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Featured Article

Cerebrospinal fluid tau, Aβ, and sTREM2 in Former National Football League Players: Modeling the relationship between repetitive head impacts, microglial activation, and neurodegeneration

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Abstract

Introduction: Cerebrospinal fluid (CSF) protein analysis may facilitate detection and elucidate mechanisms of neurological consequences from repetitive head impacts (RHI), such as chronic traumatic encephalopathy. We examined CSF concentrations of total tau (t-tau), phosphorylated tau, and amyloid $\beta_{1\text{-}42}$ and their association with RHI in former National Football League (NFL) players. The role of microglial activation (using sTREM2) was examined as a pathogenic mechanism of chronic traumatic encephalopathy.

Methods: Sixty-eight former NFL players and 21 controls underwent lumbar puncture to quantify t-tau, p-tau$_{181}$, amyloid $\beta_{1\text{-}42}$, and sTREM2 in the CSF using immunoassays. The cumulative head impact index estimated RHI.

The authors M.L.A. and Y.T. contributed equally to this work.

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Results: No between-group differences for CSF analytes emerged. In the former NFL players, the cumulative head impact index predicted higher t-tau concentrations ($P = .041$), and higher sTREM2 levels were associated with higher t-tau concentrations ($P = .009$).
Discussion: In this sample of former NFL players, greater RHI and increased microglial activation were associated with higher CSF t-tau concentrations.

Keywords: Cerebrospinal fluid; Aβ; sTREM2; Chronic traumatic encephalopathy; Microglial activation; Alzheimer's disease; Repetitive head impacts; Concussion; Subconcussive

1. Introduction

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease associated with exposure to repetitive head impacts (RHIs), such as those incurred through contact sports (e.g., tackle football, boxing) and combat military service involving blast exposures [1–4]. In a recent convenience sample of 202 deceased tackle football players, CTE was neuropathologically diagnosed in 177 participants, including 110 of 111 former National Football League (NFL) players [4]. CTE cannot be diagnosed when a person is alive, and the mechanisms by which exposure to RHI transitions to neurodegeneration are unknown. To address these knowledge gaps, current research is focused on the development of *in vivo* biomarkers for CTE [5,6]. *In vivo* fluid biomarkers play a critical role in the clinical diagnosis and study of mechanistic pathways of other neurodegenerative diseases, such as Alzheimer's disease (AD) [7]. Clinically useful fluid biomarkers for concussion and acute traumatic brain injury (TBI) are now emerging [8].

The pathognomonic diagnostic lesion of CTE is the perivascular deposition of abnormal phosphorylated tau (p-tau) in neurons and astroglia at the base of the cortical sulci [9]. Amyloid β (Aβ) plaques are sparse and diffuse and related to age [4,10]. Positron emission tomography (PET) imaging of paired helical filament tau as a diagnostic biomarker is currently under investigation to identify and grade tau pathology in patients with suspected CTE and may have value for CTE diagnosis, particularly when used in conjunction with Aβ PET. PET imaging, however, is time consuming and expensive. Although lumbar puncture (LP) is often viewed as invasive, cerebrospinal fluid (CSF) concentrations of tau (total tau [t-tau], p-tau) and Aβ represent a pragmatic biomarker that provides a direct assessment of the central nervous system (CNS). CSF concentrations of Aβ, t-tau, and p-tau are core biomarkers for AD [7,11–13]. As in AD [7], CSF p-tau$_{181}$ may be a specific marker of intraneuronal tau pathology, and CSF t-tau may be a marker of neurodegeneration in CTE. Because tau is predominantly expressed in neuronal axons, elevated CSF t-tau concentrations are usually interpreted to reflect general neuronal injury. However, CSF t-tau is nonspecific (e.g., it can be temporarily increased following stroke or acute TBI) [14–16], particularly in the absence of neuropathological examination. Elevated CSF t-tau concentrations could reflect downstream CTE-related neurodegeneration and/or neuronal injury related to long-term neurological consequences associated with RHI (e.g., axonal degeneration). Nevertheless, the specific relationship between RHI and later life CSF tau, as well as Aβ is unknown.

There is evidence that RHI and CTE are associated with increases in microglial activation [17,18]. In 66 deceased American football players with autopsy-confirmed CTE, more years of football play predicted CD68 (a marker of microglial activation), which partially mediated the effect of RHI on p-tau [18]. Tackle football players with autopsy-confirmed CTE have been shown to exhibit elevated CSF CCL11 (a marker of neuroinflammation), which was related to RHI [19]. Molecular neuroimaging studies further demonstrate chronic microglial activation (e.g., PET measures of translocator protein) in active, recently retired, and older former NFL players [20,21].

Soluble CSF concentrations of the triggering receptor expressed on myeloid cells 2 (sTREM2) may serve as an additional *in vivo* biomarker of microglial activation in CTE. TREM2 is expressed on microglia in the CNS and modulates microglial activation [22,23]. *TREM2* variants predict increased risk for other neurodegenerative diseases (e.g., frontotemporal dementia, AD) [24], with odds ratios for AD risk similar to apolipoprotein E, although the allele frequency in the population is low [25,26]. sTREM2 can be detected in the CSF, and higher concentrations are believed to reflect increased microglial activation [27–31]. CSF sTREM2 has been the focus of several recent clinical research studies of AD. sTREM2 correlates with CSF markers of AD t-tau, p-tau [27–29,32], as well as with CSF glial protein YKL-40 [27,28]. sTREM2 concentrations, however, vary with disease progression. AD cohorts have exhibited elevated [27,32], reduced [33], or normal levels [34] of sTREM2. When disease stage is considered, sTREM2 levels are higher in the early stages of the AD continuum [28,29,33] and can be increased 5 years before symptom onset [35].

Analysis of CSF t-tau, p-tau, and Aβ may be a pragmatic method to detect long-term neurological consequences associated with RHI, including early CTE pathology. Evaluation of sTREM2 levels, in conjunction with CSF t-tau, p-tau, and Aβ, may also provide insight into the role of microglial