Plasma Neurofilament Light for Prediction of Disease Progression in Familial Frontotemporal Lobar Degeneration

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Study Question
Do plasma NfL levels identify familial-FTLD mutation carriers at risk of clinical progression?

What Is Known and What This Paper Adds
Blood NfL is elevated in patients with sporadic FTLD and familial-FTLD. This study provides Class I evidence that in asymptomatic carriers of FTLD-causing mutations, elevation of plasma NfL is associated with short-term risk of clinical progression.

Methods
For these longitudinal analyses, the investigators analyzed data from members of families affected by FTLD. The original cohort comprised 277 individuals recruited through 19 North American centers, and the validation cohort comprised 297 individuals recruited through 25 centers in Europe and Canada. These individuals included symptomatic mutation-carriers, asymptomatic mutation-carriers, and mutation non-carriers, and they underwent standardized annual neurologic evaluations, neuropsychological testing, and brain MRI scans for ≤3 years in the original cohort and ≤2 years in the validation cohort. Baseline plasma NfL levels were quantified using single-molecule array methods. Linear mixed-effects models were used to test for associations between plasma NfL levels and clinical outcomes.

Results and Study Limitations
Baseline plasma NfL levels were higher in asymptomatic mutation-carriers who underwent phenoconversion or disease progression than in nonconverters (original: 11.4 ± 13.7 pg/mL vs 6.7 ± 5 pg/mL, p = 0.002; validation: 14.1 ± 12 pg/mL vs 8.7 ± 6 pg/mL, p = 0.035). Plasma NfL levels also differentiated symptomatic mutation-carriers from asymptomatic mutation-carriers or individuals with prodromal disease (original cohort cut-off: 13.6 pg/mL, 87.5% sensitivity, 82.7% specificity; validation cohort cut-off: 19.8 pg/mL, 87.4% sensitivity, 84.3% specificity). Higher baseline plasma NfL levels correlated with worse longitudinal changes in FTLD severity measures, neuropsychological function metrics, and brain atrophy measures regardless of genotype or baseline disease severity, even in asymptomatic mutation-carriers. The present study’s limitations include NfL’s nonspecificity as a neuronal injury biomarker.

Study Funding and Competing Interests
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Figure
Disease Severity in Asymptomatic FTLD Mutation Carriers

High plasma NfL at baseline was associated with worse severity scores at 2 years.

A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The corresponding author(s) of the full-length article and the journal editors edited and approved the final version.

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