Fracture-Induced Effects on the Onset & Progression of Alzheimer's Disease

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Alzheimer's disease and related dementias (AD/ADRD) are multifactorial, highly heterogeneous, and complex age-dependent disorders that severely affect memory and cognitive function, impacting nearly 35.6 million people worldwide. In the elderly, dementia increases the risk of falls and fractures by 2-3 times, due in part to neurovascular instability, low bone mineral density due to pre-existing osteoporosis, and poor musculature supporting joints due to cachexia and/or sarcopenia.

While the occurrence of fractures due to AD/ADRD is well documented, an association between fractures and AD/ADRD onset or progression is underappreciated and warrants additional investigation. We aim to investigate the mechanistic actions underlying fracture healing as a precipitating event for AD/ADRD pathogenesis.

Four-month-old, male, 5xFAD (AD model) and wild-type control (C57BL/6) mice were divided into 2 groups: surgically induced femoral fractures and uninjured mice. Prior to surgery mice underwent baseline AD behavior testing including: spontaneous alternation in the y-maze, light-dark exploration in the open field, and active place avoidance assays. Mice are undergoing weekly x-ray imaging to monitor fracture healing progression and longitudinal AD behavior testing. 22 weeks post-surgery mice will be euthanized, and femurs and brains collected. Femurs will undergo uCT imaging and histological assessment of bone healing and immunohistochemical assessment of inflammatory markers. Brains will be processed for histology and neuroinflammatory marker analysis, including Aβ plaque deposition, tau tangles, neuronal survival, neurogenesis, and activation/proliferation of microglia and astrocytes.

At the conclusion of the study, we expect to see an increase in neuroinflammatory markers and delayed fracture healing in the experimental 5xFAD group. We anticipate that compared to uninjured controls, femoral fracture results in cognitive decline, Aβ accumulation/neurodegeneration, increases in neuroinflammation, and vascular impairment. We anticipate finding a correlation between fracture and worsened AD outcomes. By uncovering the mechanisms underlying this relationship, we hope to guide future studies to develop more robust therapeutics.