Acceleration of Brain and Knee Joint Degeneration Following ACL Injury in a Mouse Model of Alzheimer's Disease

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INTRODUCTION: Alzheimer's Disease (AD) and osteoarthritis (OA) are two of the most common debilitating health conditions affecting the elderly. Several recent studies in mice and humans have described an association between OA and AD, with prevalent OA increasing the likelihood of developing AD or AD-like cognitive declines. These observations suggest that there may be a common mechanism linking AD and OA. The deposition of beta-amyloid protein (β-Amyloid) outside neurons and the accumulation of phosphorylated Tau (pTau) inside neurons are characteristic changes associated with AD. β-Amyloid has also been found in the joint capsules of osteoarthritic hips and there are suggestions of an association with chronic inflammation, supporting the hypothesis that systemic inflammation precedes both AD and OA. However, few studies have evaluated the mechanistic interaction between OA and AD progression. In this study, we investigated neurocognitive and behavioral dysfunction in a mouse model of AD in the presence or absence of OA. APP/PS1 double transgenic mice express a chimeric mouse/human amyloid precursor protein (APP) and a mutant presenilin 1 (PS1), two mutations associated with early-onset cognitive decline and amyloid plaque formation. β-Amyloid (Aβ) deposits in the brains of these mice are present by 7 months of age, particularly in female mice, while cognitive deficits are observable by 9 months. We hypothesized that prevalent OA would be associated with increased presence of Aβ and pTau in the affected joint and the brain and would be associated with greater cognitive decline in APP/PS1 mice.

METHODS: APP/PS1 mice were obtained from the Jackson Laboratory and bred in-house to generate APP/PS1 and wildtype (WT) littermate cohorts. A total of 79 mice were used for these studies, with 7-10 APP/PS1 mice and 10-14 WT mice per sex/injury group. Non-invasive knee injury (compression-induced anterior cruciate ligament rupture) was performed in 44 mice at 7 months of age in both female and male APP/PS1 and WT littermates. Sham injured mice were anesthetized and subjected to a single sub-injury compressive load. Cognitive and behavioral tests were performed 6 weeks post-injury, a timepoint at which severe OA has developed in injured joints. Neurobehavioral tests included open field, novel object recognition, spontaneous alteration, and Morris water maze. Mice were euthanized 6 weeks post-injury, knees were assessed with micro-computed tomography and whole-joint histology to quantify OA, osteophyte formation, and synovitis. Aβ, Tau, and pTau levels in the brain and knees were measured with ELISA and Western blot. Congo red and Thioflavin S staining was used to visualize amyloid in brain tissue sections.

RESULTS: We found that ACL injury led to similar OA severity in both WT and APP/PS1 mice, though female APP/PS1-OA mice had significantly more osteophyte formation than WT-OA mice and uninjured APP/PS1-Sham females also had significantly more osteophyte than WT-Sham (**Fig. 1B**). In female APP/PS1-OA mice, Aβ and pTau in the brain was significantly greater than in APP/PS1-Sham mice (**Fig. 1A,D,G,H**), and Aβ was increased in the femoral subchondral bone and articular cartilage of the injured knee joint (**Fig. 1E**). In contrast, male APP/PS1 mice had higher Aβ and Tau in the brain and knee joint than WT mice, but these levels were not affected by OA. Cognitive declines were also more severe in female APP/PS1 mice than in male mice. In the open field test, female APP/PS1 mice exhibited decreased exploratory behavior compared to WT mice, but no significant differences were observed between OA and Sham mice for either WT or APP/PS1 groups (**Fig. 1C**). For the novel object recognition test, female APP/PS1-OA mice did not have a significant preference for the novel object as expected (**Fig. 1F**). Significant differences between WT and APP/PS1 mice were also observed during the acquisition phase and the testing phase of the Morris Water Maze test, though no significant differences were observed between Sham and OA mice.

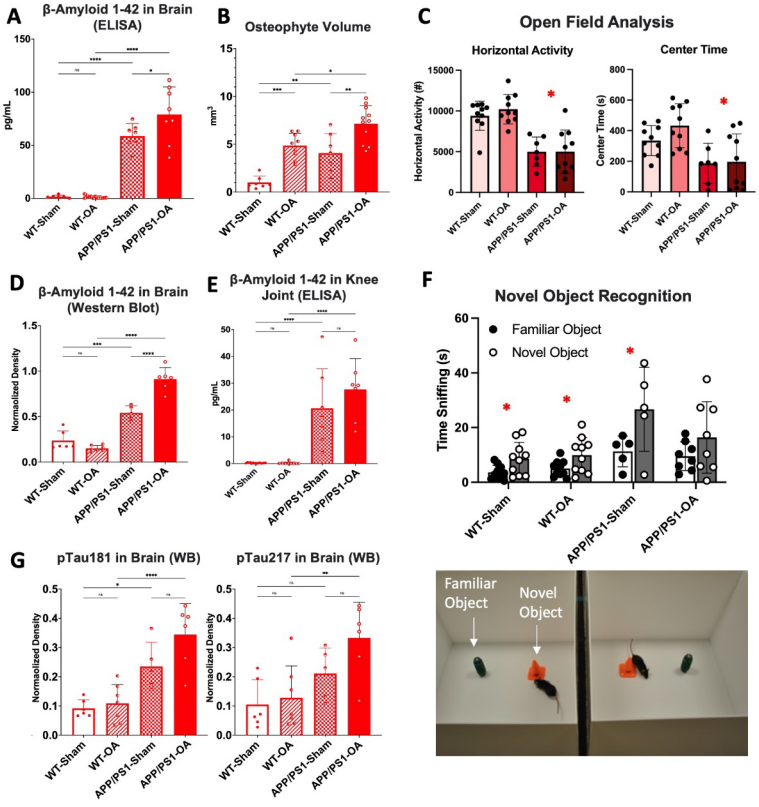

Figure 1: (A,D,E,G): Changes in Aβ and pTau expression in the brain and injured joint of female WT and APP/PS1 mice in the presence or absence of knee OA. (B): OA severity was similar for injured WT and APP/PS1 mice, but osteophyte formation was greater in female APP/PS1 mice. (C,F): Behavior and neurocognitive function were impaired in female APP/PS1 mice compared to WT mice, but was not significantly affected by prevalent OA.

DISCUSSION: This study found that OA prevalence was associated with increased Aβ and Tau accumulation in the brain and injured joints of female APP/PS1 mice and was associated with the neurocognitive decline in these mice. These results are relevant to the clinical treatment of both AD and OA and suggest potential shared mechanisms related to inflammation outside the brain with AD progression and cognitive function. Mechanisms of sex differences in AD risk factors and incidence is controversial, therefore identifying underlying molecular differences that may provide scenarios where sex differences are important could be critical for providing better treatments and care for both men and women with AD.

SIGNIFICANCE/CLINICAL RELEVANCE: These results provide insights about the pathoetiology of AD and OA and suggest possible common mechanisms connecting OA-associated inflammation to cognitive function. Most people with OA are older than 45 years; women are more commonly affected than men and tend to present at more advanced stages of OA compared to men. Similarly, women are nearly twice as likely as men to develop AD with a similar age distribution as OA. Identifying novel mechanisms of crosstalk between these two conditions could improve clinical care and quality of life for at-risk patient populations.

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