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White matter signal abnormalities in former National Football League players

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Abstract

Introduction: Later-life brain alterations in former tackle football players are poorly understood, particularly regarding their relationship with repetitive head impacts (RHIs) and clinical function. We examined white matter signal abnormalities (WMSAs) and their association with RHIs and clinical function in former National Football League (NFL) players.

Methods: Eighty-six clinically symptomatic former NFL players and 23 same-age reportedly asymptomatic controls without head trauma exposure underwent magnetic resonance imaging and neuropsychological testing. FreeSurfer calculated WMSAs. A cumulative head impact index quantified RHIs.

Results: In former NFL players, increased volume of WMSAs was associated with higher cumulative head impact index scores ($P = .043$) and worse psychomotor speed and executive function

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($P = .015$). Although former NFL players had greater WMSA volume than controls ($P = .046$), these findings are inconclusive due to recruitment of controls based on lack of clinical symptoms and head trauma exposure.

Discussion: In former NFL players, WMSAs may reflect long-term microvascular and nonmicrovascular pathologies from RHIs that negatively impact cognition.

Keywords: White matter signal abnormalities; White matter hyperintensities; Repetitive head impacts; Chronic traumatic encephalopathy; Alzheimer's disease; Cognitive function; Concussion; Subconcussive

1. Introduction

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease associated with recurrent concussive and subconcussive injuries (i.e., repetitive head impacts [RHIs]) [1,2] and is commonly observed in former boxers and professional American football players [1–4]. CTE can currently only be diagnosed through neuropathological examination [5], in part, because biomarkers that can accurately detect CTE *in vivo* do not yet exist. Research has begun to use neuroimaging to study the long-term effects of RHIs on the brain and to identify methods to detect neurological sequelae from RHIs (including CTE), focusing on former *professional* football players due to their substantial exposure to RHIs. Structural [6,7], functional [7,8], and neurochemical [6,9] brain changes have been found in this cohort, believed to be a result of RHIs, and may affect cognitive and neuropsychiatric function [10,11]. Later-life brain alterations in former football players are not fully characterized, particularly in terms of their relationship with RHIs and clinical function. Former NFL players are presumably at high risk for CTE [4] and can serve as a population to provide insight into the potential *in vivo* structural brain changes associated with CTE (e.g., Hart et al. [7], Koerte et al. [12]).

White matter signal abnormalities (WMSAs) may be common magnetic resonance imaging (MRI) findings that correlate with clinical function in former football players. WMSAs refer to regions in the white matter that appear hyperintense on T2 fluid-attenuated inversion recovery (FLAIR) but hypointense on T1-weighted images, such as magnetization-prepared rapid gradient echo (MPRAGE) scans. The etiology underlying WMSAs is nonspecific and may be multifaceted. WMSAs have been documented to accompany aging and cardiovascular disease (CVD) and usually are interpreted to reflect small-vessel cerebrovascular disease from microvascular hypoperfusion [13–17].

Reduced cerebral perfusion has been observed in active and former National Football League (NFL) players [7,8], and previous research reports greater total and deep volume WMSAs in 10 former NFL players with cognitive deficits, compared with age-matched controls [7]. Subcortical or periventricular WMSAs were also observed in 7/9 former NFL players from a clinical case series [18]. Former professional football players may be at risk for the pathologies of WMSAs due to their high rates of CVD [19,20]. WMSAs may also reflect long-term microvascular and nonmicrovascular pathologies from RHIs. In the setting of acute mild traumatic brain injury (mTBI), WMSAs can be common, perhaps from decreases in cerebral perfusion [21–23], and they predict post-mTBI cognitive outcomes [21,24]. RHIs are also associated with impaired cerebral hemodynamics in active boxers [25], and WMSAs in active collegiate ice hockey players have been shown to occur closer to the gray and white matter interface compared with controls [26]. This sulcal depth location of WMSAs was suggestive of head trauma as the precipitant cause, particularly given that the diagnostic lesion of CTE is the perivascular deposition of hyperphosphorylated tau (p-tau) at the base of the sulci [5]. There may indeed be a vascular component, including blood-brain barrier leakage, involved in the RHIs and neurofibrillary tangle formation relationship [27–30]. In autopsy cases of "dementia pugilistica," decreased microvascular density and fragmented vessels in the frontal cortex were observed, and tau and microvascular pathology correlated [29]. Along with microvascular changes, RHIs and CTE are also associated with neurometabolic disturbances (e.g., gliosis, neuroinflammation) [2,9,31,32], especially diffuse axonal injury [2,7,33,34], that could result in WMSAs [35–37].

WMSAs have long been studied in Alzheimer's disease (AD). WMSAs predict increased risk for AD dementia [38]. In fact, WMSAs have even been postulated to be a core feature of AD, given WMSAs were increased in autosomal-dominant AD patients before symptom onset and predicted cerebrospinal fluid β-amyloid levels in carriers only [39]. Although the clinical presentation of CTE is heterogeneous and includes a constellation of various cognitive (including nonmemory impairments), behavior, and mood symptoms [3,4,40], the pathologies of WMSAs may contribute to the clinical presentation of CTE as they do in AD.

This study examined the association between RHIs (using the cumulative head impact index [CHII]; [10]) and volume of WMSAs from T1-weighted MPRAGE MRI in symptomatic former NFL players. The association between WMSAs and cognitive and neuropsychiatric function was also investigated. It was hypothesized that increased volume of