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Anatomic selectivity of neuronal and glial tau in Primary Progressive Aphasia with 4R FTLD-tauopathies

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State of the art: Primary Progressive Aphasia (PPA) can present with underlying 4R-FTLD-tauopathies such as corticobasal degeneration (CBD) or progressive supranuclear palsy (PSP). This study investigated clinicopathologic concordance between PPA and regional distributions of 4R-FTLD PSP and CBD markers in language-related cortical areas and the dentate gyrus (DG) of the hippocampus.
Methodology: Sections were stained immunohistochemically with AT-8 to visualize neuronal inclusions, tufted astrocytes, and coiled bodies in 8 right-handed PPA cases with PSP. Unbiased stereology was performed in bilateral middle frontal gyrus (MFG), inferior parietal lobule (IPL), and left DG. Tau distributions were also analyzed in cases with CBD (N=4; neuronal inclusions, astrocytic plaques, and coiled bodies). One-way ANOVAs and students' t-tests were used to analyze distributions.
Results: The PSP group displayed left-sided asymmetric neocortical predominance of total tau pathology ($p<0.05$). All cortical regions in PSP had significantly more glial tau pathology (astrocytes + coiled bodies) compared to neuronal inclusions, with a ~5-fold difference in left MFG ($p<0.05$). CBD cases had significantly more neuronal inclusions than PSP in all regions, with a ~20-fold difference in DG ($p<0.01$). PSP cases displayed more glial pathology in all regions compared to CBD, with a ~10-fold difference in coiled bodies in left MFG ($p<0.05$).
Conclusions: Our finding of leftward neocortical predominance of pathology in PPA with FTLD-PSP is concordant with the aphasic phenotype. In PPA, pathologic burden in CBD is primarily neuronal, while PSP is characterized by considerably higher glial tau, offering insights into the selective vulnerability of distinct cell populations within 4R-tauopathies.

Conflicts of interest

Nothing to disclose