Tau pathology within the nucleus basalis of Meynert in athletes with traumatic brain injury

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Chronic traumatic encephalopathy (CTE) is a tauopathy, characterized by tau profiles, including neurofibrillary tangle (NFTs) and neuropil threads within the cortex similar to that seen in Alzheimer's disease (AD). Reports also indicate that neurons within the nucleus basalis of Meynert, which contain the cholinergic cortical projection neurons located within the substantia innominate, which innervate the entire cortical mantle are associated with memory dysfunction, a clinical feature of CTE. To evaluate the evolution of tau pathology within the NBM, we processed tissue obtained at autopsy from male athletes who played American football and hockey, mean age at death of 57.8 years, using antibodies that selectively label tau dimers and oligomers (tau oligomeric complex 1, TOC1), tau N-terminal (TNT1, which recognizes the phosphatase-activation domain associated with fast axonal transport (FAT) defects), and the pretangle phosphorylated tau marker (pS422) applied to paraffin embedded tissue. Cases were pathologically categorized as Stage 2, 3 or 4 according to McKee et al., 2013. Nissl counterstained sections revealed large hyperchromic neurons containing pS422 immunoreactivity, indicating a cholinergic phenotype. We found a stepwise increase in the number of neurons containing each tau epitope across CTE stages. In stage 2, the greatest number of tau-positive neurons were TOC1 positive (+), followed by TNT1+ and pS422+. In stage 3, TNT1+ neurons were the fewest, with similar significant increases in pS422 and TOC1 neurons. Stage 4 displayed the greatest number of neurons containing each tau epitope with pS422 > TOC1 > TNT1. Overlaying images of sections stained for each tau marker revealed very few pS422/TNT1+ tangles at any stage. The co-occurrence of pS422 and TOC1+ neurons was greatest in stages 3 and 4 with virtually none in stage 2. The greatest co-occurrence of TOC1 and TNT1+ neurons was seen in stage 4 with relatively few in stages 2 and 3. These findings suggest that the evolution of tau pathology in cholinergic basal forebrain neurons initiates with the formation of oligomeric TOC1 and TNT1 tau epitopes prior to the formation of aberrantly phosphorylated tau pS422. The presence of TNT1+ neurons, a marker associated with impairment in FAT, suggests ongoing trafficking deficits throughout the progression of CTE.