Poster 2

Characterization of apathy-like behaviors and their relationship to Aβ pathology in5xFAD mice

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Background: Alzheimer's disease (AD) is a neurodegenerative disease that causes progressive cognitive decline and neuropsychiatric symptoms (NPS) with apathy being highly common. The neurobiological mechanisms of apathy in AD are unclear. This study characterized apathy-like behaviors in 5xFAD mice and their relationship to amyloid-beta (Aβ) pathology in the hippocampus and prefrontal cortex (PFC).

Methods: We examined apathy-like behavior in male and female 5xFAD mice and wildtype controls at 6, 12, and 16 months of age (n = 9-14 per group). Behavioral paradigms included nest building, marble burying, and food burrowing, and we calculated apathy composite scores for each mouse from the results of these three tests. Then, we measured soluble Aβ42 in the hippocampus and PFC of the male and female 5xFAD mice with the highest and lowest apathy composites within each age group by ELISA assay. Finally, we characterized Aβ plaque density and size in the hippocampal CA1 subregion and the PFC using thioflavin-S staining and ImageJ. We conducted linear regressions to determine the effects of age, gender, genotype, or apathy status on behavioral and biochemical outcomes.

Results: Apathy-like behaviors occurred in 5xFAD mice at all ages ($p < 0.001$ at 6, 12, and 16 months), were more prominent in females, and worsened with age. In the PFC, soluble Aβ42 was greater in high-apathy than in low-apathy 5xFAD mice ($p = 0.042$) and greater at 12 and 16 months than at 6 months of age ($p < 0.05$ and $p < 0.001$, respectively). Females had more plaques than males in the PFC overall ($p = 0.003$). Plaques were larger in high-apathy than in low-apathy 5xFAD mice ($p < 0.10$) and at 6 months compared to other ages (12 months $p = 0.034$, 16 months $p < 0.05$). In the hippocampus, soluble Aβ42 was greater at 16 months than at younger ages (both $p < 0.001$) and greater at 12 than at 6 months of age ($p = 0.006$). High apathy was associated with a greater density of hippocampal plaques than low apathy in certain groups (6-month males $p < 0.10$, 12-month females $p < 0.05$).

Conclusions: Findings suggest that apathy-like behaviors start at 6 months in 5xFAD mice, significantly worsen with age, and potentially differ between sexes. Additionally, our study demonstrates that apathy correlates positively with soluble and insoluble Aβ pathology with exact relationships varying by brain region.

Lay Language: Alzheimer's disease (AD) is characterized by pathology accumulating and spreading throughout the brain, leading to significant cognitive decline. Many AD patients also develop behavioral symptoms with apathy being the most common. Researchers often use mouse models of AD to study relationships between brain pathology and cognitive impairment in great detail; however, relatively fewer animal studies have focused on behavioral symptoms in AD. We investigated apathy in a mouse model of AD in this study and found that apathetic behaviors emerged at an early age, worsened with disease progression, and correlated with more severe brain pathology. Our results suggest that apathy may be an early indicator of underlying AD and likely worsens with the progression of pathology in the brain. Further, mouse models are useful for studying behavioral symptoms in AD, and future studies with this focus have the potential to identify early targets for intervention.

Poster 9

Concordance between Neocortical Distribution of Pick's Disease and the Salience of Distinct Dementia Phenotypes

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Background: Frontotemporal lobar degeneration of the tau form (FTLD-tau) is a neurodegenerative disease that leads to different dementia syndromes. For example, primary progressive aphasia (PPA) is characterized by an isolated and progressive impairment of language, and focal atrophy of left-hemispheric regions. In contrast, behavioral variant of frontotemporal dementia (bvFTD) is characterized by progressive dysfunction in personality, and atrophy in bilateral frontal regions. Interestingly, both PPA and bvFTD can be caused by the common 3R FTLD-tauopathy of Pick's disease (PiD). This stereological study investigated the cortical distribution of Pick bodies in bvFTD and PPA to establish clinicopathologic concordance between Pick's disease and the salience of the aphasic versus behavioral phenotype.

Methods: 12 right-handed cases with PiD as the sole pathologic diagnosis were identified from the Northwestern University Alzheimer's Disease Center brain bank (bvFTD, N=6; PPA, N=6). Paraffin-embedded sections were stained immunohistochemically with AT-8 to visualize Pick bodies. Unbiased stereological analysis (MicroBrightField, MBF Bioscience) was performed on all 12 cases in 3 regions bilaterally [middle frontal gyrus (MFG), inferior parietal lobule (IPL), superior temporal gyrus (STG)] and unilaterally in occipital cortex (OCC). Bilateral anterior temporal lobe (ATL) was analyzed in PPA cases only. Paired t-tests and one-way nonparametric ANOVAs were used to compare regional and hemispheric distribution within and between groups.

Results: Highest densities of Pick bodies were found in ATL (M=31,634; SD=10,502) in PPA, whereas peak densities were evident in the MFG (M=26,036; SD=8,719) in bvFTD. In PPA cases, there was leftward asymmetry of Pick bodies in MFG, IPL, and STG, the latter of which reached statistical significance ($p<0.05$; L>R). Interestingly, the ATL showed slight rightward predominance. Cortical distributions of Pick bodies in bvFTD were generally symmetric. As expected, the occipital cortex showed extremely sparse to no pathology in both groups.

Conclusions: Stereological quantitation confirms that the distribution of Pick body pathology is concordant with salient clinical features unique to PPA vs bvFTD. In bvFTD, Pick bodies were symmetric and highest in MFG, a region implicated in behavior/comportment, while in PPA, Pick bodies showed leftward asymmetry consistent with the aphasic phenotype. The vulnerability of the ATL to Pick's disease is remarkable, raising future questions about its functional significance within the human language network and the relationship of tau pathology to neuronal degeneration.

Lay Language: Frontotemporal lobar degeneration caused by the protein tau (FTLD-tau) is a neurodegenerative disease found at autopsy that leads to different dementia syndromes. Types of FTLD-tau can cause primary progressive aphasia (PPA), characterized by progressive impairment of language and primary atrophy of left-brain regions. It can also cause behavioral variant of frontotemporal dementia (bvFTD), a dementia characterized by progressive dysfunction in personality, and atrophy in frontal regions. Interestingly, both PPA and bvFTD can be caused by a FTLD-tau subtype called Pick's disease (PiD). This study investigated the distribution of PiD pathology in various brain regions in bvFTD and PPA to establish important relationships between burden and location of the disease at death, and clinical symptoms demonstrated during life.

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Characterization of Distinct Neuropsychiatric Trajectories in FTLD-tauopathies

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Introduction: Frontotemporal lobar degeneration (FTLD) is a neurodegenerative disease commonly caused by 3R (Pick's disease, "PiD") or 4R tauopathies (corticobasal degeneration, "CBD" and progressive supranuclear palsy, "PSP"). FTLD-tauopathies can lead to language decline in primary progressive aphasia (PPA) or personality/comportmental changes in behavioral variant frontotemporal dementia (bvFTD). Patients diagnosed with these distinct dementias often develop debilitating neuropsychiatric symptoms (NPS) over time. This study examined NPS in PiD, PSP, and CBD early and late in the disease course, as well as their change over time, in participants with PPA or bvFTD.

Methods: Participants (N=44) with clinical diagnoses of PPA (N=23) or bvFTD (N=21) and autopsy-confirmed PiD (N=16), PSP (N=11), or CBD (N=17) were identified from the Mesula Center for Cognitive Neurology and Alzheimer's Disease research programs. NPS (total=12) were examined at initial and final visit (M=0.76 years before death; SD=72) with the Neuropsychiatric Inventory–Questionnaire (NPI-Q) and placed into 3 domains based on co-occurrence: 1) Behavioral/Comportmental (apathy, disinhibition, motor disturbance, and appetite changes), 2 Affective (depression, anxiety, elation, and irritability), and 3) Disruptive/Psychotic (delusion hallucinations, agitation, and nighttime behaviors). Linear and logistic regressions controlling for disease duration and dementia severity (CDR global score) compared group differences in average percentage of total and domain-specific symptoms endorsed at initial and final evaluation between PiD, PSP, and CBD with PPA or bvFTD.

Results: Across all participants with FTLD-tau, the most common symptom at initial presentation was irritability (50%) whereas apathy (68%) predominantly emerged at final evaluation. Psychosis (e.g., hallucinations) was nearly absent at both timepoints, ranging from 0-5%. Total NPS increased in CBD and PiD over time (by ~11%) and was driven by high endorsement of Behavioral/Comportmental symptoms; compared to CBD and PiD, total symptom endorsement in PSP remained relatively stable ($p<0.01$). Regardless of pathology, Behavioral/Comportmental symptoms increased in both bvFTD and PPA over time, but the magnitude of this was significantly higher in PPA (by ~25%; $p<0.05$).

Conclusions: FTLD-tauopathies can present with distinct neuropsychiatric phenotypes. PPA and bvFTD, though clinically distinct at onset, appear to converge in their neuropsychiatric presentations close to death. Findings highlight the prognostic value of identifying and monitoring NPS in non-amnestic neurodegenerative dementias.

Lay Language: Primary progressive aphasia (PPA) is a language-based dementia, whereas behavioral variant frontotemporal dementia (bvFTD) is characterized by personality changes. PPA and bvFTD can be caused by different brain pathologies that are discovered at autopsy. For a substantial proportion of patients with PPA and bvFTD, symptom arise when abnormal clumps of a protein known as tau accumulate and spread in the brain. This study examined psychiatric symptoms in participants diagnosed with PPA or bvFTD due to different tau pathologies. Psychosis (e.g., hallucinations) was relatively uncommon overall. Initially, symptoms like apathy and disinhibition were more common in bvFTD than in PPA, but these groups became more similar as their diseases progressed. Psychiatric symptoms at early and late stages of disease also varied between participants with different tau pathologies. Findings suggest that characterizing psychiatric symptoms in PPA and bvFTD at different stages may help us predict underlying brain pathology and optimize treatment strategies.