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Clinical value of serum neurofilament light chain in prodromal genetic frontotemporal dementia

Lucia Giannini, Emma van der Ende, Jackie Poos, Lize Jiskoot, Elise Dopper, Yolande Pijnenburg, Janne Papma, Eline Willemse, Lisa Vermunt, Charlotte Teunissen, John van Swieten, Harro Seelaar, Lieke Meeter

State-of-the-art: Elevated serum neurofilament light chain (NfL) is currently used as entry criterion for clinical trials targeting the prodromal stage of genetic frontotemporal dementia (FTD). Assessing NfL levels specifically in the presymptomatic-to-prodromal transition is needed to understand its clinical value in this stage.
Methodology: We studied a longitudinal cohort of mutation carriers including 61 non-converters (11=*MAPT*, 30=*GRN*, 20=*C9orf72*) and 21 converters (5=*MAPT*, 10=*GRN*, 5=*C9orf72*, 1=*TARDBP*). Serum NfL measured using Simoa NF-light assay was z-score-transformed using age-matched control data. We examined the diagnostic accuracy of cross-sectional NfL z-scores shortly before and after (±1.5 year) conversion to prodromal stage (FTD-CDR=0.5), and of annualized deltas of raw NfL scores between these time-points, compared to non-converter values. Next, we analyzed longitudinal trajectories of NfL z-scores using linear mixed-effects modeling.
Results: Converters had 1.43±0.93 mean NfL z-score (corresponding to 19.2±9.1 pg/mL raw score) shortly before conversion to prodromal stage, 2.43±1.29 (29.2±13.9 pg/mL) shortly after, and 3.13±4.69 pg/mL/year mean annualized delta. Non-converters had 0.15±0.73 mean NfL z-score (8.7±4.4 pg/mL) and 0.39±1.33 pg/mL/year mean annualized delta. Shortly before conversion, a ROC-estimated optimal cut-off of 0.94 for NfL z-scores had 72.7% sensitivity and 88.5% specificity (AUC=0.86) to distinguish converters from non-converters. Shortly after conversion, a cut-off of 1.72 had 80.0% sensitivity and 96.7% specificity (AUC=0.94). Annualized deltas (cut-off 1.45) had 77.8% sensitivity and 85.3% specificity (AUC=0.83). Longitudinal trajectories of NfL z-scores showed increase in converters relative to non-converters, which varied somewhat by mutated gene ($p<0.001$).
Conclusion: Serum NfL is useful to clinically predict and diagnose prodromal genetic FTD.

Conflicts of interest

No disclosures