Title: Increased inflammation in sleep-relevant nuclei is associated with REM sleep behavior disorder in chronic traumatic encephalopathy

Author: Suzie Marcus

Abstract:

Chronic traumatic encephalopathy is a neurodegenerative disease caused by repetitive head impacts (RHI) and is most commonly found in former athletes and combat veterans. There are many symptoms associated with CTE: memory loss, explosivity, and increased depressiveness are all possible clinical manifestations of the disease. In addition, there is an increased risk of rapid eye movement (REM) sleep behavior disorder (RBD). RBD is a sleep condition characterized by a loss of muscle atonia during REM sleep. This lack of paralysis can lead to the patient acting out dreams, sometimes violently. While RBD presents idiopathically in roughly 1% of the general population, it occurs in 30% of individuals diagnosed with CTE. In CTE, both tau pathology in the raphe nuclei and Lewy body pathologies are associated with RBD. Additionally, independent of these pathologies, the total number of years of contact sports play predicts a diagnosis of RBD. We hypothesized that this correlation between contact sports and RBD is due to RHI–related damage other than tau pathology and Lewy bodies. We investigated the possibility that brain stem axonal damage and microgliosis in areas implicated in REM sleep regulation may be another cause of the increased frequency of RBD in CTE participants. To test our hypothesis, we performed APP, CD68, and Iba-1 immunohistochemical staining of the pons and medulla oblongata from participants with CTE and with (*n=20*) and without (*n=20)* RBD. Sleep relevant nuclei (dorsal/median raphe nuclei, locus coeruleus, subcoeruleus, gigantocellular reticular formation, and nucleus ambiguus) were examined to determine whether markers of axonal damage and/or microgliosis were increased in participants with RBD. There was no significant difference in APP+ axonal spheroids between groups. However, Iba-1+ microglial cell density was significantly more likely to be severe in RBD cases in the raphe nuclei (p=0.040), subcoeruleus (p=0.021) and gigantocellular reticular formation (p=0.017). Similarly, CD68+ activated microglia/macrophage cell density was significantly more likely to be moderate to severe in RBD cases in the gigantocellular reticular formation (p=0.037). Furthermore, analysis of genetic variation associated with RBD and Parkinson's Disease showed an association between alpha-synuclein-related SNPs (*rs3756063* and *rs10005233*) and RBD in CTE. In conclusion, this study provides evidence that severe brainstem inflammation associated with contact sports participation as well as genetic variation in alpha-synuclein are associated REM sleep behavior disorder in CTE.