p-282

Friday

Neuropathological burden in presymptomatic and early-stage frontotemporal lobar degeneration with *MAPT* pathogenic variants

Lucia Giannini, Merel Mol, Lana Sarkar, Sanaz Arezoumandan, Daniel Ohm, David Irwin, Annemieke Rozemuller, John van Swieten, Harro Seelaar

State-of-the-art: *MAPT* pathogenic variants cause frontotemporal lobar degeneration (FTLD), characterized by frontotemporal paralimbic disease at end-stage, with heterogeneous inclusion morphologies and tau isoform conformation. Early-stage tissue has not been described before in FTLD-MAPT and could inform microscopic patterns of disease onset and spread.

Methodology: We obtained presymptomatic/early-stage tissue from 1 presymptomatic case with L315R variant and 2 early-stage symptomatic cases (1 P301L, 1 G272V), who died of causes unrelated to FTLD. We examined neuronal degeneration and digitally quantified tau burden in 10 cortical neuroanatomical regions from frontal, temporal and parietal lobes, and 3 subcortical regions (i.e. striatum, hippocampus, amygdala). We compared presymptomatic/early-stage neuropathological features to an intermediate/end-stage cohort with the same variants (2 L315R, 10 P301L, 6 G272V).

Results: The 68-year-old presymptomatic L315R case had no neuronal degeneration, limited tau burden morphologically similar to L315R end-stage cases in middle frontal, antero-inferior temporal and inferior parietal cortex, amygdala and striatum, next to age-related Alzheimer change in the (para-)hippocampus (Braak 3). The 59-year-old early-stage P301L case had mild-to-moderate frontotemporal neuronal degeneration and highest tau burden in anterior cingulate, anterior temporal and superior frontal cortex, and amygdala. The 45-year-old early-stage G272V case had mild frontotemporal neuronal degeneration and highest tau burden in subiculum, CA1, fronto-insular, superior frontal and anterior cingulate cortex. Including intermediate/end-stage cases, we are developing a neuroanatomical staging model of these *MAPT* variants, postulating variant-specific patterns of tau spread.

Conclusion: Tau pathology is present in presymptomatic/early-stage FTLD-MAPT and shows divergent early-stage distribution in specific variants, potentially related to different underlying mechanisms.

Conflicts of interest

Nothing to disclose