POLY-GP DIPEPTIDE REPEATS AND NEUROFILAMENT LIGHT CHAIN AS BIOMARKERS IN PRESYMPTOMATIC AND SYMPTOMATIC FRONTOTEMPORAL DEMENTIA CAUSED BY C9ORF72 REPEAT EXPANSIONS

Lieke H.H. Meeter, Tania F. Gendron, Ana C. Sias, Lize C. Jiskoot, Caroline Graff, Adam L. Boxer, Raquel Sánchez-Valle, Yolande A.L. Pijnenburg, Luisa Benussi, Roberta Ghidoni, Barbara Borroni, Robert Laforce Jr., M. Jorge Cardoso, Sebastien Ourselin, David M. Cash, Martina Bocchetta, Jonathan D. Rohrer, Leonard Petrucelli, John C. van Swieten, Suzee Lee

Background

A pathogenic repeat expansion in chromosome 9 open reading frame 72 (C9orf72) is the most common genetic cause of frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). Therapies that target C9orf72 repeat expansions will enter clinical trials this year and robust monitoring markers are critically needed, but to date, lacking. C9orf72 repeat expansions are translated via repeat-associated non-ATG (RAN) translation into repeating dipeptide units. One of these dipeptide-repeats, poly(GP), is detectable in the cerebrospinal fluid (CSF) of presymptomatic carriers and patients with C9orf72-ALS and thus shows promise as a potential pharmacodynamic biomarker. In contrast, neurofilament light chain (NfL), a marker for axonal death, is elevated in neurodegenerative diseases in general, including C9orf72-FTD and C9orf72-ALS, but remains at normal levels during the presymptomatic phase. Thus, we aimed to compare poly(GP) and NfL in presymptomatic and symptomatic carriers and identify potential associated gray matter deficits.

Methods

poly(GP) and NfL were measured in CSF samples from GENFI sites and an American cohort: 12 controls, 25 presymptomatic C9orf72 carriers and 66 C9orf72 patients, including 38 behavioral variant FTD, 2 ALS, 9 FTD-MND. Presymptomatic carriers were required to have no behavioral, cognitive or motor changes. Comparisons of poly(GP) and NfL levels between groups and associations with clinical characteristics (phenotype, cognitive scales, survival) and regional brain volumes (both region of interest and voxel-wise analyses) were explored.

Results

CSF poly(GP) was absent in controls and elevated in C9orf72 carriers, without statistical differences between presymptomatic carriers and patients (medians respectively 0.75 and 1.44 ng/ml, $p=0.11$, Figure 1). CSF NfL levels were higher in patients (1915 pg/ml) than in presymptomatic carriers (429 pg/ml, $p<0.001$, Figure 2), and controls (333 pg/ml, $p<0.001$), without difference between the latter two groups ($p=0.79$). CSF poly(GP) did not correlate with CSF NfL ($rs=0.08$, $p=0.47$) in the C9orf72 carriers.

Conclusions

Poly(GP) is detectable in presymptomatic and symptomatic C9orf72 repeat expansion carriers and thus a potential pharmacodynamic biomarker, whereas NfL may additionally be helpful for disease staging. Abnormalities in CSF poly(GP) and NfL levels show promise as complementary biomarkers reflecting different phases during the C9orf72 lifespan.