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Traumatic Brain Injury History is Associated with an Earlier Age of Dementia Onset in Autopsy-confirmed Alzheimer's Disease

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Abstract

Objective—To evaluate whether a history of traumatic brain injury (TBI) with reported loss of consciousness (LOC) is a risk factor for earlier onset of Alzheimer's disease (AD) in an autopsy-confirmed sample.

Method—Data from 2,133 participants with autopsy-confirmed AD (i.e., at least Braak neurofibrillary tangle stages III to VI and CERAD neuritic plaque score moderate to frequent) were obtained from the National Alzheimer's Coordinating Center (NACC). Participants were categorized by presence/absence of self-reported remote (i.e., > 1 year prior to their first Alzheimer's Disease Center visit) history of TBI with LOC (TBI+ vs. TBI−). Analyses of Covariance (ANCOVA) controlling for sex, education, and race compared groups on clinician-estimated age of symptom onset and age of diagnosis.

Results—Average age of onset was 2.34 years earlier ($p = .01$) for the TBI+ group ($n = 194$) versus the TBI− group ($n = 1900$). Dementia was diagnosed on average 2.83 years earlier ($p = .002$) in the TBI+ group ($n = 197$) versus the TBI− group ($n = 1936$). Using more stringent neuropathological criteria (i.e., Braak stages V–VI and CERAD frequent), both age of AD onset and diagnosis were 3.6 years earlier in the TBI+ group (both p's < .001).

Conclusions—History of TBI with reported LOC appears to be a risk factor for earlier AD onset. This is the first study to use autopsy-confirmed cases, supporting previous investigations that used clinical criteria for the diagnosis of AD. Further investigation as to possible underlying mechanisms of association is needed.

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Keywords

National Alzheimer's Coordinating Center (NACC); traumatic brain injury (TBI); Alzheimer's disease (AD); age of onset; autopsy

Introduction

Traumatic brain injury (TBI) has received increasing support as a risk factor for the later development of cognitive decline, including all-cause dementia (Barnes et al., 2014; Wang et al., 2012), mild cognitive impairment (MCI) (Li, Risacher, McAllister, & Saykin, 2016; LoBue, Denney, et al., 2016), Alzheimer's disease (AD) (LoBue, Wadsworth, et al., 2016; Plassman et al., 2000), and frontotemporal dementia (FTD) (Deutsch, Mendez, & Teng, 2015; LoBue, Wilmoth, et al., 2016). Although several studies have found that moderate to severe TBI increases dementia risk (Gedye, Beattie, Tuokko, Horton, & Korsarek, 1989; Plassman et al., 2000; Wang et al., 2012), others have failed to find an association (Crane et al., 2016; Dams-O'Connor et al., 2013), and evidence for mild TBI as a risk factor is limited, making it difficult to draw firm conclusions. Nonetheless, a series of autopsy and imaging studies have found evidence that a single moderate to severe TBI may contribute to the accumulation of amyloid-beta (Aβ) plaques and neurofibrillary tangles (NFTs) (Johnson, Stewart, & Smith, 2012, 2013; Scott et al., 2016), the hallmark pathology of AD, suggesting a potential mechanistic association between TBI and an increased risk for dementia in some individuals.

TBI is thought to contribute to an accumulation of AD-related pathology by disrupting neurometabolic processes (Johnson et al., 2013). Rotational and shearing forces can lead to traumatic axonal injury, characterized by cytoskeletal damage, axonal swelling, and deficient neuronal transport (Johnson, Stewart, & Smith, 2010). These processes are believed to lead to the accumulation of intracellular Aβ (Ikonomovic et al., 2004; Johnson et al., 2013), and eventually the formation of Aβ plaques after being released into the surrounding brain tissue following progressive cell death (Johnson et al., 2010). Approximately 33% of individuals who died from a single, moderate to severe TBI were observed to have Aβ plaques at autopsy (Johnson et al., 2012; Roberts et al., 1994), and nearly 30% of individuals who survived at least one year post-TBI had Aβ plaques and/or NFTs present (Johnson et al., 2012). Aβ plaques have also been found to be more common *in vivo* in individuals with a history of moderate to severe TBI when compared to controls, with the accumulation being linked to TBI-related white matter damage, which overlapped the pattern of deposition observed in AD (Scott et al., 2016). Although an association between a single TBI and NFTs is less clear, significantly higher percentages of NFTs were found in individuals at least one year after sustaining a single moderate to severe TBI compared to age-matched controls (Johnson et al., 2012). Thus, it appears that for some individuals, a history of TBI can be associated with an increased risk for later developing AD neuropathology, although the mechanism underlying this risk is poorly understood.

Since TBI may contribute to an accumulation of AD-related pathology, TBI may accelerate clinical expression of cognitive disorders later in life. For example, in a series of large

multicenter investigations, our group examined individuals diagnosed with AD, mild cognitive impairment, and frontotemporal dementia, and consistently found that a remote history of TBI (> 1 year prior to evaluation) with reported loss of consciousness (LOC) was linked to an approximately 2.5 year earlier age of onset for each condition (LoBue, Denney, et al., 2016; LoBue, Wadsworth, et al., 2016; LoBue, Wilmoth, et al., 2016). However, previous studies have differed in the degree of this association, with some reporting that a TBI history can accelerate the onset of AD by 7 to 9 years (Gedye et al., 1989; Nemetz et al., 1999; Sullivan, Petitti, & Barbaccia, 1987), while others found no relationship between TBI and earlier AD onset (Guo et al., 2000; Plassman et al., 2000; Rasmusson, Brandt, Martin, & Folstein, 1995). Notably, previous studies have used clinical criteria for diagnosing AD rather than more reliable neuropathological criteria (Beach, Monsell, Phillips, & Kukull, 2012). As such, the primary aim of this study was to determine whether TBI is associated with earlier age of AD onset in an autopsy-confirmed sample. The findings would provide clarity to the currently mixed literature and generate additional insight into TBI as a risk factor for earlier onset of AD.

Methods

Participants

Data for this study were obtained from the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) and Neuropathology Data Set. NACC has collected clinical, autopsy, demographic, and genetic data on healthy controls and those diagnosed with mild cognitive impairment, AD, and other types of dementia from Alzheimer's Disease Centers (ADCs) across the United States from September 2005 (Morris et al., 2006). All ADCs are funded by the National Institute on Aging (NIA). Written informed consents were obtained from participants at each ADC and approved by the ADC's Institutional Review Board (IRB). Research using the NACC database was approved by the University of Washington IRB. Selection criteria for this study included participants from UDS versions 1 and 2 who were a) aged 50 years or older, b) had a clinical diagnosis of all-cause dementia during initial/follow-up visits up to March 2015, and c) had significant AD-related pathology at autopsy. In total, data were drawn from 32 ADCs in this sample. A clinical diagnosis of dementia was made by a team of multi-disciplinary ADC clinicians using established guidelines for possible/probable AD (NINCDS/ADRDA criteria; (McKhann et al., 1984), Lewy body dementia (McKeith et al., 2005), vascular dementia (NINDS-AIREN; Roman et al., 1993), frontotemporal dementia (Neary et al., 1998), and other medical conditions (Diagnostic and Statistical Manual for Mental Disorders, 4th edition). A pathological diagnosis of AD was inferred from the NIA-AA criteria (Hyman & Trojanowski, 1997) using Braak neurofibrillary tangle stages and CERAD neuritic plaque scores. Braak stages refer to patterns of distribution and severity depositions of NFTs, where stages I–II indicate transentorhinal involvement, III–IV indicate limbic and hippocampal involvement, and V–VI indicate extensive neocortical involvement (Braak & Braak, 1991). CERAD neuritic plaque scores are used in combination with Braak staging, and indicate the density of neuritic plaques (primarily composed of Aβ deposits) in select neocortical regions (Mirra, Hart, & Terry, 1993). In the current study, the combination of Braak stages III–VI with *moderate* or *frequent* CERAD plaque scores (Hyman & Trojanowski, 1997) indicated

that AD-related pathology was a sufficient explanation for cognitive impairment, and can be considered a minimum threshold for a histopathological diagnosis of AD (Beach et al., 2012). From this initial sample, an additional sample was derived to assess whether findings remained using criteria where the probability of histopathologic AD was the highest (i.e., Braak stages V–VI and *frequent* CERAD scores) (Hyman & Trojanowski, 1997).

Measures

The NACC dataset consisted of three questions related to TBI history that were answered by participant or informant report during ADC visits. Specifically, it was asked if participants had ever sustained a TBI resulting in LOC < 5 minutes, ≥ 5 minutes, or a chronic deficit. Responses to these three questions were coded as *absent*, *recent/active*, *remote/inactive*, or *unknown*. *Recent/active* was defined as having a TBI < 1 year ago or requiring ongoing treatment and *remote/inactive* was defined as having a TBI ≥ 1 year ago with recovery or no current treatment. Because time since injury was unknown, we examined the effect of a history of remote TBI by including participants who reported a *remote/inactive* TBI (i.e. occurring ≥ 1 year prior) at the initial ADC visit, while excluding those who were coded as having a *recent/active* TBI at the initial visit or anytime thereafter. To limit potential confounding of cognitive decline directly related to an injury, those reporting a chronic deficit from a TBI were also excluded. Therefore, only those participants who reported a *remote/inactive* TBI at the initial visit with no ongoing chronic deficits (TBI+) or an absence of TBI history at every visit (TBI−) were included in this study.

Age of dementia onset was defined as: 1) the ADC clinician's estimated age of cognitive decline based on participant/informant report, medical records, and observation, and 2) the participant's age at the ADC visit in which they were diagnosed with dementia. Because demographics (e.g., age, sex, race, education), family history of dementia (e.g., a first-degree relative), apolipoprotein E ε4 status (Apoe4; number of alleles), and depression (i.e., lifetime history) have been linked to an increased risk for dementia, these were examined to assess their potential influence on age of dementia onset. Depression history was defined through NACC as having been seen by a clinician regarding depressed mood, having been prescribed an antidepressant medication, or having been diagnosed with a mood disorder (i.e., major depression, dysthymia, bipolar disorder). Depression and a family history of dementia were coded in the NACC database as *absent, present*, or *unknown.*

Statistical Analyses

Chi-square analyses were used to assess whether TBI+ and TBI− groups differed by demographics, number of Apoe4 alleles, family history of dementia, and depression history. To test whether years of education differed between groups, an Independent sample *t* test was used. Any differences in these variables were then used as covariates in primary analyses. An Analysis of Covariance (ANCOVA) was used to assess whether age of dementia onset (clinician estimated age of cognitive decline and age at diagnosis) was significantly different between the TBI+ and TBI− groups. Additional ANCOVAs were performed to assess whether associations remained for participants with the highest probability that their dementia was explained by AD (i.e., Braak stages V–VI in combination with *frequent* CERAD scores) (Hyman & Trojanowski, 1997). Afterward, ANCOVAs were

performed again only for participants *without* co-morbid frontotemporal lobar degeneration and/or Lewy body pathology to determine if effects remained after excluding those with mixed pathologies known to have an earlier symptom onset. Assumptions for analyses were reviewed, and while there was homogeneity of regression slopes (no significant interactions between TBI history and any covariate), violations of homogeneity of variance occurred. Welch Analyses of Variance (ANOVA) were used to reduce the chances of a Type I error to account for inequality of variance. Missing data were assessed for each individual analysis and participants missing relevant data were not included in analyses. All analyses were conducted using IBM SPSS Statistics V24 (IBM Corp, SPSS Statistics V24, Armonk, New York, USA, 2013) with $p < 0.05$ as the level of significance.

Results

Clinical, demographic, and sample characteristics

A total of 2,153 participants with autopsy-confirmed AD were included, of which 197 reported a history of TBI (TBI+) and 1,956 did not (TBI−). One participant was missing information regarding race, 1% ($n = 20$) were missing years of education, 10% ($n = 217$) family history of dementia, 15% ($n = 314$) Apoe4 status, 1% ($n = 20$) age of diagnosis, and 3% ($n = 59$) clinician-estimated age of symptom onset. TBI+ and TBI− groups were primarily Caucasian (94%) and well-educated ($M = 15.18$), and they did not differ in lifetime history of depression, depression within the last 2 years of dementia diagnosis, family history of dementia, or number of Apoe4 alleles. TBI+ and TBI− groups differed on race, sex, and years of education, as the TBI− group had a smaller proportion of Caucasians, fewer males, and lower levels of education than the TBI+ group (See Table 1). Similar results were observed among participants with the highest probability that their dementia was explained by AD (i.e., groups differed by sex, race, and education).

TBI history and age of symptom onset and dementia diagnosis

After excluding participants with missing data and controlling for race, sex, and years of education, the average age of clinician-estimated symptom onset was 2.35 years earlier ($p = .01$, $d = 0.23$, 95% CI [0.08, 0.38]) for the TBI+ group compared to the TBI− group. Similarly, the average age at which participants received a dementia diagnosis was 2.83 years earlier ($p = .002$, $d = 0.28$, 95% CI [0.13, 0.43]) for the TBI+ group compared to the TBI-group (See Table 2). Among cases with the highest probability of dementia due to AD, a 3.6-year earlier onset and diagnosis (both p's $< .001$, both d's $= 0.36$, 95% CI [0.19, 0.54]) was observed in the TBI+ group compared to the TBI-group (See Table 2). Of the covariates, only male sex was associated with earlier onset and diagnosis of AD, which was seen in both samples (both p's $< .001$). Inequality of variance was significant for the overall sample ($p < 0.01$) and the sample with more stringent neuropathological criteria ($p = .029$). However, Welch ANOVAs showed that the TBI+ group had a significantly earlier age of symptom onset and age of diagnosis for both samples (both p's < 0.01) compared to the TBI − group, supporting the initial findings. Similarly, examining only participants with an absence of frontotemporal lobar degeneration or Lewy body pathology showed a 3.6 year earlier dementia onset ($p = .014$, $d = 0.35$, 95% CI [0.10, 0.59]) and a 3.44 year earlier

diagnosis (p = .022, d = 0.34, 95% CI [0.09, 0.58]) in those with (n = 69) vs. without (n = 751) a history of TBI.

Discussion

A history of TBI with reported LOC occurring more than one year prior to diagnosis was associated with an approximately 3-year earlier age of symptom onset and diagnosis in individuals with autopsy-confirmed AD. While these findings are consistent with previous reports in well-characterized individuals clinically diagnosed with MCI (LoBue, Denney, et al., 2016), FTD (LoBue, Wilmoth, et al., 2016), and AD (LoBue, Wadsworth, et al., 2016), this is the first study to utilize an autopsy-confirmed AD sample. Despite mixed findings in the literature, it appears that a history of TBI with LOC can hasten the onset of AD for some individuals.

Axonal injury is one proposed mechanism of increasing dementia risk following a TBI, and some injuries have been suspected of initiating chronic neurodegeneration, at least after moderate to severe TBI (Johnson et al., 2013). In a longitudinal study, Tomaiuolo et al. (2012) evaluated group differences in white matter volume in normal controls and survivors of severe TBI at 1 and 8 years post-injury. The study revealed significantly smaller corpus callosum volumes in TBI survivors compared to controls and more importantly, significant loss of corpus callosum volume between 1 and 8 years post-injury, suggesting axonal degeneration that exceeded the time frame of acute injury effects (Tomaiuolo et al., 2012). Because accelerated white matter degeneration has been found to be associated with increased risk for cognitive decline in aging individuals (Silbert et al., 2012), it is possible that some injuries may be linked to an earlier dementia onset via a progressive loss of white matter connections. However, it is unknown if degenerative changes continue beyond this timeframe or occur in less severe injuries. It is suspected that the effects of TBI may lead to a greater accumulation of pathological burden that overlaps several neurodegenerative conditions similar to AD, and as a result, might accelerate onset of neurodegenerative dementias (for a review, see LoBue, Cullum, Didehbani, et al., in press). Alternatively, rather than initiating a neurodegenerative process, TBI may induce a static reduction in brain and cognitive reserve that lowers the threshold for manifestation of cognitive dysfunction related to AD and other dementia conditions. If so, TBI may reduce the brain's ability to compensate for an underlying neurodegenerative process, which could increase the risk of earlier dementia onset (for a review, see Bigler & Stern, 2015). Thus, the mechanistic link between TBI and earlier dementia onset remains unknown.

Despite some individuals having shown increased AD neuropathology following moderate to severe TBI (Johnson et al., 2012), not all studies have supported this link. For example, Crane et al. (2016) conducted a large retrospective analysis to examine a history of TBI as a risk factor for the development of various neuropathological changes in 1,589 community dwelling older adults. Specifically, the authors concluded that a remote TBI with LOC was associated with increased Lewy bodies and cerebral microinfarcts, but not AD pathology in the 213 cases that came to autopsy. Although other lines of evidence suggest that Lewy bodies can accumulate following traumatic axonal injury (Sundman, Hall, & Chen, 2014; Uryu et al., 2007), one possible explanation for the lack of an association observed with AD

may relate to the use of a very high threshold to define AD pathology in that study (i.e., the authors' quantified NFTs in the neocortex, or only Braak Stages V and VI), and the results may have differed if more inclusive criteria were used. Alternatively, it is possible that some neuropathological features may plateau early in the disease process (Serrano-Pozo, Frosch, Masliah, & Hyman, 2011), thus making it difficult to measure an increase in neuropathological features at autopsy. Nonetheless, not all individuals with a history of TBI have higher levels of AD pathology (Johnson et al., 2012) or are at an increased risk for AD (Dams-O'Connor et al., 2013).

TBI severity, age at injury, and repeated injuries may be factors that moderate the risk for later developing dementia. For example, Gardner et al. (2014) found that a moderate to severe TBI sustained after age 55 was associated with an increased risk of all-cause dementia (hazard ratios ranged from 1.31 to 1.65) when followed for 7 years, while an association with mild TBI was only observed among individuals injured after age 65 (hazard ratios 1.22 to 1.26). The risk for dementia was doubled for individuals who sustained multiple TBIs of any severity, though other studies have not found such an association with all-cause dementia (Mehta, Ott, Kalmijn, et al., 1999; Dams-O'Connor et al., 2013). Methodological differences, such as duration of followup, TBI classification, and methods of determining dementia diagnosis, may help explain the mixed literature regarding TBI and the risk of AD and other dementias.

There are several methodological limitations that could limit the generalizability of our findings. First, because of the limitations in the available data, the time of injury in NACC cases UDS versions 1 and 2 is unknown, and TBIs may have occurred between one-year and several decades earlier, even though individuals with more recent injuries were excluded. As such, it is possible that the clinician-estimated age of cognitive decline (i.e. symptom onset) could have preceded injury in some individuals. Second, UDS versions 1 and 2 in the NACC database does not include indices of TBI severity, presence of multiple TBIs, and/or other relevant symptoms beyond LOC. Furthermore, the NACC database does not capture information regarding presence or duration of post-traumatic amnesia, which can be confused for brief LOC in individual cases, and as such, it is unknown if some patients reported a brief LOC in place of post-traumatic amnesia (e.g., see Ruff, Iverson, Barth, Bush, & Broshek, 2009). Finally, although cases were selected from a national registry, most were well-educated Caucasians, which could limit generalizability.

Despite these limitations, this is the first study to find that a history of TBI with LOC was associated with an approximately 3-year earlier onset of AD in a neuropathologically confirmed sample, consistent with a previous report from a large national sample using clinical diagnoses (LoBue, Wadsworth, et al., 2016). These findings provide further evidence for TBI as a risk factor for earlier onset of AD, and highlight the importance for further research. Future neuropathological and imaging studies are needed to assess whether TBI results in increasing neuropathological burden through continued white matter degeneration or lowers neuronal reserve. In addition, investigations to help elucidate specific injury characteristics that may predispose some individuals to develop dementia and earlier symptom onset are needed.

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Public Significance Statement

This study adds to the growing body of evidence that a traumatic brain injury (TBI) with loss of consciousness (LOC) is a risk factor for developing Alzheimer's-related dementia earlier than someone without a history of TBI with LOC. Future research is needed to understand what specific injury and demographic characteristics may put some individuals more at risk than others, and the mechanism by which TBI may accelerate the onset of these disorders.

Table 1

Demographics of an autopsy-confirmed Alzheimer's disease sample with and without a history of TBI

	TBI+ (n=197)	TBI− (n=1956)	Statistic (*p*-value)
Education in years, *M* (*SD*)	15.87 (3.01)	15.11 (3.25)	−3.15 (002*)
Males, *n* (%)	134 (68%)	1047 (54%)	15.18 (< .001**)
Non-Hispanic Caucasian, *n* (%)	195 (99%)	1826 (93%)	9.9 (.007*)
Family history of dementia, *n* (%)	116 (62%)	1113 (64%)	.11 (.74)
Number of *APOE ε4* alleles			.42 (.81)
Zero *APOE ε4* alleles, *n (%)*	71 (43%)	691 (41%)	
One *APOE ε4* allele, *n (%)*	71 (43%)	758 (45%)	
Two *APOE ε4* alleles, *n (%)*	24 (14%)	224 (13%)	
Depression			
Lifetime, *n* (%)	95 (49%)	927 (49%)	.003 (.96)
Within 2 years of diagnosis, *n* (%)	87 (45%)	847 (44%)	.05 (.83)

* $p < .05$,

** $p < .001$

Note. APOE ε4 indicates apolipoprotein E *ε4*.

Table 2

Differences in age of dementia diagnosis and symptom onset in those with and without a history of TBI

			N	*M* (*SD*)	$M_{difference}$	*F* (*p*-value)	*d* [95% CI]
Intermediate	Onset	TBI +	194	68.02 (11.58)	2.35	6.72 (.01)	0.23 [0.08, 0.38]
		TBI−	1900	70.37 (10.09)			
	Diagnosis	TBI +	197	74.18 (11.22)	2.83	10.08 (.002)	0.28 [0.13, 0.43]
		TBI−	1936	77.01 (10)			
High	Onset	TBI +	135	65.11 (10.38)	3.63	13.53 (< .001)	0.36 [0.19, 0.54]
		TBI−	1349	68.74 (9.94)			
	Diagnosis	TBI +	136	71.72 (10.72)	3.64	12.92 (< .001)	0.36 [0.19, 0.54]
		TBI−	1362	75.36 (9.91)			

Note. Race, Sex, and Education were entered as covariates into the ANCOVA. “Intermediate” and “High” samples refer to the likelihood that dementia was due to AD according to NIA-AA criteria.