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Neurofilament Light Chain as a Biomarker of Disease Progression in Lafora Disease

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Abstract

Background and Objectives

Lafora disease (LD) is a severe, ultra-rare childhood-onset progressive myoclonus epilepsy caused by biallelic pathogenic variants in either *EPM2A* or *NHLRC1* and currently without cure. Body fluid–derived biomarkers have remained largely unexplored in LD. Neurofilament light chain (NfL) levels in serum (sNfL) and CSF (cNfL) reflect ongoing neurodegeneration and have been established as prognostic and therapeutic biomarkers in various neurologic disorders. In this study, we assessed the utility of NfL as a biomarker of LD in a multicenter cohort of patients with LD.

Methods

We conducted cross-sectional and longitudinal measurements of NfL levels in serum (n = 32) and CSF (n = 25) samples from a cohort of 31 patients with LD (26 independent families; mean age 21 years; age range 10.2–40.3; f:m = 16:15; *EPM2A*:*NHLRC1* = 16:15) at diverse disease stages (median LD stage 2) and age-matched control participants with transient minor neurologic conditions (mean age 21.9 years; age range 11.1–41.3; f:m 22:8), treated at 3 referral centers in Ulm, Bologna, and Dallas. At each visit, we assessed LD stage (median LD stage 2; range 0–4) and LD clinical performance score (median score 10.5; range 0–18), allowing for correlation with NfL measurements.

Results

When compared with control participants (mean sNfL 7.72, 95% CI 6.79–8.65; mean cNfL 306.8, 95% CI 251.5–362.2), CSF and serum NfL levels were increased in patients with LD (mean sNfL 13.95, 95% CI 11.20–16.69; mean cNfL 576.9, 95% CI 465.3–688.5). cNfL values exhibited less variability than sNfL, resulting in superior discriminatory performance between those with LD and controls in receiver operating characteristic (ROC) analyses (AUC sNfL = 0.80; cNfL = 0.88). NfL levels tended to increase longitudinally when samples had been collected ≥12 months after baseline. sNfL levels correlated with both disease stage ($r = 0.56$) and LD Clinical Performance Scale score ($r = -0.49$), but not with disease duration (owing to genotype-dependent clinical heterogeneity).

Discussion

Our findings support the utility of NfL, particularly sNfL, as a promising biomarker of disease progression in LD. While further research is needed to fully elucidate the potential of NfL in this context, it holds immediate promise as an exploratory outcome measure in ongoing and future clinical trials.

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Glossary

ALS = amyotrophic lateral sclerosis; **ASO** = antisense oligonucleotide; **LD** = Lafora disease; **LDPS** = LD Clinical Performance Scale; **NfL** = neurofilament light chain; **PNS** = peripheral nervous system; **ROC** = receiver operating characteristic.

Introduction

Lafora disease ([LD], EPM2) is an ultra-rare, severe progressive myoclonus epilepsy that affects previously healthy children and adolescents. It is characterized by drug-resistant epilepsy, myoclonus, and dementia, leading to loss of autonomy and death in young adulthood. LD is caused by biallelic pathogenic variants in the gene *EPM2A*, encoding laforin, or *NHLRC1* (a.k.a. *EPM2B*), encoding malin, resulting in the accumulation of insoluble polyglucosan aggregates (Lafora bodies) in peripheral tissues and the nervous system, leading to neurodegeneration.[1] The phenotype is relatively consistent across cases, but specific variants can influence age at onset and rate of progression. The best-known example is the *NHLRC1* variant c.436G > A, p.D146N, which is associated with a milder phenotype characterized by later onset, slower progression, and longer survival.[2] At present, treatment of LD is limited to symptomatic and palliative care.[1] Recent studies show that targeting glycogen synthesis or enhancing its degradation can be effective in mouse models.[3-5] Two candidates, GYS1-antisense oligonucleotide (ASO; an ASO targeting glycogen synthase) and VAL-1221 (a glycogen-degrading fusion protein), are in, or being prepared for, clinical trials (NCT06609889 and EudraCT 2023-000185-34).[6] Body fluid–derived (i.e., "wet") biomarkers are urgently needed to support the evaluation of disease progression and treatment efficacy in these trials.

Neurofilaments (Nf), particularly neurofilament light chain (NfL), have excelled as diagnostic, therapeutic, and prognostic surrogate markers of (axonal) neurodegeneration across various neurologic disorders, including motor neuron diseases, dementias, ataxias, neuroinflammatory conditions, polyneuropathies, and structural epilepsies.[7-9] Composed of NfL, NfM, NfH, α-internexin, and peripherin, they form essential structural elements of neuronal axons.[10] Upon neuronal damage, Nf are released into the interstitial fluid and are measurable in CSF and blood. Levels are age-dependent—high in infancy, declining in adolescence, and rising again with age—necessitating age-adjusted reference values.[11,12] While comorbidities can influence Nf levels, this is less relevant in younger populations.[13] Nf levels vary across diseases and reflect the severity and pace of neuroaxonal damage. In epilepsy, they remain normal in idiopathic generalized epilepsies but increase in structural epilepsies and status epilepticus, especially when treatment-refractory.[14] LD combines multiple Nf-elevating factors, including progressive neurodegeneration, refractory epilepsy with frequent seizures and status epilepticus, and, occasionally, peripheral neuropathy and muscle denervation.[15] Consequently, we hypothesized that LD would be associated with increased NfL levels in serum and CSF, reflecting disease progression, and that NfL might serve as a biomarker for clinical staging and functional decline.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the medical ethical review boards of the indicated cooperating universities. Written informed consent for participation and publication was obtained in accordance with institutional requirements, and the study fulfilled the principles of the Declaration of Helsinki.

Patient Data and Biosamples

We included patients with genetically confirmed LD (i.e., who tested positive for biallelic pathogenic variants in *EPM2A* or *NHLRC1*) treated at 3 referral centers in Ulm (Germany), Bologna (Italy), and Dallas (United States). Serum, CSF, and clinical data were collected from patients with LD and control probands and stored in the local biobanks according to recommended biobanking protocols at −80°C until use.

Clinical Scoring

LD Stage

The stage of disease progression may be evaluated using a disability scale based on the residual motor and mental functions, daily living activities, and social abilities previously described[16]: (0) asymptomatic; (1) mild cognitive and motor impairment, with preserved daily living activities and social interaction; (2) moderate mental decline, limitations in motor activities, and limited social interaction; (3) severe mental and motor impairment, needing help with walking, regular assistance in daily living activities, and poor social interaction; and (4) wheelchair-bound or bedridden, with no significant daily living activities or social interaction.[16]

LD Clinical Performance Scale

The LD Clinical Performance Scale (LDPS) assesses disease severity across 6 domains, each scored from 0 to 3: generalized tonic-clonic seizures, myoclonus, ambulation, cognition, speech, and function.[17] The total score ranges from 0 to 18, with lower scores indicating greater severity (eTable 1).

Measurement of NfL

The commercially available Simple Plex Human NfL Cartridge for the enzyme-linked lectin assay microfluidic system (Bio-Techne GmbH, Minneapolis) was used to measure NfL

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concentrations in serum and CSF, as previously described.[18] All samples were measured at the same time (batch analysis) in the same laboratory.

Statistical Analysis

For comparison of more than 2 groups without normal distribution of data, the Kruskal-Wallis test was used, followed by the Dunn multiple comparisons post hoc test. For comparison of 2 groups without a normal distribution of data, the Mann-Whitney test was used. Data are presented as means ± SEM in bar graphs. The hybrid Wilson/Brown method was used to compute the CI in the receiver operating characteristic (ROC) analyses. Nonparametric Spearman correlation was used to analyze sNfL/cNfL pairs. The Wilcoxon signed-rank test was used to test differences in NfL levels for longitudinal measures. Statistical significance is reported by the p value of the statistical test procedures and was assessed as significant (*, $p < 0.05$), strongly significant (**, $p < 0.01$), or highly significant (***, $p < 0.001$; ****, $p < 0.0001$). All statistical analyses were performed with Prism software (version 10.3.0; GraphPad Software).

Data Availability

All data can be found in this article and its supplementary data.

Results

We analyzed NfL levels in CSF (n = 32) and/or serum (n = 25) samples from a cohort of 31 patients with LD (26 independent families; mean age 21 years; age range 10.2–40.3; f:m = 16:15; *EPM2A*:*NHLRC1* = 16:15) at diverse disease stages, treated at 3 referral centers in Ulm (Germany), Bologna (Italy), and Dallas (United States). The control group consisted of 30 age-matched individuals (mean age 21.9 years; age range 11.1–41.3; f:m 22:8) presenting with transient, nonstructural neurologic conditions. Within the LD cohort, we collected a total of 57 samples: 11 matched pairs of serum and CSF samples from 10 patients, 21 serum-only samples from 17 patients, and 14 CSF-only samples from 6 patients. At each visit, we assessed LD stage (median LD stage 2; range 0–4) and LD clinical performance score (median score 10.5; range 0–18) (in the Methods section), which allowed for correlation with NfL measurements. Detailed clinical characteristics and individual NfL values of patients with LD and controls are provided in eTables 2 and 3. Summary statistics for serum and CSF NfL (sNfL and cNfL) levels are presented in eTable 4.

We first compared NfL levels between patients with LD (mean sNfL 13.95 pg/mL, 95% CI 11.20–16.69; mean cNfL 576.9 pg/mL, 95% CI 465.3–688.5) and controls (mean sNfL 7.72 pg/mL, 95% CI 6.79–8.65; mean cNfL 306.8 pg/mL, 95% CI 251.5–362.2). Both sNfL and cNfL values were elevated in patients with LD ($p < 0.0001$ for both sNfL and cNfL) (Figure 1, A–E). However, among the 11 serum and CSF sample pairs, no correlation was observed between sNfL and cNfL (Figure 1C). Notably, cNfL values exhibited less variability than sNfL, resulting in superior discriminatory performance between patients with LD and controls in ROC analyses (AUC sNfL = 0.80; cNfL = 0.88, $p < 0.0001$ for both sNfL and cNfL) (Figure 1, F and G). sNfL levels showed a stronger association with clinical disease stage (S0–S4, in the Methods section) than cNfL (S4 LD group vs controls: $p < 0.0001$ for sNfL vs $p = 0.01$ for cNfL) (Figure 1, H and I). Of interest, some presymptomatic individuals (S0) already displayed elevated cNfL levels prior to clinical disease onset, although these differences did not reach statistical significance, while this trend was less evident for sNfL. NfL levels in both serum and CSF did not differ between *EPM2A* and *NHLRC1* genotypes, but each genotype group per se showed higher levels compared with controls (Figure 1, J and K). Longitudinal samples were available for a subset of patients (sNfL, n = 5 [4 with 2 samples, 1 with 3 samples]; cNfL, n = 6 [4 with 2 samples, 2 with 3 samples]), obtained with variable time intervals (median 14 months, range 2–20 months). When sampling was performed ≥12 months after baseline, all 5 patients had an increase in cNfL (mean value 596 vs 396 pg/mL; $p = 0.06$) and 2 of 4 patients had an increase in sNfL (mean value 9.40 vs 8.78 pg/mL; $p = 0.6$), despite minimal to no variations in clinical disease severity (cNfL cohort, median change in LDPS score = 1; sNfL cohort, median change in LDPS score = 0) (Figure 1, L and M).

Next, we evaluated associations between NfL levels and clinical measures of disease progression, including disease duration, clinical stage, and LD performance score (LDPS, in the Methods section). We found that sNfL levels correlated with both disease stage ($r = 0.56$, $p = 0.0009$) and LDPS score ($r = -0.49$, $p = 0.0045$), but not with disease duration (Figure 2, A–C). Of note, homozygous carriers of the *NHLRC1* c.436G > A (p.D146N) variant clustered at lower sNfL levels, consistent with their milder clinical phenotype (Figure 2C). By contrast, cNfL values did not show statistically significant correlations with any of the clinical measures (Figure 2, D–F).

Discussion

In this study, we assessed serum and CSF NfL levels in a comparatively large, multicenter cohort of patients with LD and age-matched controls and examined their relationship with clinical measures of disease severity. We found that both sNfL and cNfL were elevated in LD, irrespective of whether *EPM2A* or *NHLRC1* was affected. cNfL demonstrated superior efficacy in distinguishing patients with LD from controls while sNfL levels better reflected clinical progression, correlating with functional disability as measured by LDPS score and disease stage. These findings underscore the potential of NfL levels as biomarkers of LD, which are currently lacking.

Of interest, we found that sNfL levels did not correlate with disease duration. This reflects the heterogeneous progression rates observed in LD, as evidenced by the distinct clustering of patients homozygous for the *NHLRC1* p.D146N variant.

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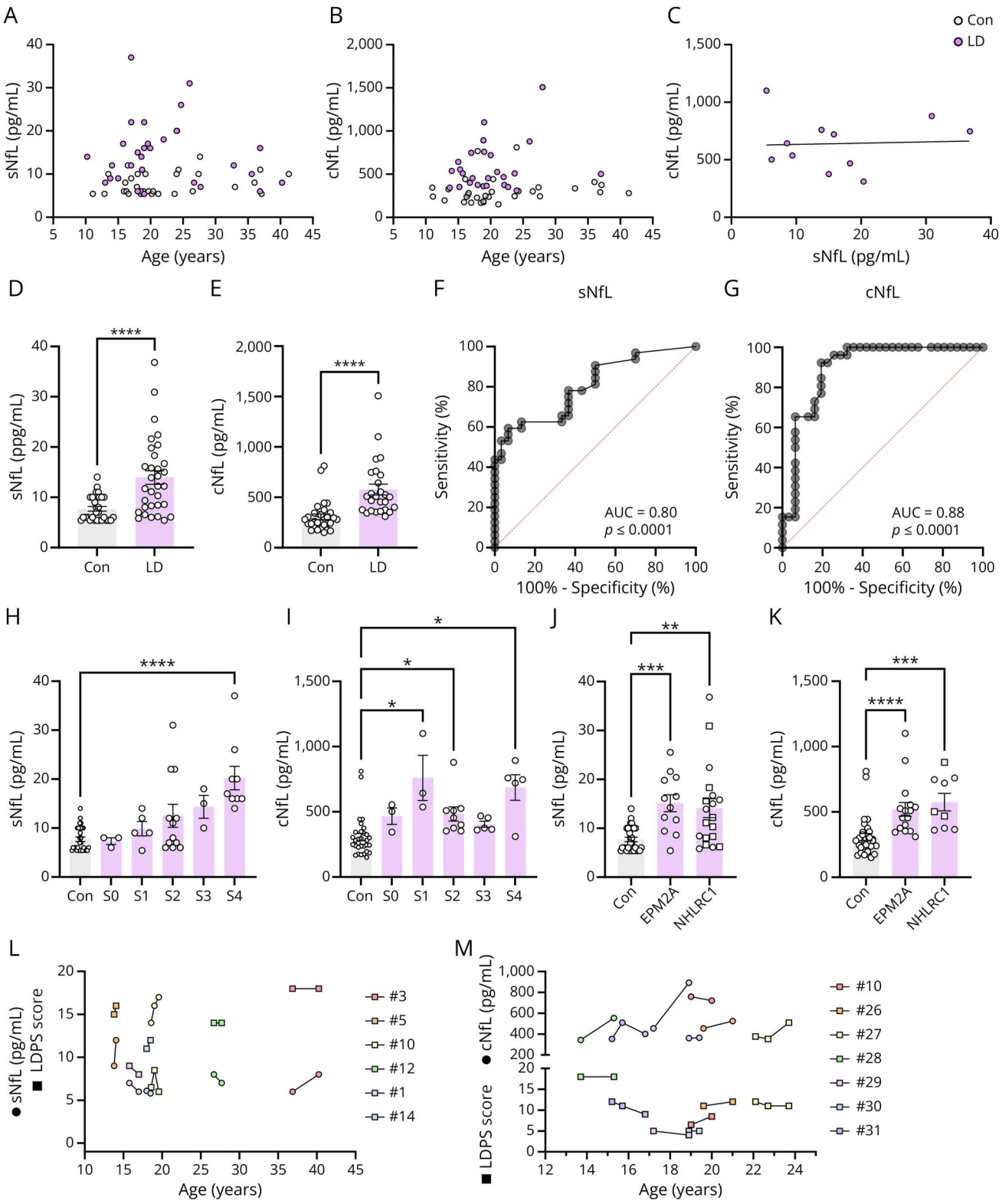
Figure 1 Serum and CSF NfL Levels in Patients With LD



(A and B) Serum and CSF NfL levels in patients with LD compared with in-house age-matched controls. (C) Correlation of available sNfL/cNfL pairs. (D and E) sNfL and cNfL levels in patients with LD vs controls. (F and G) ROC analysis comparing sNfL and cNfL levels between patients with LD and controls. (H and I) Group analysis of NfL levels of controls vs patients with LD grouped according to disease stages (ranging from S0, presymptomatic, to S4, end-stage disease). (J and K) Group analysis of NfL levels of patients with EPM2A or EPM2B vs controls. Patients bearing the *NHLRC1* p.D146N variant are indicated by square symbols. (L and M) Display of available longitudinal sNfL and cNfL measurements, stratified by Lafora disease Clinical Performance Scale (LDPS) score, ranging from 0 (most severe) to 18 (asymptomatic). cNfL = CSF neurofilament light chain; sNfL = serum neurofilament light chain.

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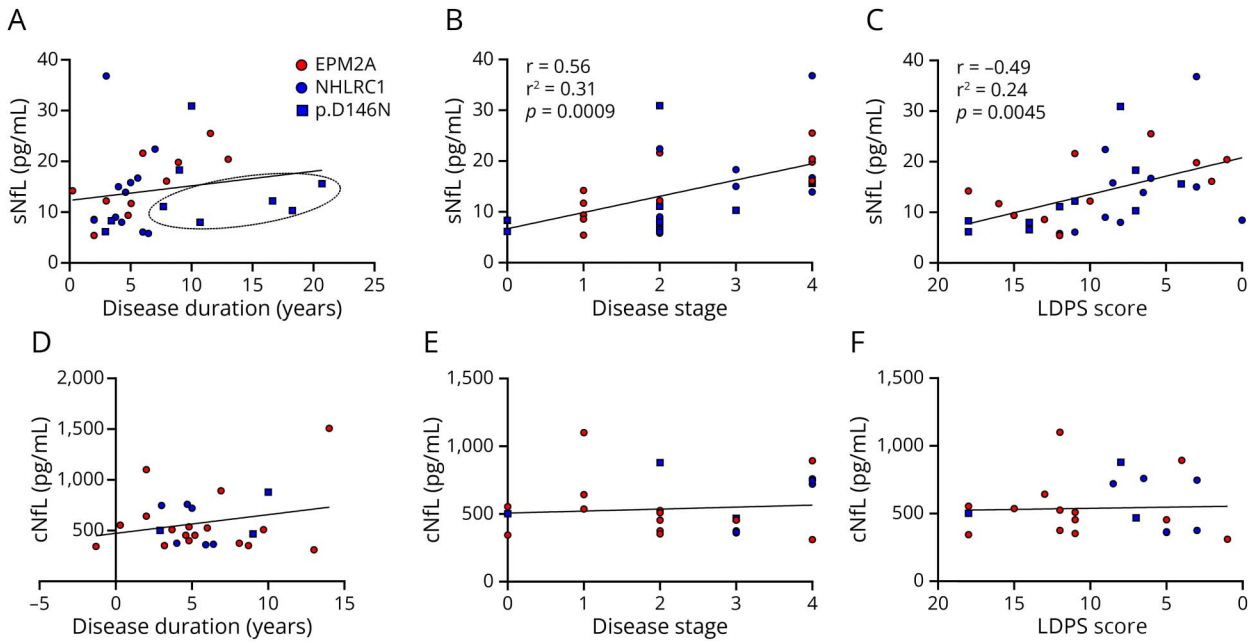
Figure 2 Correlation of Serum and CSF NfL Levels With Clinical Measures



(A and D) Correlation of sNfL or cNfL levels with disease duration. (B and E) Correlation of sNfL or cNfL levels with disease stage. (C and F) Correlation of sNfL or cNfL levels with LD performance score (LDPS). Only statistically significant correlations are indicated (nonparametric Spearman correlation). sNfL = neurofilament light chain.

These patients are known to present with milder phenotypes characterized by later onset, slower progression, and prolonged survival.[2] Consequently, disease duration alone is not a reliable proxy for disease progression in slowly progressive LD cases bearing (mild) hypomorphic pathogenic variants. Another relevant observation from our longitudinal data, although limited to a subset of participants, is that NfL levels, notably in CSF, tended to increase over time despite minimal changes in disease severity, suggesting their potential utility as dynamic biomarkers for tracking disease evolution.

Elevated NfL levels in LD can be attributed to several factors. First, LD is a neurodegenerative condition that primarily affects the CNS but may also involve the peripheral nervous system (PNS) to a lesser extent.[15] Damage to both the CNS and PNS is associated with increased NfL levels.[7,19] Second, LD is a progressive epilepsy with highly frequent tonic-clonic seizures and episodes of status epilepticus, conditions linked to increased NfL levels.[14]

In our study, we found that sNfL and cNfL did not correlate with each other, suggesting distinct release dynamics or sources of release: cNfL likely reflects CNS damage more directly, possibly capturing earlier pathologic changes, while sNfL may further reflect PNS involvement. Moreover, the sNfL data set was larger, enhancing statistical robustness.

This study has some limitations, largely inherent to the ultra-rareness of LD (prevalence <1/million people). The number of CSF samples was relatively small (n = 17), compared with 28 available serum samples, and paired serum-CSF samples were available in only 10 patients. In addition, longitudinal measurements were limited to a minority of patients. Future studies should aim to include a larger cohort of patients with longitudinal measures, ideally incorporating additional clinical end points such as neuropsychological assessment, neuroimaging, and quantitative EEG, which were not addressed in this analysis.

An intriguing area for future investigation is whether NfL levels respond to disease-modifying therapies, as has been demonstrated in other neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) and multiple sclerosis.[8] In ALS, NfL levels remain relatively constant at a plateau during the disease, and response to therapy with the ASO tofersen is reflected by reduction in NfL levels at single-patient level in SOD1-ALS.[20] Clinical trials of ION283 (NCT06609889) and VAL-1221 (EudraCT 2023-000185-34) in LD offer unique opportunities to explore the question whether NfL levels are drug-responsive using archived biosamples. Given that NfL levels did not change significantly over short time frames (<1 year), NfL could be compared between baseline (untreated) and after treatment to evaluate responsiveness of NfL levels to therapy—similarly, to how it is performed in SOD1-ALS.[20]

In summary, our findings support the utility of NfL, particularly sNfL, as a promising biomarker for disease progression in LD. While further research is needed to fully elucidate the potential of NfL in this context, it holds immediate promise as

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an exploratory outcome measure in ongoing and future clinical trials. Larger, well-characterized cohorts will be essential to establish NfL's role in monitoring disease activity and therapeutic response in LD.

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Author Contributions

L. Muccioli: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. B. Ganceviciute: major role in the acquisition of data. F. Becker: major role in the acquisition of data. R. Minardi: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Tappatà: major role in the acquisition of data. F. Bachhuber: analysis or interpretation of data. M. Alkhatib: major role in the acquisition of data. S. Cirak: major role in the acquisition of data. J. Weishaupt: major role in the acquisition of data. M. Verma: major role in the acquisition of data. H. Tumani: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. J. Wagner: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. S. Messahel: major role in the acquisition of data. F Nitschke: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. B.A. Minassian: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. F. Bisulli: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. D. Brenner: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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Disclosure

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