Clinical features of limbic and subcortical Pick body distribution in behavioral variant Frontotemporal Dementia (bvFTD)

Rachel Keszycki1,3, Allegra Kawles1, Grace Minogue1, Stacey Juthapan1, Michaela Riley1, Callen Spencer1, Jaclyn Lilek1, Ivan Ayala1, Robert Shepard1, Kaouther Ajroud2, Alexander Feldman2, Qinwen Mao2, Margaret E. Flanagan2, Sandra Weintraub1,3, M.-Marcel Mesulam2, Eileen Bigio2, Changiz Geula1, Tamar Gefen1,3

1Mesulam Center for Cognitive Neurology & Alzheimer’s, Northwestern University; 2Department of Pathology, Northwestern University Feinberg School of Medicine; 3Department of Psychiatry, Northwestern University Feinberg School of Medicine

Introduction: Behavioral variant frontotemporal dementia (bvFTD) is an early-onset dementia syndrome characterized by progressive decline in executive functioning and comportment. Several pathologies may underlie the pattern of bilateral, frontotemporal cortical atrophy typically observed in this syndrome, including Pick’s disease (“PiD”), a 3R tauopathy. This study examined the clinical features of bvFTD with PiD. Unbiased stereological counting permitted clinicopathologic correlations between Pick bodies and antemortem features in cortical, limbic, and subcortical brain regions.

Methods: Six right-handed participants with antemortem clinical diagnoses of bvFTD and autopsy confirmed PiD were selected from the Northwestern University Alzheimer’s Disease Center brain bank. Twelve neuropsychiatric symptoms (NPS) were assessed longitudinally (M=1.10 years between visits) with the Neuropsychiatric Inventory—Questionnaire (NPI-Q), an informant-based screener. AT-8 immunostaining identified Pick bodies, which were quantified via unbiased stereological analysis across bilateral middle frontal gyrus (MFG), inferior parietal lobule (IPL), superior temporal gyrus (STG), dentate gyrus (DG) and CA1 region of the hippocampal complex, and unilateral caudate, amygdala, and anterior cingulate cortex (ACC).

Results: Average age of disease onset was 59.5 years (range, 46-70 years). Mean disease duration was 11.5 years (range, 8-14 years), with average age of death at 71 years (range, 58-82 years). Results of a paired t-test revealed a significant increase in total NPS from initial visit to final visit before death (p<0.05). Pick body density was highest in DG (M=71652 per mm^3), followed by caudate (M=58951 per mm^3), then CA1 (M=42994 per mm^3). Pearson correlations showed a significant, positive correlation between age of onset and Pick bodies in ACC (r = 0.94, p<0.01). Interestingly, densities of Pick bodies in caudate were positively associated with disease duration (r = 0.98, p<0.01).

Conclusions: Later disease onset seems to be associated with greater Pick bodies in the ACC. The vulnerability of the caudate to pathology appears to be related to disease duration and the emergence of NPS over time. While frontotemporal cortical atrophy is typically associated with clinical symptoms in bvFTD, this study demonstrates that at the cellular level, Pick bodies in limbic and subcortical brain regions also have significant clinical relevance.