BRIEF REPORT

Longitudinal Dynamics of Plasma Neurofilament Light Chain in Hereditary Spastic Paraplegia Type 11 (HSP-*SPG11*) and Type 15 (HSP-*ZFYVE26*)

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ABSTRACT: Background: HSP-*SPG11* and HSP-*ZFYVE26* are autosomal-recessive forms of hereditary spastic paraplegias (HSPs). As therapeutic trials emerge, validated biomarkers are critically needed.
Objectives: To evaluate plasma neurofilament light chain (pNfL) as a biomarker for neurodegeneration and disease progression.
Methods: We analyzed pNfL levels in 57 patients (36 HSP-*SPG11*, 21 HSP-*ZFYVE26*) and matched controls using single-molecule array technology. Longitudinal clinical and biomarker data were collected over 5 years.
Results: Baseline pNfL levels were significantly elevated in patients: 33.85 pg/mL (IQR 25.15–47.38) in HSP-*SPG11*, 46.70 pg/mL (IQR 29.95–54.84) in HSP-*ZFYVE26*, and 4.90 pg/mL (IQR 3.48–6.90) in controls ($P < 0.001$). No significant difference was observed between HSP-*SPG11* and HSP-*ZFYVE26*. In matched pair analysis, pNfL showed inverse correlation with age ($\rho = -0.463$, $P < 0.001$). Baseline pNfL did not predict future clinical progression.
Conclusions: Elevated pNfL reflects early neuroaxonal injury in HSP-*SPG11* and HSP-*ZFYVE26*; however, it could not be used as a surrogate for disease progression.

Key Words: axonal degeneration; biomarker; hereditary spastic paralysis; neurofilament light chain; spasticity

The hereditary spastic paraplegias (HSPs) are a group of neurogenetic disorders marked by progressive lower limb spasticity.[1,2] HSP-*SPG11* (or SPG11) and HSP-*ZFYVE26* (or SPG15) are the most common autosomal-recessive subtypes, with overlapping phenotypes that include early-onset spasticity, parkinsonism, ataxia, and characteristic magnetic resonance imaging (MRI) features like thinning of the corpus callosum and the "ears of the lynx" sign.[3] The causative proteins, spatacsin (encoded by *SPG11*) and spastizin (encode by *ZFYVE26*), interact in endolysosomal and autophagy-related pathways.[3,4]

Biomarkers that reflect disease severity and progression are needed but are currently lacking.[5,6] Most existing data are cross-sectional and do not capture intra-

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individual change over time.[7,8] Neurofilament light chain (NfL), a biomarker of neuroaxonal damage validated in diseases such as amyotrophic lateral sclerosis and multiple sclerosis,[5,9,10] has shown promise in some forms of HSP.[5,7,8,11-15] Although longitudinal studies have examined NfL dynamics in HSP-*SPG11* and HSP-*ZFYVE26*, these have been limited by small sample sizes and short follow-up durations. We investigated whether plasma NfL (pNfL) reflects disease severity and progression, aiming to support future clinical trial readiness.

Methods and Participants

The study protocol was approved by the Institutional Review Board at Boston Children's Hospital (IRBP00033016), and written consent was obtained. Methods are described in detail in the Supplemental Material. Patients were recruited from the Natural History Study for Early-Onset Hereditary Spastic Paraplegia (NCT04712812). Serial clinical evaluations and venous blood sampling were performed at two centers (Boston Children's Hospital and IRCCS Stella Maris) with predefined intervals to assess disease progression and pNfL changes. Age- and sex-matched healthy controls were recruited from the PrecisionLink Biobank. For probands, venous blood was collected in PST tubes (BD Biosciences; #367962); for healthy controls, plasma was derived from EDTA-treated tubes (BD Biosciences; #366643). Previous validation studies have demonstrated that these tube types can be used for reliable NfL quantification.[16] pNfL levels were quantified via single-molecule array (Simoa) using Quanterix HD-X. Statistical analyses included Kruskal–Wallis and Wilcoxon tests for group comparisons, receiver operating characteristic (ROC) curve analysis for diagnostic utility, and pairwise correlation analysis for age, sex, HSP subtype, disease duration, and disease severity measured by Spastic Paraplegia Rating Scale (SPRS) score[17] and the FARS disability staging score (range 1–6: no, minimal, mild, moderate, severe, and total disability).[18] Piecewise linear regression was used to assess nonlinear associations between pNfL and age with a statistically determined cutoff.[19,20] Longitudinal changes in disease severity and disability were modeled using linear mixed-effects models with fixed effects for log-transformed pNfL, disease duration, age, sex, and age and log(pNfL) interactions, and random intercepts to account for inter-subject variability. Backward elimination via Akaike information criterion (AIC) was used for model selection. To examine progression, we calculated annualized change in SPRS scores using linear regression and evaluated baseline pNfL as a predictor. R version 4.4.1 was used.

Results

Participant Characteristics

Demographic, molecular, and clinical characteristics are summarized in Table 1. A total of 57 individuals were enrolled, including 36 with HSP-*SPG11* and 21 with HSP-*ZFYVE26*. Gene variants were primarily nonsense in *SPG11* (Fig. 1A) and *ZFYVE26* (Fig. 1B). One-year follow-up plasma samples were available for 17 HSP-*SPG11* patients (47.2%) and 4 HSP-*ZFYVE26* patients (19.0%). In total, 28 participants (49.1%) had at least one follow-up assessment (Fig. S1A). Participants with multiple visits and those with a single visit did not differ significantly in age, disease severity, disability, or pNfL levels (all $P > 0.05$). The only difference was a higher proportion of males in the single-visit group (83% vs. 46%, Fisher's exact $P = 0.0002$, OR = 6.7, 95% CI: 2.2–24.9). Aside from this sex imbalance, the longitudinal cohort appeared broadly representative of the overall sample. Twelve participants included in this cohort had been previously reported,[8] and their baseline data were incorporated. Although follow-up durations varied across individuals, all patients were categorized according to the longest available timepoint for analysis. Follow-up durations ranged from 6 months to 5 years.

pNfL Levels Are Elevated in HSP-*SPG11* and HSP-*ZFYVE26*

Baseline pNfL levels were significantly elevated in both HSP-*SPG11* and HSP-*ZFYVE26* patients compared with age- and sex-matched healthy controls. Median (IQR) pNfL levels were significantly higher in patients than controls: 33.85 (25.15–47.38) pg/mL in HSP-*SPG11*, 46.70 (29.95–54.84) pg/mL in HSP-*ZFYVE26*, and 4.90 (3.48–6.90) pg/mL in controls ($P < 0.001$). No difference was observed between HSP-*SPG11* and HSP-*ZFYVE26* ($P = 1.00$) (Fig. 1C, D), also evidenced by a low area under the ROC curve (area under the curve [AUC] = 0.62, 95% CI: 0.47–0.78) (Fig. S1B).

pNfL Associations with Age, Disease Duration, and Severity

In our cohort, pNfL was inversely associated with age, disease duration, and severity scores, whereas age and disease duration were positively associated with severity (Fig. 1F). These associations were consistent across subtypes (Table S2) and showed no sex differences (Fig. S1F). In matched patient–control pairs, pNfL ratios (patient/control) demonstrated an inverse correlation with age ($\rho = -0.463$, $P < 0.001$), indicating that patient–control differences were greatest at younger ages (Fig. 1E).

TABLE 1 *Summary of the cohorts*

Parameter	SPG11 ($n = 36$)	SPG15 ($n = 21$)	Control ($n = 57$)
Age at first visit, years	25.8 ± 10.9	23.9 ± 7.7	24.6 ± 10.2
Age at onset, years	11.4 ± 8.9	6.8 ± 8.3	N/A
Duration from onset, years	14.4	15.4	N/A
Male sex, n (%)	21 (55.9)	16 (76.2)	34 (59.6)
Variant type (n):			N/A
Truncating/truncating	30	11	
Indel/truncating	2	0	
Structural/truncating	2	0	
Missense/missense	1	0	
Missense/unknown	1	0	
Missense/truncating	0	6	
N/A	0	4	
SPRS score	22.8 ± 12.1	20.4 ± 10.9	N/A
	($n = 35$)	($n = 15$)	
FARS disability staging score	3.4 ± 1.4	4.0 ± 1.8	N/A
Mean pNfL, pg/mL	37.8 ± 17.2	46.1 ± 20.8	5.4 ± 2.8
Median pNfL, pg/mL	33.9 (25.2, 47.4)	46.7 (30.0, 54.8)	4.9 (3.5, 6.9)
Follow-up data of pNfL (n):			
Early (<12 months)	5	1	N/A
1-year (12–23 months)	17	4	N/A
2-year (24–35 months)	5	2	N/A
3-year (36–47 months)	4	4	N/A
4-year (48–59 months)	1	0	N/A
5-year (60 months)	2	1	N/A

Note: Data are reported as mean ± standard deviation or median (interquartile range).
Abbreviations: FARS, Friedreich Ataxia Rating Scale; N/A, not available; pNfL, plasma neurofilament light chain; SPRS, Spastic Paraplegia Rating Scale.

Age-Stratified Exploratory Analysis of pNfL and Clinical Severity

To examine potential age-related patterns, we performed piecewise linear regression, selecting the optimal model based on the AIC. Two inflection points, at 18.3 and 33.9 years, defined three strata: pediatric (<18.3 years, $n = 15$), young adult (18.3–33.9 years, $n = 31$), and adult (>33.9 years, $n = 11$) (Fig. 1G). While sample sizes within each group were limited, visual inspection suggested distinct slope trends across age strata. Applying these age bins to clinical severity measures (Fig. 1H) revealed that pNfL concentrations were highest in younger individuals with moderate symptoms and declined in older adults with more advanced disease. These exploratory, hypothesis-generating findings suggest that pNfL may predominantly reflect early neurodegenerative processes and decrease with chronic disease progression.

Longitudinal Trends of pNfL

In the linear mixed-effects model, the relationship between pNfL and disease severity (SPRS score) significantly varied with age (interaction $\beta = 0.75$, $P = 0.0039$), such that higher pNfL levels were more strongly associated with greater severity in older individuals (Fig. 2A). When averaged across ages, neither pNfL ($P = 0.823$) nor age ($P = 0.873$) showed independent associations with SPRS after accounting for the interaction term. Disease duration, however, was independently associated with worsening severity ($\beta = 0.78$ SPRS points/year, $P < 0.0001$), whereas subtype and sex were not significant predictors. Random effects demonstrated substantial

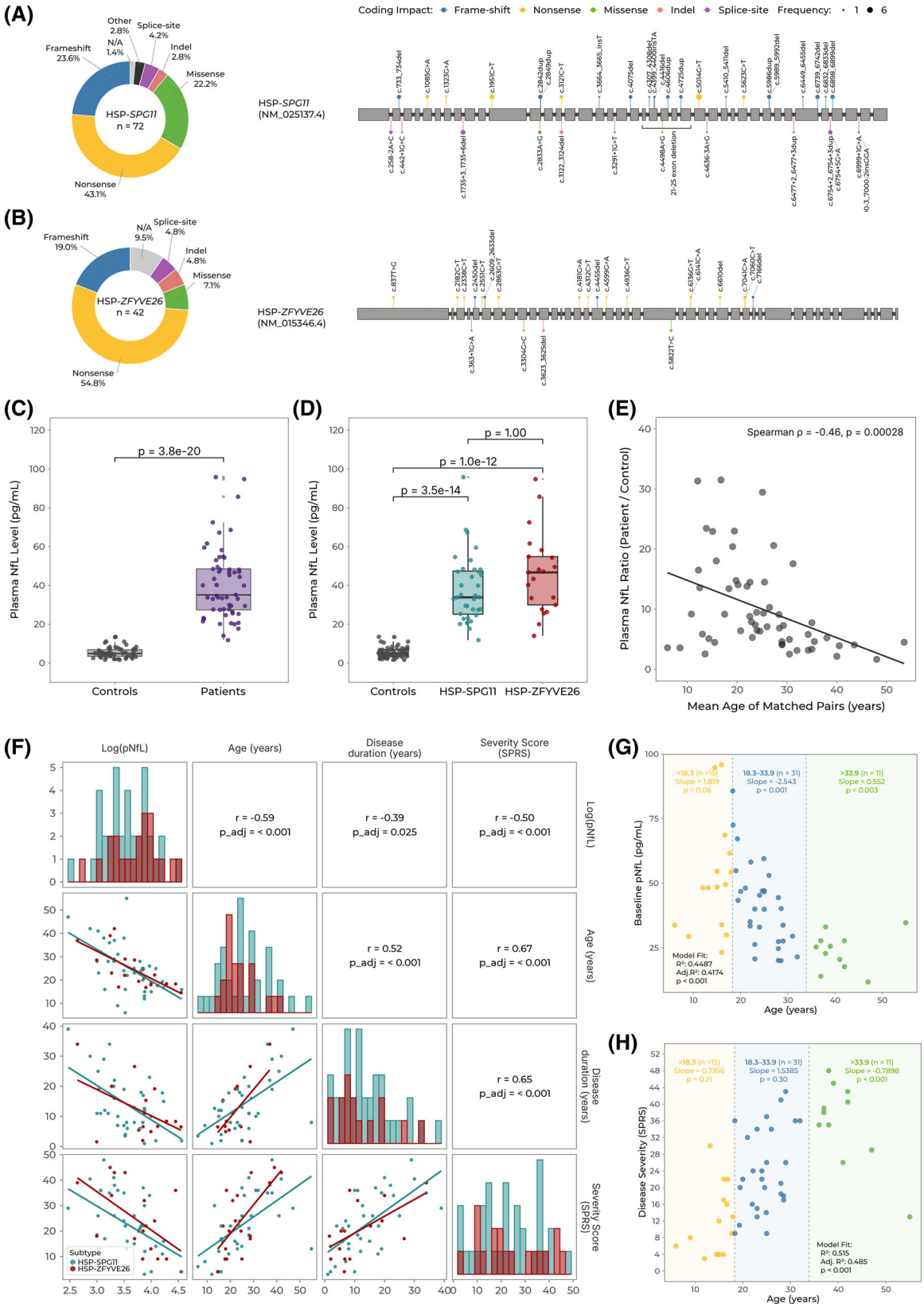

FIG. 1. Pathogenic variants and baseline plasma neurofilament light chain (pNfL) findings in HSP-*SPG11* and HSP-*ZFYVE26*. (A) Pathogenic variants identified in *SPG11*. 'Other' includes one case with a large exon deletion and one with maternal uniparental isodisomy. N/A indicates unavailable data. (B) Pathogenic variants identified in *ZFYVE26*. (C) Box and scatter plots comparing baseline pNfL levels between controls and hereditary spastic paralysis (HSP) patients, showing significantly elevated levels in patients ($P < 0.001$). (D) Subgroup analysis showing elevated pNfL levels in both HSP-
FIG. 1. Legend on next page.

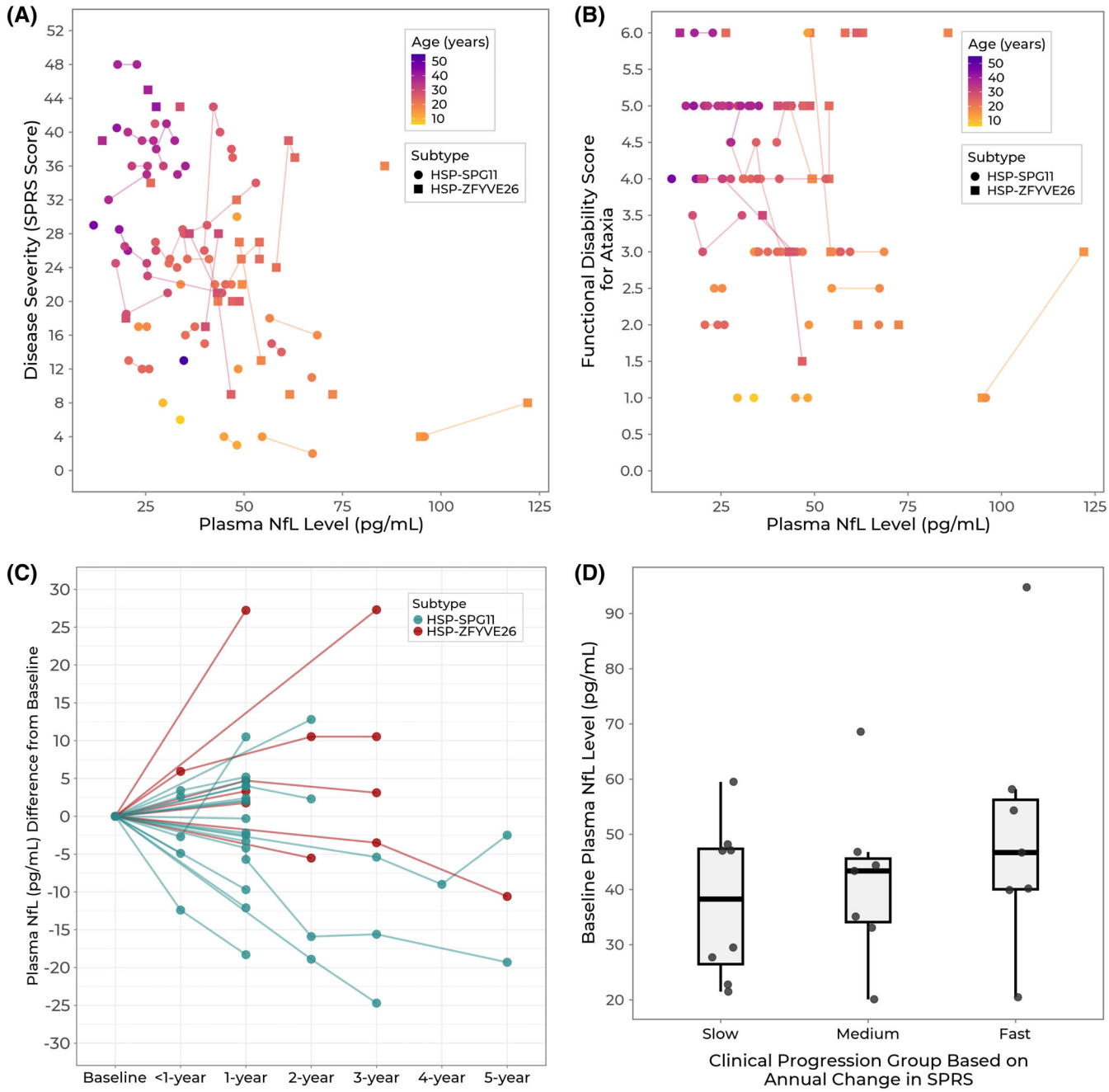

FIG. 2. Plasma neurofilament light chain (pNfL) does not predict disease progression in HSP-*SPG11* and HSP-*ZFYVE26*. (A) Scatter plot of disease severity (Spastic Paraplegia Rating Scale [SPRS] score) versus pNfL levels. (B) Scatter plot of disability (Functional Disability Staging for Ataxia score) versus pNfL levels. Data points are color-coded by age (yellow–purple gradient) and shaped by subtype. Longitudinal measurements from the same individual are connected by lines. (C) Longitudinal trajectories of pNfL in HSP-*SPG11* and HSP-*ZFYVE26* patients, normalized to individual baseline levels. Most patients exhibited stable or declining values; a minority showed marked fluctuations. (D) Baseline plasma pNfL levels do not predict disease progression as measured by the individual slopes of the total SPRS score. Progression groups (slow, medium, fast) were defined for visualization by tercile split of SPRS slopes. [Color figure can be viewed at wileyonlinelibrary.com]

SPG11 and HSP-*ZFYVE26* compared with controls ($P < 0.001$). (E) Negative correlation between pNfL ratio (patient/control) and age across matched pairs (Spearman's $\rho = -0.463$, $P < 0.001$), indicating greater pNfL elevation in younger patients. (F) Pairwise correlations between log-transformed pNfL, age, disease duration, and Spastic Paraplegia Rating Scale (SPRS) severity score. Upper panels display Pearson or Spearman correlation coefficients, with significance levels adjusted for multiple comparisons using the Bonferroni correction. Lower panels show scatter plots with fitted regression lines, and diagonal panels depict variable distributions stratified by group. (G) Segmented regression identified two inflection points at 18.3 and 33.9 years, revealing distinct age-related patterns in pNfL levels. (H) SPRS total scores modeled against age using the same segmented regression cutoffs as in panel G. [Color figure can be viewed at wileyonlinelibrary.com]

between-subject variability (SD = 8.32) compared with residual error (SD = 3.20).

For disease disability (FARS disability staging score), disease duration was again significantly associated with progression (β = 0.086, $P = 0.00058$). An age-by-pNfL interaction (β = 0.087, $P = 0.0107$) indicated that the association between pNfL and disability became more pronounced with age, while main effects of pNfL, age, and sex were not significant. Random effects again highlighted marked between-subject variability (SD = 1.06) relative to residual error (SD = 0.45) (Figs 2B and S1C, Table S3).

Baseline pNfL Does Not Predict Clinical Progression in HSP-*SPG11* or HSP-*ZFYVE26*

We assessed whether baseline pNfL levels could serve as a prognostic marker by analyzing 23 patients with longitudinal SPRS data and matched plasma samples. Annualized progression rates varied and were stratified into tertiles (slow, medium, fast progressors; Fig. 2D). Linear regression revealed no association between baseline pNfL or age and SPRS progression ($P = 0.278$ and $P = 0.713$, respectively; Fig. S1F). A similar lack of association was observed using the SPRS spasticity subscore (items 7–10; Fig. S1E). These findings suggest that baseline pNfL does not predict future clinical trajectory in *SPG11*- or *ZFYVE26*-associated HSP.

Discussion

We demonstrate that pNfL is significantly elevated in HSP-*SPG11* and HSP-*ZFYVE26*, particularly in younger patients and early disease stages, supporting its role as a marker of active neuroaxonal injury. However, pNfL did not distinguish between the two subtypes and did not predict future progression, limiting its utility as a standalone prognostic biomarker.

Axonal loss is central to HSP pathology but manifests heterogeneously across genotypes. pNfL, a cytoskeletal component of large myelinated axons, is a robust marker of axonal injury in several neurodegenerative diseases.[9,21-23] In HSP, blood-based pNfL elevation across subtypes has been consistently reported (Table S4),[5,7,8,11-15] though its longitudinal trajectory remained unresolved.

Our exploratory age-stratified analysis revealed that younger adults (aged ~18–34 years) exhibited elevated pNfL despite only moderate SPRS scores, whereas older patients with greater severity had lower levels. This pattern suggests that pNfL reflects early, active axonal degeneration but declines as axonal reserve is depleted, consistent with broader NfL biology.[24] Statistical modeling further confirmed that age modifies the relationship between pNfL and clinical severity, with stronger associations at older ages. Yet, baseline pNfL did not predict subsequent progression, in line with prior studies reporting weak or inconsistent correlations with SPRS.[7,11,14] Thus, while pNfL may capture dynamic axonal injury, it does not appear to reflect cumulative disability.

Strengths of our study include its prospective design, multi-year follow-up, and use of matched controls. Limitations include the modest cohort size, which constrained subgroup and longitudinal analyses, and reliance on SPRS as the primary outcome, which may have limited sensitivity in younger participants and underrepresent non-motor symptoms, patient-reported outcomes, and quality of life. Variability in age at onset and recall-based duration estimates may have introduced bias. Future studies should validate these findings in larger, multicenter cohorts, and integrate complementary approaches – including omics-based biomarkers, digital assessments, and composite clinical endpoints – to improve prognostication and sensitivity to therapeutic change.[25]

Conclusion

Our findings suggest that pNfL is most informative early in HSP-*SPG11* and HSP-*ZFYVE26*, when neurodegeneration is most active and less reliable as disease advances. This limits its utility as a standalone progression biomarker but supports its value as an early diagnostic marker.

Author Roles: (1) Research Project: A. Conception, B. Design, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Editing of the Final Version.H.A.P.A: 1B, 1C, 2B, 3A, 3B.
J.E.A.: 1B, 1C, 2B, 3A, 3B.
A.T.: 1C, 3B.
H.-M.K.: 1C, 3B.
J.R.: 1C, 3B.
N.B.: 1C, 3B.
K.W.: 1C, 3B.
R.M.: 1C, 3B.
N.S.: 1C, 3B.
M.B.: 1C, 3B.
G.Y.: 1C, 3B.
Y.T.: 1C, 3B.
J.M.: 1C, 3B.
K.B.: 1C, 3B.
K.Y.: 1C, 3B.
L.S.: 1C, 3B.
F.M.S.: 1C, 3B.
D.E.-F.: 1B, 1C, 2B, 3A, 3B.

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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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.