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Burden of pathology in hippocampal subregions can distinguish amnestic dementia with comorbid Alzheimer's and TDP-43 pathology from pure Alzheimer's and FTLD-TDP

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State of the Art. We investigated hippocampal tau and TDP-43 positivity in individuals with amnestic dementia due to Alzheimer's disease and TDP-43 (AD/TDP), due to Alzheimer's disease alone (AD), and non-amnestic dementia due to TDP-43 proteinopathy associated with frontotemporal lobar degeneration (FTLD-TDP).

Methodology. Seventeen individuals with AD/TDP, 14 individuals with AD, and 19 individuals with FTLD-TDP were identified from the Northwestern AD Research Center brain bank. AD/TDP and AD cases carried an antemortem diagnosis of amnestic dementia and FTLD-TDP cases carried a clinical diagnosis of primary progressive aphasia or behavioral variant frontotemporal dementia. Paraffin-embedded sections from left hippocampi were stained immunohistochemically with phosphorylated TDP-43 and AT-8 antibodies to visualize TDP-43 and tau-positive immunoreactivity, respectively. HALO software (Indica Labs) was used to generate percent area occupied by immunopositivity in the dentate gyrus (DG), CA1, and CA3 subfields of the hippocampal complex. Student t-tests and one-way ANOVAs were used to determine group differences.

Results. As expected, TDP-43 immunoreactivity was significantly greater across CA1, CA3, and DG in FTLD-TDP compared to AD/TDP ($p<0.05$). In AD/TDP, TDP-43 immunoreactivity was low across all hippocampal subregions with CA1 showing greatest relative TDP-43 burden, whereas in FTLD-TDP the DG was most affected. Interestingly, AT-8 immunoreactivity was significantly greater in DG and CA3 in AD/TDP compared to pure AD ($p<0.05$).

Conclusion. AD/TDP can be distinguished from AD and FTLD-TDP based on differential regional distribution of tau and TDP-43 pathology in the hippocampus. Findings suggest that the severity of neurofibrillary degeneration in AD/TDP may be influenced by TDP-43 proteinopathy.

Conflicts of interest

No disclosures to report.