NEJM Journal Watch

NEJMGROUP.ORG

Plasma NfL Levels in Familial Frontotemporal Lobar Degeneration

Plasma neurofilament light chain concentrations may inform phenoconversion and disease progression in familial frontotemporal lobar degeneration.

In this study, researchers analyzed whether plasma neurofilament light chain (NfL) levels, a sensitive biomarker for neurodegeneration, could predict individuals with familial frontotemporal lobar degeneration (FTLD) who were at risk for clinical phenoconversion or disease progression from an original (n=277) and validation (n=297) cohort. Carriers included those with *C9orf72*, *GRN*, or *MAPT* mutations. Participants underwent neurologic assessments, caregiver/companion interviews, neuropsychological testing, neuroimaging, and clinical scales over 2 to 3 years. Clinical phenotypes were classified as asymptomatic, prodromal with mild behavioral impairment or mild cognitive impairment (MBI/MCI), and full phenotype (behavioral variant frontotemporal dementia, frontotemporal dementia with amyotrophic lateral sclerosis, primary progressive aphasia, or corticobasal syndrome).

Median baseline plasma NfL concentrations were higher in those with full phenotype than in asymptomatic noncarriers, asymptomatic carriers, and those with MBI/MCI; this difference was true in both cohorts and in those with all genotypes except for *C9orf72*. Within the *C9orf72* group, median baseline plasma NfL concentrations were higher in those with the full phenotype compared with asymptomatic carriers and noncarriers and in those with MBI/MCI compared with asymptomatic carriers. Higher median baseline plasma NfL concentrations were associated with phenoconversion after 2 years among asymptomatic individuals in both cohorts and among those with MBI/MCI in the validation cohort. A plasma NfL concentration cut point of ≥13.6 pg/mL in the original cohort and ≥19.8 pg/mL in the validation cohort showed an 87% to 88% sensitivity and 83% to 84% specificity in discriminating between individuals with the full phenotype versus asymptomatic or MBI/MCI individuals. These cut points also predicted clinical progression in the asymptomatic carrier, MBI/MCI, and full phenotype groups.

COMMENT

Plasma NfL concentrations may predict those with familial FTLD who are at risk for clinical progression, including asymptomatic mutation carriers. Those who have concentrations above a certain cut point may be at increased risk. Understanding whether plasma NfL concentrations can predict clinical phenotype may also assist in counseling those with familial FTLD in the future.

— Jennifer Rose V. Molano, MD

Dr. Molano is Associate Professor, Department of Neurology and Rehabilitation Medicine, University of Cincinnati.

Rojas JC et al. Plasma neurofilament light for prediction of disease progression in familial frontotemporal lobar degeneration. **Neurology** *2021 Apr 7; [e-pub]. (https://doi.org/10.1212/WNL.0000000000011848)*

Note to readers: At the time we reviewed this paper, its publisher noted that it was not in final form and that subsequent changes might be made.