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Short Communication

Mild Traumatic Brain Injury is Related to Elevated Cerebrospinal Fluid Tau in Alzheimer's Disease Dementia

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Abstract. Few studies have examined an association between mild traumatic brain injury (mTBI) and Alzheimer's disease (AD). For this reason, we compared an AD dementia group with an mTBI history ($n = 10$) to a matched AD control group ($n = 20$) on measures of cognitive function, cerebral glucose metabolism, and markers of amyloid and tau deposition. Only a trend and medium-to-large effect size for higher phosphorylated and total tau was identified for the mTBI group. A history of mTBI may be associated with greater tau in AD, indicating a potential pathway for increasing risk for AD, though further evaluation with larger samples is needed.

Keywords: Biomarkers, concussion, dementia, neurodegeneration, risk factor, tau formation, traumatic brain injury

INTRODUCTION

A history of traumatic brain injury (TBI) has been reported to be a risk factor for the development of Alzheimer's disease (AD), though whether *mild* traumatic brain injury (mTBI) can be a risk factor is unclear and remains an important area for investigation [1]. Several theoretical mechanistic models have been proposed for how TBI, including mTBI, may contribute to the risk of developing AD [2–5]. Most propose that mTBI may accelerate AD pathophysiological processes such as deposition of amyloid-β or tau in some individuals, which might lessen the required burden for symptom manifestation [2–9]. However, others have posited that mTBI may instead cause neuronal loss directly from the trauma, decreasing neuronal reserve as well as cognitive function that may make some individuals more vulnerable to AD

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wpcontent/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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pathophysiological processes [5]. The purpose of this pilot study was to begin evaluating whether mTBI may be associated with pathophysiological markers of amyloid and tau deposition or measures of neuronal loss and cognitive function in AD. If so, the findings would indicate that mTBI may relate to the development of AD and also serve as an initial step to better understanding a mechanistic pathway in future research.

MATERIALS AND METHODS

Dataset

The Alzheimer's Disease Neuroimaging Initiative (ADNI; versions 1/Go/2; http://adni.loni.usc.edu) is a multicenter project involving sites in the US and Canada that collects sociodemographic, medical, neuropsychological, genetic, lumbar puncture, MRI, and PET data in individuals with AD dementia. A clinical diagnosis of AD dementia is made by ADNI clinicians using a clinical interview, neurological exam, and evidence of cognitive decline adhering to NINCDS/ADRDA criteria [10]. Inclusion criteria for this analysis were participants diagnosed with AD dementia at the initial visit to an ADNI site.

Study cohort

ADNI participants, in combination with a study partner, undergo interviews with clinicians to acquire a general medical history that is recorded as text notes in a log. Participants are asked if there is a history of significant head trauma, and if endorsed, the best estimate of the date of injury(s) and some details (e.g., cause, signs/symptoms) are recorded. The medical history was searched to identify an AD dementia group with a history of mTBI and an AD dementia control group with no history of TBI using the following search terms: *head trauma, head injury, traumatic, brain injury (TBI), concussion, and loss of consciousness (LOC)*. Participants with injuries suggestive of a moderate/severe TBI were excluded. mTBI was classified if a "concussion" was recorded, or if there was an indication of a blow to the head/body that produced symptoms reflective of mTBI based on commonly used guidelines [11, 12] (e.g., "head injury with brief LOC"). Because ADNI does not record if participants deny having had head trauma, an absence of head trauma within the medical history notes was used to identify participants with no history of TBI. For the control group, AD dementia participants were additionally selected by matching to the mTBI group on sex, age (±5 years), education (±3 years), and apolipoprotein ε4 (*APOE4*) status.

Measures

Medical co-morbidities associated with changes in neuronal/cognitive functions were recorded to account for their potential influence in our analyses. These included: substance use disorders, mood disorder symptoms, thyroid disease, stroke, coronary artery disease, hypertension, hypercholesterolemia, and diabetes. Each participant completed a brief neuropsychological battery at the initial visit assessing global cognitive abilities, attention, and memory using the Alzheimer's Disease Assessment Scale –13 item Cognitive scale, Rey Auditory Verbal Learning Test, Wechsler Memory Scale Logical Memory, and Trail Making Test Part B. Cerebrospinal fluid (CSF) collection and fluorodeoxyglucose (FDG) PET were also completed at baseline for participants willing to undergo the procedures. CSF and FDG PET data were collected and processed using standardized protocols that are described in detail at http://adni.loni.usc.edu/methods/documents. Briefly, all CSF samples collected across ADNI sites were shipped on dry ice to the ADNI Biomarker Core Laboratory and concentrations of amyloid-β_{1-42}, phosphorylated tau_{181}, and total tau were measured using INNO-BIA AlzBio3 kits (Innogenetics, Ghent, Belgium) on a multiplex xMAP Luminex platform (Luminex Corp, Austin, TX, USA). For FDG PET data, scans were co-registered to MRI, averaged for spatial normalization, and divided by a reference region (i.e., pons) to determine cerebral glucose metabolism for regions typically affected in AD. ADNI provides an average reuptake value of FDG PET for three regions of interest, involving the angular gyrus, inferior/middle temporal gyrus, and posterior cingulate.

Statistical analysis

Chi-square analyses, Mann-Whitney U tests, and analyses of variance were used where appropriate to compare sociodemographic, medical, neuropsychological, CSF, and FDG PET data. Because no differences were observed on sociodemographic variables or medical co-morbidities (Table 1), no covariates were entered for analyses. Statistical significance was defined as $p < 0.05$, with no correction for multiple comparisons to reduce the chances of

Table 1
Demographic, medical, and clinical characteristics

	mTBI History Group[a]	Control Group[b]	*p*
Demographics			
Age of Dementia Onset (M % ± SD)	71.8 ± 7.1	70.8 ± 9.0	0.90
Age at initial ADNI visit (M % ± SD)	73.8 ± 8.3	74.2 ± 7.8	0.82
Education, y (M % ± SD)	15.0 ± 2.5	15.2 ± 2.7	0.85
Sex, female, %	50	50	0.47
Race, Caucasian %	100	95	0.73
APOE4 Status			
0 alleles	(40)	(40)	
1 allele	(40)	(50)	
2 alleles	(20)	(10)	
Medical History			
Diabetes	(0)	(10)	0.30
Hypertension	(50)	(50)	1.00
Hypercholesterolemia	(60)	(35)	0.19
Thyroid disease	(20)	(35)	0.40
Coronary artery disease	(0)	(10)	0.30
Remote stroke	(0)	(10)	0.30
Remote alcohol disorder	(10)	(5)	0.61
Remote drug use disorder	(0)	(0)	
Mood disorder symptoms	(50)	(60)	0.60
mTBI History			
mTBI Classification			
Single injury	(70)		
Multiple injuries	(30)		
mTBI Features			
No LOC	(20)		
With LOC	(50)		
Unknown LOC	(30)		
mTBI Cause			
Sports	(40)		
MVA	(20)		
Assault	(10)		
Other/Unspecified	(30)		
Years since last mTBI (M % ± SD)	33.9 ± 22.7		

mTBI, mild traumatic brain injury; M, Mean; SD, standard deviation; #, number of cases for each factor; LOC, loss of consciousness; p, *p*-value; MVA, motor vehicle accident. [a]Number of subjects in the mTBI history group is 10. Number missing data = age of dementia onset (1) and years since last mTBI (1). [b]Number of subjects in the control group is 20.

Table 2
Neuropsychological, cerebrospinal fluid markers, and FDG PET data

	mTBI History Group[a] M ± SD	Control Group[b] M ± SD	*p*
Neuropsychological Scores			
ADAS-13	33.4 ± 10.5	30.2 ± 9.0	0.38
RAVLT Trials 1–5 Total	19.2 ± 8.7	22.7 ± 7.5	0.26
RAVLT Learning	1.6 ± 1.5	1.6 ± 1.7	1.00
RAVLT Forgetting #	4.3 ± 2.2	4.5 ± 2.0	0.85
WMS LM Delayed Recall	2.0 ± 1.5	1.4 ± 1.6	0.32
TMT Part B Time	237.0 ± 75.1	232.5 ± 83.3	0.90
CSF Markers			
Amyloid beta	623.1 ± 212.9	571.8 ± 234.9	0.62
Phosphorylated tau	41.8 ± 16.7	31.5 ± 9.8	0.07
Total tau	420.7 ± 158.6	319.5 ± 93.4	0.07
FDG PET			
Cerebral glucose metabolism	1.0 ± 0.2	1.1 ± 0.1	0.63

mTBI, mild traumatic brain injury; M, Mean; SD, standard deviation; Total #, total number of cases for each factor; LOC, loss of consciousness; *p*, *p*-value; ADAS-13, Alzheimer's Disease Assessment Scale Cognitive subscale total score; RAVLT, Rey Auditory Verbal Learning Test; Learning, Trial 5 minus Trial 1 Recall; Forgetting #, Trial 5 minus Delayed Recall; WMS LM, Wechsler Memory Scale Logical Memory II total score; TMT, Trail Making Test. [a]Number of subjects in the mTBI history group is 10. Number missing data = TMT B (2) and CSF markers (2). [b]Number of subjects in the control group is 20. Number missing data = TMT B (2), CSF amyloid (6), CSF phosphorylated and total tau (5), and FDG PET (10).

Type II error given this was a pilot study. All analyses were conducted using IBM© SPSS Statistics V26.

RESULTS

Eleven ADNI participants with AD dementia having an mTBI history were identified. However, one had a hemorrhagic stroke requiring surgical evacuation nearly 1 year before the initial ADNI visit, and thus, this individual was excluded. Among the remaining 10 participants in the mTBI group (AD-mTBI), 70% had a single injury and were on average nearly 34 years from injury (range = 6–66 years). Twenty participants with AD dementia and no history of TBI were identified who matched the mTBI participants on sex, age, education, and *APOE4* status and served as the control group in analyses. Both of the AD-mTBI and AD-control groups were predominantly white, well-educated, had similar numbers (60%) of participants with at least one *APOE4* allele, and a similar disease duration (see Table 1).

Cognitive functioning

MMSE scores did not significantly differ between the AD-mTBI (Mean = 21.8; SD = 1.7) and AD-control groups (Mean = 23.1; SD = 1.8). Likewise, the two groups performed similarly across all of the neuropsychological measures, with no statistically significant differences (see Table 2).

CSF markers

CSF levels of amyloid-β_{1-42} did not differ between the AD-mTBI ($M = 623.1$; SD = 212.9) and AD-control groups ($M = 571.8$; SD = 234.9). While not statistically significant, there was a trend for higher phosphorylated tau_{181} and total tau levels in the AD-mTBI group relative ($M_{ptau} = 41.8$, SD = 16.7; $M_{ttau} = 420.7$, SD = 158.6) to the AD-control group ($M_{ptau} = 31.5$, SD = 9.8; $M_{ttau} = 319.5$, SD = 93.4). Effect sizes were calculated given the small sample sizes, and a history of mTBI demonstrated a medium-to-large effect size for phosphorylated tau_{181} ($d = 0.75$) and total tau ($d = 0.78$) levels in AD.

FDG PET

Cerebral glucose metabolism across regions often reduced in AD did not significantly differ between the AD-mTBI and AD-control groups.

DISCUSSION

Later-in-life effects of a history of mTBI have been of significant interest across the globe, but very few studies have examined mTBI as a risk factor for developing neurodegenerative conditions such as AD [13]. Of these, reports of an association between mTBI and AD leave unanswered questions about a possible dementia process already in progress at the time of injury, which makes reverse causality a concern. This has limited our understanding of a potential link between mTBI and AD [1]. Furthermore, knowledge about an association between mTBI and AD has also been limited by the absence of studies evaluating whether an mTBI history relates to biological or cognitive markers in AD to indicate a potential pathway for how mTBI might be a risk factor [1]. As such, this pilot study is the first investigation to our knowledge to look for biological evidence that may suggest a mechanism by which mTBI could contribute to the development of AD.

In this small sample with AD dementia, a history of mTBI was not associated with worse cognitive functioning, or neuronal functioning as assessed with FDG PET, in abilities or regions typically affected early in the disease. In CSF, pathophysiological markers of amyloid formation also did not relate to a history of mTBI, but interestingly, there was a statistical trend and medium-to-large effect size for higher levels of phosphorylated tau and total tau in the AD-mTBI group relative to AD-controls. For this reason, we performed a power analysis that not surprisingly demonstrated this pilot study was underpowered (0.46) for observing statistical differences. Higher levels of phosphorylated tau reflects greater formation of neurofibrillary tangles, whereas higher total tau reflects increased neuronal damage. AD is the only condition well-known to show increases in both phosphorylated tau and total tau, with several other neurodegenerative conditions only being associated with increases in total tau [14]. Thus, our pilot study findings are important and indicate that mTBI may serve as a risk factor for AD by leading to an increase in tau formation and neuronal injury.

There are multiple reasons why tau levels may be higher in the AD-mTBI group compared to AD-controls, and alternative explanations need to be considered. Higher CSF tau has been linked to several possible biological explanations, including more advanced disease stage [15], greater burden of medical co-morbidities [16, 17], and a higher proportion of *APOE4* carriers [18]. It is plausible that our AD-mTBI group may differ from our AD-control group on one of these factors to explain the higher CSF tau. However, each of these factors seem unlikely to explain the difference in our sample, where the two groups were highly similar on disease duration, all neuropsychological measures, history of medical co-morbidities, and *APOE4* status. After considering these alternative explanations, the hypothesis that mTBI might be associated with greater accumulation of tau in AD dementia would appear supported. However, we cannot exclude the possibility that genetic risk factors unavailable in the dataset might relate to the higher CSF tau levels. For instance, the H1/H1 genotype for the microtubule-associated protein tau is overrepresented in some tau-related neurodegenerative diseases [19] and multiple genes have recently been found to be associated with tau markers in AD [20]. Thus, one or more of these could relate to the tau differences. Future studies are needed replicating the results in large, well-matched samples across the AD spectrum (pre-clinical and clinical) accounting for genetic risk factors beyond *APOE4* to provide more robust conclusions about whether increased tau relates mTBI to an increased risk for AD.

As proposed by mechanistic models, TBI (including mTBI) may directly increase pathophysiological processes related to tau in some individuals, which might lead to greater overall tau deposition and neuronal injury to contribute to the development of AD dementia (readers are referred to [2, 3] for an in-depth discussion on theoretical mechanisms).

For instance, AD-related tau neurofibrillary tangles have been shown to be more widespread at autopsy in patients who survived at least a year from a moderate-to-severe TBI relative to a control group [21]. Also, higher CSF levels of both *phosphorylated* and *total* tau have been found in cognitively normal older veterans on average nearly 30 years out from any TBI (mild and more severe) when compared to cognitively normal individuals with no TBI history [22]. In a tau PET study using the ADNI dataset, older adults having cognitive impairment (MCI or dementia) with a history of "head injury" (not following a common definition of TBI) had greater tau deposition in the frontal, temporal, and parietal regions than those with cognitive impairment having no documented head impacts [23]. Our findings extend the evidence by indicating specifically that mild injuries occurring several decades prior may be associated with increased phosphorylated and total tau within AD dementia.

Despite ours and others findings, a biological process through which TBI/mTBI may directly induce tau accumulation has not been established. Animal research has shown that mice progressively accumulate *phosphorylated* tau pathology when autopsied at various time points (weeks to months later) following multiple head impacts relative to sham controls [24]. However, mTBI has been difficult to simulate in animal research, leaving questions about the translational relevance of such models. Indeed, in human studies, only increases in *total* tau (not phosphorylated) have been seen in CSF following milder and more severe injuries, and these elevations normalize within months, [25, 26]. Thus, there is no clear basis for phosphorylated tau or total tau markers to be elevated chronically in humans due to direct injury effects. For this reason, the timing as well as the longitudinal trajectory (stable versus progressive) for tau accumulation that may be induced by TBI/mTBI will require further research to fill this critical knowledge gap and understand how some individuals with TBI/mTBI could have increased tau formation and neuronal injury to contribute to the development of AD.

While this study relied on well-matched groups and focused on mTBI, our study does have several limitations. These include a small sample size, potential for recall bias with injuries, lack of information regarding the criteria used by ADNI clinicians in recording a "concussion," absence of tau-related genetic risk factors beyond *APOE4*, and a lack of diversity. Thus, this study serves as an important, early step in suggesting that mTBI may serve as a risk factor for AD by increasing tau pathophysiology. Future studies are needed attempting to replicate the results, understand whether increased tau relates mTBI to an increased risk for AD, and identify the longitudinal relationship mTBI may have with tau across pre-clinical and clinical stages in AD.

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