostic groups were compared using the KruskalWallis rank test. Within PD, cross-sectional associations between NfL and Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) and Mattis Dementia Rating Scale (DRS-2) scores were assessed by linear regression; longitudinal analyses were performed using linear mixed-effects models and Cox regression.

Results: Plasma and CSF NfL levels correlated substantially (Spearman r = 0.64, $P < 0.001$); NfL was highest in neurocognitive disorders. PD participants with high plasma NfL were more likely to develop incident cognitive impairment (HR 5.34, $P = 0.005$).

Conclusions: Plasma NfL is a useful prognostic biomarker for PD, predicting clinical conversion to mild cognitive impairment or dementia.

Keywords

neurofilament light chain protein; NfL; biomarkers; Parkinson's disease; prognosis

Across neurodegenerative diseases, biomarkers can improve diagnostic accuracy, aid in prognostication, and inform clinical trial design. Although biomarkers are routinely used in Alzheimer's disease (AD),[1,2] biomarker development has proven more challenging in Parkinson's disease (PD).[3] Unlike amyloid-beta and tau in AD, no radioligand exists for detection of alpha-synuclein, the hallmark pathological protein in PD, and cerebrospinal fluid (CSF) levels of alpha-synuclein overlap between patients and controls.[3,4] To date, no specific blood or CSF biomarkers are used in the clinical diagnosis or management of PD.

In recent years, neurofilament light chain protein (NfL) has emerged as a promising biomarker in multiple neurodegenerative diseases. NfL is a neuron-specific component of the axonal cytoskeleton that can enter the extracellular space after axonal injury or death[5,6]; NfL has been quantified in plasma, serum, and CSF.[7] Though relatively non-specific, NfL values from these compartments serve as candidate biomarkers for neuroaxonal damage.[8]

In idiopathic PD, studies of NfL as a biomarker are increasingly reported. For example, NfL may distinguish between PD and atypical parkinsonian syndromes such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal syndrome (CBS), as the latter conditions are associated with greater degrees of axonal degeneration and higher NfL levels.[9–11] However, few large-scale studies have conducted longitudinal analyses of both plasma and CSF NfL, and, to our knowledge, no prior studies have explored the question of whether plasma NfL levels at a single time point predict longitudinal clinical outcomes.

Using a large single-center cohort, we aimed to determine whether levels of plasma and CSF NfL (1) correlate with each other and differ across neurodegenerative diseases, (2) correlate with levels of CSF total tau (t-tau) and amyloid-beta (Abeta42), (3) associate cross-sectionally with Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) and Mattis Dementia Rating Scale (DRS-2) scores in PD, and (4) predict longitudinal motor and cognitive decline in PD.

Methods

Participants met formal criteria for the following diagnoses: memory-predominant mild cognitive impairment (MCI); AD; primary progressive aphasia (PPA); behavioral variant frontotemporal dementia (bvFTD); CBS; PSP; dementia with Lewy bodies (DLB); and PD.[12] All participants and healthy controls who provided one NfL sample from plasma, CSF, or both sources were included in the initial analysis. PD participants in the cross-sectional cohort had a UPDRS-III score or DRS-2 score documented within 6 months of NfL sample date, while those in the longitudinal cohort had two or more scores. The average follow-up time was 4.60 (range 0.9–10.8) years from plasma sample date and 5.08 (range 0.3–12.1) years from CSF sample date. A cognitive diagnosis (cognitively normal, MCI, or dementia) was determined based on baseline and annual/biannual neuropsychological testing and expert clinical consensus[13] using published diagnostic criteria.[14,15] All analyses were performed in R (http://www.r-project.org); tests were two-sided with an alpha of 0.05. Detailed methods and R-scripts are included in the supplement (Appendix S2).

Results

Patient Cohort

Six hundred and fifteen participants met inclusion criteria for the initial group analysis: 335 (55%) provided samples for NfL measurement from both plasma and CSF, 261 (42%) from plasma alone, and 19 (3%) from CSF alone (Fig. 1A). Details for the plasma and CSF cohorts are provided in (Table 1).

For PD participants, median plasma NfL (measured in 139 individuals) was 15.6 pg/mL, and median CSF NfL (measured in 149 individuals) was 1024.0 pg/mL. Some 136/139 PD patients providing plasma samples also provided CSF samples, and the demographics did not differ between these groups. Of those providing a plasma sample, 94 were cognitively normal, 34 had MCI, and eight had dementia at the time of sampling; for three individuals, cognitive status was unknown. Median levodopa equivalent daily dose (LEDD) was 600 mg (interquartile range [IQR] 300–890), median UPDRS-III was 19 (IQR 14–26), median raw DRS-2-total score was 139.5 (IQR 135–141), and median age-adjusted DRS-2 score was 11 (IQR 9–13). Of those providing a CSF sample, 100 were cognitively normal, 39 had MCI, and nine had dementia at the time of sampling; for one individual, cognitive status was unknown. Median LEDD was 550 mg (IQR 325–813), median UPDRS-III was 19 (IQR 14–26), median raw DRS-2-total score was 139 (IQR 135–142), and median age-adjusted DRS-2 score was 11 (IQR 9–13).

Plasma and CSF NfL Levels are Correlated Across Diagnostic Groups

NfL levels for plasma and CSF correlated among all participants (Spearman r = 0.64, CI 0.57–0.70, $P < 0.001$) (Fig. 1B). Comparing plasma NfL levels across diagnostic groups, median levels were highest in participants with neurocognitive disorders, with significant differences from neurologically normal controls found in five diagnostic groups (MCI $P = 0.020$, AD $P < 0.001$, PPA $P < 0.001$, bvFTD $P = 0.001$, and PSP/ CBS $P < 0.001$, Fig. 1C). Comparing CSF NfL levels across diagnostic groups, median levels were also highest in participants with neurocognitive disorders, with significant differences from neurologically normal controls found in five groups (AD $P < 0.001$, PPA $P < 0.001$, bvFTD $P < 0.001$, PSP/CBS $P < 0.001$, and PD $P = 0.036$, Fig. 1D). Both plasma and CSF NfL values increased significantly for participants across the neurologically normal control–MCI–AD continuum (H^2=29.62, $P < 0.001$ and H^2=27.26, $P < 0.001$, respectively) (Fig. 1C,D).

Plasma and CSF NfL Levels are Correlated With CSF t-Tau and Abeta42 Levels

In 95 participants who had plasma NfL and CSF biomarkers drawn simultaneously, plasma NfL correlated with CSF t-tau (Spearman r = 0.39, CI 0.21–0.55, $P < 0.001$) and negatively correlated with CSF Abeta42 (Spearman r =0.23, CI 0.04 to 0.41, $P = 0.024$) (Figure S1). In 224 participants who had all CSF biomarkers drawn simultaneously, CSF NfL also correlated with CSF t-tau (Spearman r = 0.36, CI 0.23–0.47, $P < 0.001$) and negatively correlated with Abeta42 (Spearman r =0.26, CI 0.14 to 0.37, $P < 0.001$) (Figure S1).

Plasma NfL Associates With UPDRS-III Score in PD

In a cross-sectional analysis of 152 PD patients, we examined associations between plasma or CSF NfL and both motor (UPDRS-III) and cognitive (DRS-2) performance.

Using Spearman correlations, we found that both plasma and CSF NfL levels correlated with baseline UPDRS-III score (Figure S2A,B), while neither plasma nor CSF NfL levels correlated with baseline DRS-2 score (Figure S2C,D).

UPDRS-III scores may be influenced by age, sex, disease duration, and LEDD, and DRS-2 scores may be influenced by age, sex, disease duration, and education, so we evaluated associations between NfL measures and cognitive or motor performance in models adjusting for these variables. We found that only the relationship between plasma NfL and UPDRS-III remained significant ($P = 0.005$).

Plasma and CSF NfL Values Predict Motor and Cognitive Decline in PD

We next asked whether NfL values obtained at a single time point could predict subsequent motor or cognitive decline in PD, using linear mixed-effects models to evaluate longitudinal data from 118 PD patients with plasma NfL measures and 145 PD patients with CSF NfL measures.

Both plasma and CSF NfL measures predicted the subsequent rate of change in UPDRS-III score ($P = 0.005$ and $P < 0.001$, respectively) in models adjusted for age, sex, disease duration, LEDD, and baseline UPDRS-III score. Greater age and higher NfL measures associated with faster rate of motor decline.

Similarly, both plasma and CSF NfL measures predicted the subsequent rate of change in DRS-2 score ($P = 0.028$ and $P = 0.001$, respectively) in models adjusted for age, sex, disease duration, education, and baseline DRS-2 score. Higher NfL measures associated with faster rate of cognitive decline.

Plasma NfL Level Predicts Conversion to MCI or Dementia in PD

We finally asked whether NfL measures might predict clinically meaningful change in PD for up to 8 years of follow-up.

An increase of five points on the UPDRS-III has been reported as clinically relevant,[16,17] so we performed Cox proportional hazards analyses using this benchmark. In models adjusted for age, sex, disease duration, LEDD, and baseline UPDRS-III, we found no significant differences in this motor outcome comparing individuals across plasma or CSF NfL tertiles (Figure S3).

In contrast, PD individuals with high initial plasma NfL values differed in subsequent cognitive outcome: those in the highest NfL tertile were more likely to convert from normal cognition to MCI or dementia, or MCI to dementia (HR 5.34, CI 1.65–17.25, $P = 0.005$) in Cox proportional hazards model adjusted for age, sex, disease duration, education, and baseline DRS-2 score (Fig. 1E,F). More conversion to MCI or dementia was also observed in individuals with higher CSF NfL, but this association was not significant (HR 1.96, CI 0.82–4.70, $P = 0.13$) (Fig. 1G,H).

Finally, we used receiver operating characteristic (ROC) curve analysis and Youden's index to identify the optimal cut-point for plasma NfL in predicting clinical conversion to MCI or dementia. Among 94 participants with normal cognition at the time of plasma collection, the area under the curve for conversion to MCI or dementia was 0.60 (CI 0.48–0.72) and the optimal cut-point was 14.6 pg/mL (sensitivity 74.2%, specificity 54.0%) (Figure S4).

Discussion

We report Nfl measures in 615 individuals across the neurodegenerative disease spectrum, finding that (1): levels of plasma and CSF NfL correlated with each other in all diseases and were highest in neurocognitive disorders; (2) levels of plasma and CSF NfL correlated with CSF t-tau and Abeta42 levels; (3) in PD, plasma NfL levels associated with UPDRS-III scores, but not DRS-2 scores, after adjusting for covariates; (4) higher plasma and CSF NfL measures predicted faster rate of change in UPDRS-III and DRS-2 scores longitudinally; and (5) PD participants with higher initial plasma NfL values were more likely to convert to MCI or dementia.

Our study confirms prior work demonstrating that NfL values are elevated in most neurodegenerative conditions.[8,18,19] We also confirm prior reports that CSF NfL levels increase in a stepwise manner across the control–MCI–AD continuum.[6] Lastly, NfL levels were significantly correlated with CSF t-tau and Abeta42 levels, suggesting that plasma-based biomarkers may serve as a future proxy for CSF biomarkers in dementia risk assessment.[20]

In PD, we demonstrate that both plasma and CSF NfL levels at a single time point predicted future rate of change in UPDRS-III and DRS-2 scores using linear mixed-effects models. Importantly, we also found that PD individuals with plasma NfL values in the highest tertile were five times more likely to convert to MCI or dementia during follow-up. This latter result has not been previously reported in the literature. Specifically, comparator studies have shown that (1) in the PPMI cohort, serum NfL measures increased in individuals over time and doubling of serum NfL values associated with motor and cognitive decline;[21] (2) in the De Novo Parkinson Cohort (DeNoPa), higher CSF NfL levels predicted worse MDS-UPDRS-III scores 4 years after initial PD diagnosis;[22] (3) in a large single-center study, CSF NfL measures correlated with motor impairment and cognitive dysfunction;[23] and (4) in an 85-person subset of our Penn PD cohort, higher CSF NfL measured using a different assay associated with greater change over time in DRS-2 scores.[6] However, no prior study has shown that blood-based NfL measures predict clinically significant cognitive decline in PD.

Our study has limitations. First, our PD cohort had a median disease duration of 6 years at biofluid sampling, so our study is not informative about NfL's performance in earlier disease stages. Second, clinical diagnoses were not confirmed by pathologic findings at autopsy and may be susceptible to misclassification. Third, ROC analysis demonstrated only modest performance for plasma NfL used alone to predict conversion from normal cognition to MCI or dementia on an individual basis, suggesting that plasma NfL will need to be incorporated in a multi-marker panel for more accurate prediction of clinical conversion.

These limitations notwithstanding, our study is the largest longitudinal cohort to examine effects of both baseline plasma and CSF NfL values on UPDRS-III and DRS-2 scores over time, expanding the existing literature. The value of our study lies not only in validating prior findings, but also in showing that plasma NfL measures predict clinically meaningful cognitive decline in PD. The ability to prognosticate based on a blood sample renders NfL practical as a biomarker in many different settings. The fact that high plasma NfL levels predict not just a change in test score, but a change in cognitive diagnosis, gives this biomarker clinical significance, amplified by the large effect size.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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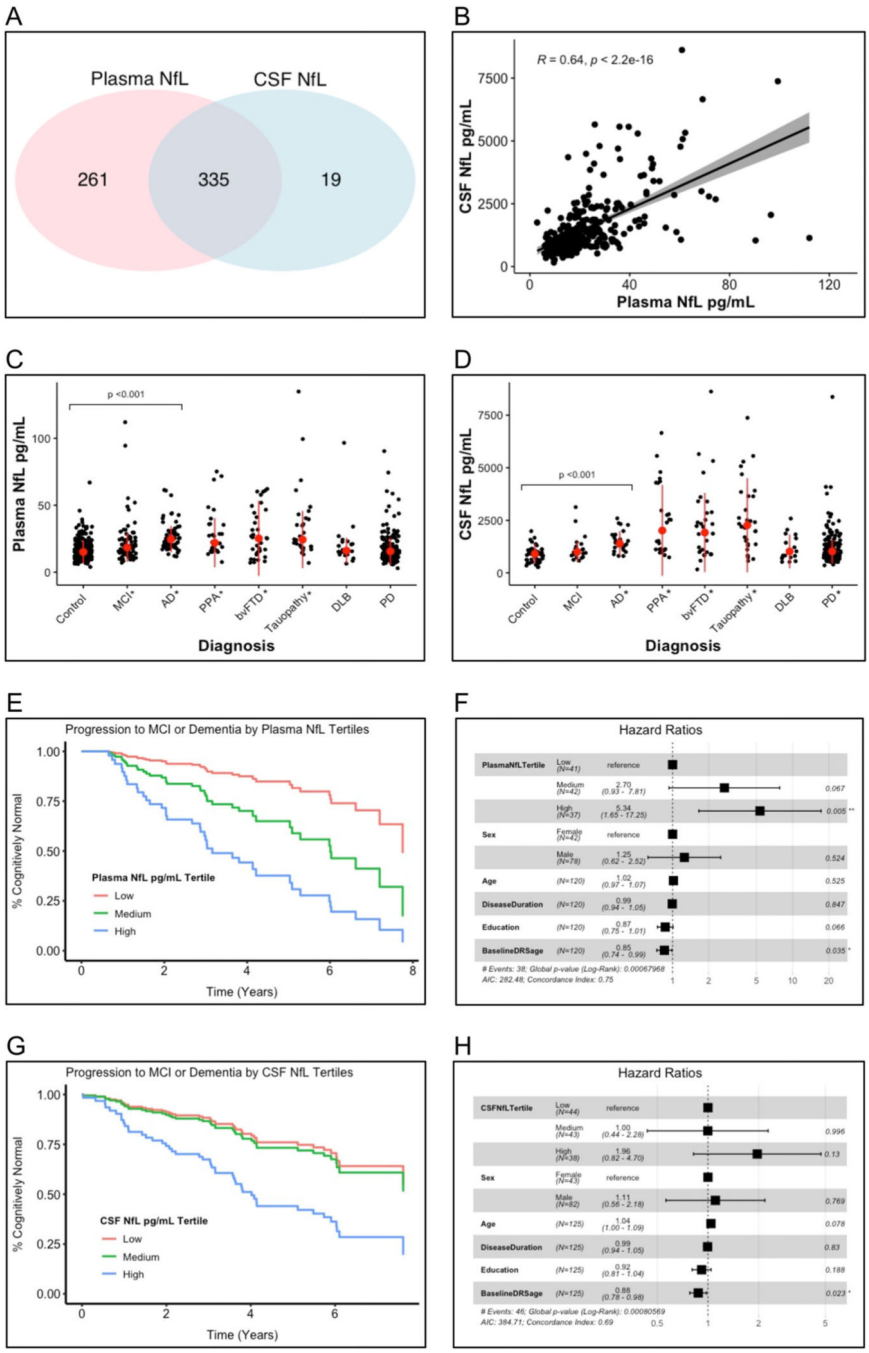

FIG. 1.

Six hundred and fifteen participants provided one plasma and/or cerebrospinal fluid (CSF) sample for neurofilament light chain protein (NfL) measurement. Three hundred and thirty-five participants provided both CSF and plasma samples (**A**). Plasma and CSF values of NfL are significantly correlated. Spearman correlation coefficient is shown (**B**). When compared to neurologically normal controls, plasma NfL values were significantly greater in participants with mild cognitive impairment (MCI), Alzheimer's disease (AD), primary progressive aphasia (PPA), behavioral variant frontotemporal dementia (bvFTD),

and progressive supranuclear palsy/corticobasal syndrome (PSP/CBS) (tauopathy), denoted by asterisks. Plasma NfL values also increased across the controlMCIAD continuum (KruskalWallis H test *P* value shown above bracket) (**C**). CSF NfL values were significantly greater in participants with AD, PPA, bvFTD, PSP/CBS (tauopathy), and PD, denoted by asterisks. CSF NfL values also increased across the controlMCIAD continuum (KruskalWallis H test *P* value shown above bracket) (**D**). Cox proportional hazards analysis investigating differences in rates of clinical conversion from normal cognition to MCI or dementia, or MCI to dementia, stratified by NfL level at baseline. Adjusted Cox regression curves show predicted trajectories by NfL tertile (**E, G**). Forest plots depict hazard ratios and 95% confidence intervals for groups defined by each predictor (**F, H**). PD participants in the highest plasma NfL tertile were 5.34 times more likely to convert to MCI or dementia.

TABLE 1

Participant demographic and baseline characteristics collected on neurofilament light chain protein sample date for plasma (A) and cerebrospinal fluid (B)

A. Plasma

Characteristic	Control (n = 198)	MCI (n = 79)	AD (n = 65)	PPA (n = 30)	bvFTH (n = 35)	Tauopathy (n = 30)	DLB (n = 20)	PD (n = 139)
Plasma NfL, pg/mL	15.1 (11.7–20.4)	18.5 (13.8–25.1)	24.7 (19.7–29.6)	22.1 (17.1–35.9)	25.3 (14.2–44.4)	24.4 (18.6–40.4)	16.2 (13.2–22.9)	15.6 (11.5–22.1)
Age at NfL draw, years	69 (65–74)	70 (65–78)	73 (65–79)	65 (62–67)	62 (58–67)	65.5 (62–73)	66 (60–71)	66 (61–72)
Sex (%)								
Male	65 (33)	37 (47)	37 (57)	15 (50)	23 (66)	12 (40)	16 (80)	91 (65)
Female	133 (67)	42 (53)	28 (43)	15 (50)	12 (34)	18 (60)	4 (20)	48 (35)
Education, years	16 (14–18)	16 (16–18)	16 (14–18)	16 (12–18)	16 (14–18)	16 (12–18)	15 (14–16)	16 (14–18)
Disease duration, years	-	3 (2–4)	4 (2–5)	3 (2–4)	4 (2–5)	3 (2–4)	3 (2–4)	6.5 (4–10)

B. Cerebrospinal fluid

Characteristic	Control (n = 51)	MCI (n = 20)	AD (n = 26)	PPA (n = 28)	bvFTH (n = 31)	Tauopathy (n = 30)	DLB (n = 19)	PD (n = 149)
CSF NfL, pg/mL	899.7 (579–1080)	998.8 (785–1317)	1400.6 (1180–1816)	2020.0 (1131–3623)	1920.9 (982–2887)	2268.5 (1369–3653)	1020.6 (730–1646)	1024.0 (799–1386)
Age at NfL draw, years	67 (63–72)	64 (60–70)	67 (61–77)	65 (61–69)	62 (58–67)	65.5 (63–73)	67 (58–72)	66 (62–72)
Sex, n, (%)								
Male	24 (47)	11 (55)	13 (50)	15 (54)	21 (68)	11 (37)	15 (79)	100 (67)
Female	27 (53)	9 (45)	13 (50)	13 (46)	10 (32)	19 (63)	4(21)	49 (33)
Education, years	16 (16–18)	16 (16–18)	16 (15–18)	16 (12–18)	17 (14–18)	16 (12–18)	14 (14–16)	16 (14–18)
Disease duration, years	-	2 (2–4)	3 (2–4)	3(2–4)	3 (2–4)	3 (2–4)	3(2–4)	6 (3–10)

All values are represented as median (interquartile range) unless otherwise specified.

Abbreviations: MCI, mild cognitive impairment; AD, Alzheimer's disease; PPA, primary progressive aphasia; bvFTD, behavioral variant frontotemporal dementia; DLB, dementia with Lewy bodies; PD, Parkinson's disease; NfL, neurofilament light chain protein; CSF, cerebrospinal fluid.