PET Scanning of Brain Tau in Retired National Football League Players: Preliminary Findings

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Objective: Mild traumatic brain injury due to contact sports may cause chronic behavioral, mood, and cognitive disturbances associated with pathological deposition of tau protein found at brain autopsy. To explore whether brain tau deposits can be detected in living retired players, we used positron emission tomography (PET) scans after intravenous injections of 2-(1-{6-[2-(2-[F-18]fluoroethyl)(methyl)amino]-2-napthyl}ethylidene)malononitrile (FDDNP). Methods: Five retired National Football League players (age range: 45 to 73 years) with histories of mood and cognitive symptoms received neuropsychiatric evaluations and FDDNP-PET. PET signals in subcortical (caudate, putamen, thalamus, subthalamus, midbrain, cerebellar white matter) and cortical (amygdala, frontal, parietal, posterior cingulate, medial and lateral temporal) regions were compared with those of five male controls of comparable age, education, and body mass index. Results: FDDNP signals were higher in players compared with controls in all subcortical regions and the amygdala, areas that produce tau deposits following trauma. Conclusions: The small sample size and lack of autopsy confirmation warrant larger, more definitive studies, but if future research confirms these initial findings, FDDNP-PET may offer a means for premorbid identification of neurodegeneration in contact-sports athletes. (Am J Geriatr Psychiatry 2013; 21:138–144)

Key Words: Positron emission tomography, FDDNP, tau, amyloid, mood disorder, depression, mild cognitive impairment, dementia

According to recent CDC estimates, 1.6–3.8 million sports-related traumatic brain injuries (TBIs) occur each year, including those never reported to healthcare professionals. Most are minor concussions; many are repeated injuries and subconcussive blows.
Repetitive mild TBI due to contact sports may lead to chronic mood, behavioral, and cognitive changes. Studies of retired contact-sport athletes, such as National Football League (NFL) players, show a higher rate of personality, behavioral, and mood disturbances (e.g., depression, irritability, impulsiveness), mild cognitive impairment (MCI, a risk state for dementia), and dementia compared with controls. Professional athletes exposed to repetitive mild TBIs are prone to develop chronic impairment, and available evidence suggests a possible dose response. Retired NFL players with three or more reported concussions during their career were three times more likely to be diagnosed with depression and five times more likely to be diagnosed with MCI.

Several investigators have described chronic traumatic encephalopathy (CTE), a clinicopathological entity that includes mood, personality, cognitive, and behavioral changes (e.g., suicidality), and motor symptoms (e.g., abnormal gait, tremor) associated with a range of autopsy findings, particularly widespread accumulation of phosphorylated tau protein as neurofibrillary tangles (similar to those observed in Alzheimer disease), astrocytic tangles, neurites, diffuse axonal injury, white matter abnormalities, inflammation, and immune proinflammatory cytokine responses in traumatized brain regions. Immunoreactive deposits are found in neocortical, subcortical (e.g., thalamus, caudate, putamen, midbrain, and cerebellar white matter), and medial temporal (hippocampus, entorhinal cortex, and amygdala) regions, where neuronal loss may be observed. TDP-43 proteinopathy may accompany tauopathy in CTE cases and is more prominent in motor neuron disease cases. Amyloid deposition has been reported in approximately 40% of CTE cases and generally consists of diffuse plaques with relatively few cortical neuritic plaques. Currently, CTE in former football players is only diagnosed at autopsy.

Our group invented 2-(1-6-[2-[F-18]fluoroethyl](methyl)amino)-2-naphthyl]ethylidene)malononitrile (FDDNP)-positron emission tomography (PET) for measuring both tau tangle and amyloid plaque deposition in living brains. FDDNP signals differentiate Alzheimer disease from MCI and normal aging and predict future cognitive decline in nondemented subjects. Although other tau tracers have been tested in human brain tissue sections and animal models, FDDNP is the only PET probe of tau that has been studied in vivo in human imaging trials. FDDNP is not specific for tauopathies, but previous autopsy follow-up studies indicate regional specificity in patients with Alzheimer disease, wherein FDDNP-PET shows high signals in medial temporal regions where autopsy studies indicate a preponderance of tau tangles, as well as high signal in lateral temporal regions, where amyloid plaques are highly concentrated.

Despite the devastating consequences of TBIs due to contact sports and the large number of people at risk, no method for early detection of such pathology has yet been established. To address this issue, we performed PET scans after intravenous injections of FDDNP to explore whether brain tau deposits could be detected in a small group of retired NFL players with cognitive and mood symptoms and compared them with a group of male controls of comparable age, educational achievement, and body mass index (BMI).

### METHODS

Neuropsychiatric evaluations were performed on five retired players aged 45 years or older who were recruited for this study because of a history of cognitive or mood symptoms. Through organizational contacts, NFL retirees with MCI-like symptoms were referred for testing. Of the 19 potential volunteers, 14 did not participate because of non-response or disinterest (N = 10), age (too young; N = 2), or medical illness (N = 2).

Subjects had screening laboratory tests and structural imaging scans (computed tomography [CT] or magnetic resonance imaging [MRI]) to rule out other causes of mental symptoms (e.g., stroke, tumor) and for co-registration with PET scans for region-of-interest (ROI) analyses. One player and two control subjects had CT scans because they could not tolerate MRI (claustrophobia, body metal, body size).

The Mini–Mental State Examination (MMSE), Hamilton Rating Scale for Depression (HAM-D), and a neuropsychological test battery were administered to confirm diagnoses. Clinical assessments were performed within 4 weeks of scanning, and clinicians were blinded to scan results. Informed consent was obtained in accordance with UCLA Human Subjects Protection Committee procedures. Cumulative radiation dosimetry was below the mandated...
maximum annual dose and in compliance with state and federal regulations.

PET scans were performed using an ECAT HR+ PET or Biograph PET/CT camera (both Siemens/CTI, Knoxville, TN) as detailed previously.8,9 In brief, subjects were injected with 10 mCi of FDDNP. FDDNP binding data were quantified using Logan graphical analysis: The slope of the linear portion of the Logan plot is the relative distribution volume (DVR) of the tracer in an ROI divided by that in the reference region (cerebellum). ROIs were traced on co-registered MRI or CT scans for subcortical (caudate, putamen, thalamus, subthalamus, midbrain, cerebellar white matter) and cortical (amygdala, frontal, parietal, posterior cingulate, and medial and lateral temporal) regions.8,9 Each DVR or binding value was expressed as an average of left and right regions. All scans were read and ROIs drawn by individuals blinded to clinical assessments.

Given the small number of players available for analyses, only non-parametric tests were performed. Controls for comparisons with players were identified using a propensity score matching method, wherein pairs of subjects are matched through a minimum distance estimator that can encompass several covariates.12 This method thus mitigates potential biases and ensures that controls and players are as similar as possible in other characteristics that can affect FDDNP regional binding levels. FDDNP scans were available for 35 normally aging males from previous studies. We chose age, BMI, years of education, and dementia family history as covariates to match players and controls and used the greedy matching algorithm to identify controls to compare with players. Descriptive statistics were computed for players and controls, and the two-sample Wilcoxon test was used to compare groups on FDDNP binding levels, a global cognitive score (MMSE), and a depression measure (HAM-D). We explored possible relationships between FDDNP binding values and the number of concussions in the players using plots and Spearman correlations in those regions that showed higher signals in players compared with controls.

RESULTS

The players represented a range of positions and diagnoses (linebacker with MCI; quarterback with normal aging; guard with dementia/depression; defensive lineman with MCI/depression; center with MCI) and played professionally from 10–16 (median, 14) years (Fig. 1). Players and controls were comparable in age (median age for players [controls]: 59 [60]; range: 45–73 [45–66], BMI (players [controls]: 32 [34], 28–42 [28–38]), years of education (players [controls]: 17 [15], 15–18 [13–22]), race (4 white and 1 African American for players and controls) and dementia family history (present in 3 players and 3 controls) (Table 1). Players had significantly higher HAM-D scores (median: 8, range: 5–17) compared with controls (0, 0–3; p = 0.03) and a trend towards lower MMSE scores (median: 28, range: 17–30 versus 30, 29–30, p = .09) (Table 1).

Players had significantly higher FDDNP signals compared with controls in caudate (median levels: 1.48 versus 1.23, p = 0.03), putamen (1.47 versus 1.20, p = 0.05), thalamus (1.48 versus 1.29, p = 0.03), subthalamus (1.45 versus 1.25, p = 0.03) midbrain (1.31 versus 1.14, p = 0.03), and cerebellar white matter (1.15 versus 1.09, p = 0.05) regions. The two groups did not differ significantly in FDDNP binding in cortical regions except for the amygdala (1.30 versus 1.14, p = 0.03) (Table 1; Figs. 1, 2).

Plots of FDDNP binding values versus number of concussions in regions that showed higher signals in players compared with controls are presented in Figure 3. Although none of the Spearman correlations reached statistical significance (as expected due to the small sample size), the plots show an increase in FDDNP binding levels with increase in number of concussions.

DISCUSSION

These initial FDDNP-PET findings in retired NFL players with histories of cognitive and mood symptoms demonstrate high signals in the amygdala and subcortical regions compared with controls. Although the subject groups were matched for important variables, such as age, BMI, and educational achievement, these preliminary results need interpretation with caution given the small sample size and multiple uncorrected statistical comparisons. Also, not all subjects had MRI scans for co-registration with PET, which could influence ROI values, although comparable numbers of players and controls had MRI scans (4 and 3, respectively). Other factors that could influence the results would be differences in cerebrovascular health and genetic risk between players and...
FIGURE 1. FDDNP-PET scan results for NFL players and a control. Coronal and transaxial FDDNP-PET scans of the retired NFL players include:

NFL1: 59-year-old linebacker with MCI, who experienced momentary loss of consciousness after each of two concussions;

NFL2: 64-year-old quarterback with age-consistent memory impairment, who experienced momentary loss of consciousness and 24-hour amnesia following one concussion;

NFL3: 73-year-old guard with dementia and depression, who suffered brief loss of consciousness after 20 concussions, and a 12-hour coma following 1 concussion;

NFL4: 50-year-old defensive lineman with MCI and depression, who suffered two concussions and loss consciousness for 10 minutes following one of them;

NFL5: 45-year-old center with MCI, who suffered 10 concussions and complained of light sensitivity, irritability, and decreased concentration after the last two.

The players' scans show consistently high signals in the amygdala and subcortical regions and a range of cortical binding from extensive to limited, whereas the control subject shows limited binding in these regions. Red and yellow areas indicate high FDDNP binding signals.
controls. Despite such limitations, these elevated amygdala and subcortical FDDNP binding patterns in players are consistent with the fibrillary tau deposition patterns observed at autopsy in CTE cases.\(^5\) Only patchy cortical tau deposits have been reported in mild CTE cases, except for the amygdala, where they are dense.\(^4\)

The pattern of higher FDDNP binding values in players with a greater number of concussions (Fig. 3) suggests a link between the players’ history of head injury and FDDNP binding. Moreover, these binding patterns (high subcortical and low cortical binding except for the amygdala) are consistent with tau deposition patterns observed in autopsy studies of CTE.\(^7\) and differ from those observed in patients with cognitive and mood symptoms without prior head trauma, who mainly present with increased cortical FDDNP binding. In patients with geriatric depression, FDDNP binding is highest in the posterior cingulate and lateral temporal regions,\(^8\) whereas patients with Alzheimer dementia show high binding values throughout the cortex (parietal, medial and lateral temporal, frontal, and posterior cingulate regions).\(^7\)–\(^9\) In patients with MCI, FDDNP binding is high in medial temporal, frontal, and parietal regions.\(^8\)

FDDNP binds to both fibrillary tau and amyloid, but neuropathological studies indicate that amyloid plaques (mostly diffuse cortical) are observed in less than a third of CTE cases in retired football players.\(^5\) This suggests that a high proportion of the FDDNP signal in the players represents fibrillary tau deposition. Using a tau marker for detection and tracking of neurodegenerative disease is critically important because severity of tau load, rather than amyloid burden, correlates with rates of neuronal loss.\(^9\) To date, FDDNP is the only available imaging probe that provides in vivo measures of tau in humans.

Players had greater depressive symptoms than controls, as well as evidence of cognitive impairment (3 MCI, 1 dementia). Elevated FDDNP binding is associated with depressive symptoms in normal aging\(^14\) and geriatric depression,\(^15\) and with cognitive symptoms in normal aging, MCI, and dementia.\(^8\)\(^9\) Thus, these increased FDDNP signals appear to reflect a range of mental symptoms that have been observed in CTE cases.

Despite the devastating consequences of mild TBI from contact sports and military exposure to explosive blasts and the large group of those exposed, the syndrome has only recently received heightened attention. Specific treatments have not been developed, and no method for early detection has yet been established. Early recognition and identification of those at high risk would allow clinicians to develop strategies and interventions to protect those with early symptoms rather than attempt to repair damage once it becomes extensive.

Previous studies in patients with MCI show that FDDNP-PET patterns may predict future cognitive decline and development of dementia.\(^9\) Large-scale longitudinal studies are necessary to determine the utility of detecting tau pathology in head trauma victims who are not yet experiencing mood or cognitive symptoms and whether this technology will facilitate development of prevention strategies. Further, the added health benefits of FDDNP scanning on a large scale remains to be addressed. Previous analysis, however, indicates that appropriate use of PET for evaluating early dementia in geriatric patients can add valuable information to the clinical work-up.
without adding to the overall costs of evaluation and management, resulting in a greater number of patients being accurately diagnosed for the same level of financial expenditure.\textsuperscript{16}

These findings suggest that FDDNP-PET could facilitate early recognition and intervention of trauma-related neurodegeneration through premorbid detection. Providing a non-invasive means of early
detection is a critical first step to developing interventions to prevent symptom onset and progression. Direct and indirect costs of TBI totaled an estimated $77 billion in the United States in 2000.17 Given the large number of people at risk—not just athletes but military personnel, auto accident victims, and others—the potential public health impact is considerable.

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References