REPLY

# Reply to: Mathematical Comments on Linking Neurofilament Light Chain Levels to Disease Severity in Hereditary Spastic Paraplegia Subtypes SPG11 and SPG15

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We thank Dr. Fischer for his thoughtful engagement with our report.[1] His commentary proposes that neurofilament light chain (NfL) levels reflect the *rate* of ongoing axonal loss, whereas disease severity accumulates as its *integral* over time,[2] such that a cross-sectional correlation between the two is not mathematically expected when the NfL trace is nonmonotonic. We find substantial convergence between this framework and our empirical findings and offer several clarifications and caveats.

Our data are consistent with the proposed model. The inverse association of plasma NfL (pNfL) with age ($\rho = -0.463$, $P < 0.001$) and piecewise regression inflection points at 18.3 and 33.9 years align with a peak-shaped NfL trajectory that antecedes cumulative clinical severity. We wish to clarify, however, that our conclusions did not assert that pNfL lacks clinical utility. We explicitly described elevated pNfL as reflecting "early neuroaxonal injury" and as a potential marker that can further support a clinical and molecular diagnosis. What our data did not support was the use of a single, cross-sectional baseline value as a prognostic surrogate for future disease progression - a distinct question not addressed by cross-sectional correlation alone. Our prospective analysis of 23 patients with longitudinal Spastic Paraplegia Rating Scale (SPRS) data found no association between baseline pNfL and annualized progression ($P = 0.278$), a finding not directly predicted by the integral model.

We commend the simulation as a valuable conceptual contribution, while noting that its key parameters - the NfL peak timing, rate of post-peak decline, and mapping to SPRS - are assumed rather than derived from empirically measured HSP-*SPG11*/HSP-*ZFYVE26* trajectories, where individual heterogeneity is substantial. Furthermore, the assumption that pNfL tightly reflects instantaneous axonal loss rate is complicated by kinetic evidence that NfL release into the extracellular compartment involves active, delayed mechanisms with a cerebrospinal fluid (CSF) half-life exceeding 3 months,[3,4] further cautioning against simple proportionality between measured NfL levels and the rate of ongoing axonal loss.

We share the optimism that longitudinal pNfL *change* may be a more sensitive trial endpoint than cross-sectional SPRS, as supported by precedents from multiple sclerosis, spinal muscular atrophy, and Huntington's disease.[3,5,6] However, most patients in our longitudinal cohort exhibited stable or declining pNfL over 1–5 years of follow-up (fig. 2C in Ref. 1), consistent with a post-peak trajectory in which treatment-related reductions would need to be distinguished from physiological decline. Scenarios of slow progression or limited compound efficacy further underscore the need for pretreatment run-in measurements and empirical characterization of within-individual NfL trajectories before pNfL can be confidently deployed as a trial endpoint in HSP-*SPG11* and HSP-*ZFYVE26*.

In conclusion, the commentary's framework and our empirical findings converge on a common view: pNfL is most informative early in the disease course, and longitudinal rather than cross-sectional measurements will

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be essential for its application in therapeutic trials.[1,7] Realizing this potential will require natural history studies with dense longitudinal sampling, complementary biomarkers, and composite clinical endpoints - goals we look forward to pursuing collaboratively in the Spastic Paraplegia Centers of Excellence Research Network (SP-CERN, https://sp-cern.rarediseasesnetwork.org/) and with international partners.

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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.

# References


1. Agianda HAP, Alecu JE, Tam A, et al. Longitudinal dynamics of plasma neurofilament light chain in hereditary spastic paraplegia type 11 (HSP-SPG11) and type 15 (HSP-ZFYVE26). Mov Disord 2025;41 (3):785–791. https://doi.org/10.1002/mds.70142
2. Fischer G. Mathematical comments on linking neurofilament light chain levels to disease severity in HSP subtypes SPG11 and SPG15. Mov Disord 2026;
3. Khalil M, Teunissen CE, Lehmann S, et al. Neurofilaments as biomarkers in neurological disorders — towards clinical application. Nat Rev Neurol 2024;20:269–287.
4. Leckey M, Giovannucci TA, Coulton JB, et al. Neurofilament light chain kinetics and release mechanisms in the central nervous system: implications for biomarker interpretation. Brain Commun 2025;7(6): fcaf468. https://doi.org/10.1093/braincomms/fcaf468
5. Freedman MS, Gnanapavan S, Booth RA, et al. Guidance for use of neurofilament light chain as a cerebrospinal fluid and blood biomarker in multiple sclerosis management. EBioMedicine 2024;101: 104970.
6. Miller T, Cudkowicz ME, Genge A, et al. Trial of antisense oligonucleotide tofersen for SOD1 ALS. N Engl J Med 2020;383:109–119.
7. Krumm L, Winkler J, Winner B, Regensburger M. Plasma neurofilaments: potential biomarkers of SPG11-related hereditary spastic paraplegia. Mov Disord 2024;39(4):755–757.