Traumatic Brain Injury and Age at Onset of Cognitive Impairment in Older Adults

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ABSTRACT

There is a deficiency of knowledge regarding how traumatic brain injury (TBI) is associated with age at onset (AAO) of cognitive impairment in older adults. Participants with a TBI history were identified from the Alzheimer's Disease Neuroimaging Initiative (ADNI 1/GO/2) medical history database. Using an analysis of covariance (ANCOVA) model, the AAO was compared between those with and without TBI, and potential confounding factors were controlled. The AAO was also compared between those with mild TBI (mTBI) and moderate or severe TBI (sTBI). Lastly, the effects of mTBI were analyzed on the AAO of participants with clinical diagnoses of either mild cognitive impairment (MCI) or Alzheimer's disease (AD). The AAO for the TBI group was 68.2 ± 1.1 years (95% confidence interval (CI): 66.2-70.3, n=62), which was significantly earlier than the AAO for the non-TBI group of 70.9 ± 0.2 years (95% CI: 70.5-71.4, n=1197) (p=0.013). Participants with mTBI history showed an AAO of 68.5 ± 1.1 years (n=56), which was significantly earlier than the AAO for the non-TBI group (p=0.032). Participants with both MCI and mTBI showed an AAO of 66.5 ± 1.3 years (95% CI: 63.9-69.1, n=45), compared to 70.6 ± 0.3 years for the non-TBI MCI group (95% CI: 70.1-71.1, n=935) (p=0.016). As a conclusion, a history of TBI may accelerate the AAO of cognitive impairment by 2 or more years. These results were consistent with reports of TBI as a significant risk factor for cognitive decline in older adults and TBI is associated with an earlier AAO found in patients with MCI or AD.

Introduction

Traumatic brain injury (TBI) has been studied as a risk factor associated with cognition deterioration for several decades [1]. However, the details of how TBI associates with onset of cognitive impairment is still unclear due to a number of factors such as varied criteria for defining TBI severity [2], as well as various types and severity of cognitive impairment. A history of TBI has been found to correlate with an elevated risk for developing cognitive impairment [3-7]. For example, a 5-year follow-up study found that TBI could increase the risk of developing dementia by 1.7 fold after adjusting for covariates [8]. The dementia associated with TBI could be either the Alzheimer's disease (AD) type or the non-AD type [2, 9, 10]. The TBI severity plays an important role for dementia development [2, 5, 11]. Moderate to severe TBI (sTBI) was confirmed as a risk factor for developing dementia [5, 12, 13]. Even mild TBI (mTBI) was shown as an independent significant risk factor for developing dementia with a hazard ratio between 1.6 and 3 [2, 14, 15]. In this study, we tested the hypothesis that a history of TBI and the severity of TBI are associated with the age at onset (AAO) of cognitive impairment in older adults. In addition, we assessed whether mTBI influences the AAO in patients with clinical diagnoses of cognitive impairment (mild cognitive impairment (MCI) versus or AD).

Methods

Alzheimer's Disease Neuroimaging Initiative (ADNI)

Data used in preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). The ADNI was launched in 2003 and has been sponsored by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2. To date these three protocols have recruited over 1500 adults, ages 55 to 90, to participate in the research, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. The follow up duration of each group is specified in the protocols for ADNI-1, ADNI-2 and ADNI-GO. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2. Further information can be found at http://www.adni-info.org/ and in previous reports [16-21].

Selection of Participants with a TBI History

Self-reported medical history data were collected from all participants at all ADNI clinical sites. Both participants and their study partners (informants) were the sources of the medical history information. We assessed all participants first for history of TBI, subsequently including only those with cognitive impairment (e.g. MCI and AD) in whom AAO was recorded. Therefore, the final sample included 81 participants with a history of TBI. Demographic and clinical information for the 81 participants with TBI history was summarized in Table 1. The age at injury of TBI showed a bimodal distribution and the average age at injury is 35.4 ± 24.8 years old. According to the Mayo Clinic TBI standards [22], 8 of these 81 participants have a diagnosis of sTBI and 73 participants had mTBI.

Data Analyses

AAO referred to the age at which a participant first reported cognition impairments for:

- a memory complaint reported by either participant or informant; and

- an objective memory loss measured by education adjusted scores on delayed recall of one paragraph from Wechsler Memory Scale Logical Memory II (between approximately 0.5 and 1.5 standard deviation below the mean of normal cognition); and

- a clinical dementia rating of 0.5 or more.

The AAO was the dependent variable in all analyses and results were presented in the format of mean ± standard error. In total, 19 of the 81 participants with TBI history were recruited as healthy control participants and thus, did not have a

reported AAO. Therefore, the final sample of participants with a reported AAO includes 1197 without a TBI history and 62 with a TBI history.

The following analyses were completed using SPSS version 22.0. First, the AAO was compared between the TBI and the non-TBI groups by one-way univariate ANCOVA analysis with gender, years of education, *APOE* ε4 carrier status (+/-), and baseline diagnosis group as covariates. Then, the AAO was compared among non-TBI (n=1192), mTBI (n=62), and sTBI (n=6) using a one-way univariate ANCOVA analysis covaried for gender, years of education, *APOE* ε4 carrier status (+/-), and baseline diagnosis group. Lastly, the effects of mTBI on AAO were studied in participants with either AD or MCI using a two-way ANCOVA model (cognition diagnosis by TBI status) with controlling for gender, years of education, and *APOE* ε4 carrier status (+/-). The Bonferroni test was used for post-hoc comparisons between subgroups. The significance level of p value < 0.05 was set for all analyses, and all graphs were created by using Sigmaplot version 10.0.

Results

An earlier AAO of cognitive impairment is associated with a TBI history

The AAO of cognitive impairment was compared between participants with TBI (TBI) or without TBI (non-TBI). The TBI group (n=62) had a significantly earlier AAO of 68.2 ± 1.1 years (95% confidence interval (CI): 66.2-70.3, n=62) than the

non-TBI group (AAO: 70.9 ± 0.2 years; 95% CI: 70.5-71.4; n=1197; p=0.013) (Fig1 and Table 2).

mTBI but not sTBI is related to an earlier AAO of cognitive impairment

Then the effects of TBI severity were investigated by comparing the AAOs among participants without TBI (none), with mTBI, or with sTBI. The AAO for non-TBI group was 70.9 ± 0.2 years (95% CI: 70.5-71.4; n=1197) and the AAO was 68.5 ± 1.1 years for mTBI group (95% CI: 66.3-70.7; n=56). For the sTBI group, the AAO was 66.0 ± 3.4 years (95% CI: 59.3-72.6, n=6). The more severe the TBI, the earlier an AAO was observed for the participants with a TBI history, although only non-TBI group and the mTBI group have significantly different AAOs (p=0.032) (Fig2 and Table 2).

mTBI is associated with an earlier AAO in participants with MCI

Based on having mTBI or not, participants with cognitive impairment (MCI or AD) were divided into four subgroups: MCI, MCI + mTBI, AD and AD + mTBI. The AAOs for these four groups were as follows: 70.6 ± 0.3 years for the MCI group (95% CI: 70.1-71.1, n=935); 66.5 ± 1.3 years for the mTBI + MCI group (95% CI: 63.1-69.1, n=45); 72.3 ± 0.6 years for the AD group (95% CI: 71.1-73.5, n=193); and 70.2 ± 2.6 years for the mTBI + AD group (95% CI: 65.1-75.3, n=10). The participants with both MCI and mTBI history showed a significantly earlier AAO than the MCI group of approximately 4 years (p=0.016). Participants with both AD and mTBI history had an earlier AAO (< 2 years) than the AD group. However, the difference was not statistically significant (Fig3 and Table 2).

Discussion

Previous studies have shown that TBI is an important risk factor for developing either AD or non-AD type dementia [2, 9, 10]. There has been less research quantifying how TBI or severity of TBI is associated with the AAO of cognitive impairment [11]. In our retrospective study, participants with a TBI history had an accelerated AAO of cognitive impairment. In considering possible mechanisms of impact on onset of cognitive decline, we note that in humans, axons damaged by TBI have been shown to serve as a large reservoir of amyloid-beta, which may explain the observed amyloid plaques found in the brains of TBI subjects [23]. In a rat model, the overexpression of amyloid-beta precursor protein (APP) was also observed following TBI [24]. Since the presence of amyloid-beta plaques is a key feature of AD, these data indirectly support TBI as a risk factor for associating with cognition deterioration as well as an earlier AAO than in older adults without a TBI history.

Although the sTBI group shows a trend of having an earlier AAO than the mTBI group, the present study did not have sufficient power to test the difference. The sample size for the sTBI group is small due to the enrollent criteria for the ADNI. Participants with a history of significant head trauma followed by persistent neurologic deficits or known structural brain abnormalities were excluded from the ADNI (see exclusion criteria in the protocols for the ADNI 1/GO/2). An underlying mechanism for developing cognitive impairments from mTBI was suggested by findings that white matter abnormalities from symptomatic mTBI patients show a similar distribution pattern as in early AD type dementia [25]. By contrast, severe TBIs can initiate AD-type pathological processes as an acute

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phase response to TBI by overexpressing APP and leading to amyloid-beta plaque deposition [26]. Both mTBI and sTBI appeared to influence onset of cognitive decline, although the difference between AAOs based on TBI severity was not significant in this study.

Although some symptoms from mTBI can be resolved within a few months post-injury [1], a history of mTBI was shown to be associated with a significantly earlier AAO of cognitive impairment by more than 4 years in patients with a cognition diagnosis of MCI. The mTBI has a smaller non-significant effect (less than 2 years) on the AAO of cognitive impairment observed in patients with a diagnosis of AD.

Our findings have important implications for clinical diagnosis and prognosis, as well as for applying therapeutic interventions to decrease the likelihood of developing cognition impairments after TBI. As for any retrospective study, one limitation for this study comes from the possible recall bias for either TBI history or cognitive symptoms, which were reported by the participants. The second limitation is that the effects of mTBI on AAO were only studied in patients with either MCI or AD. Individuals with TBI could have different etiologies for cognitive impairment other than AD or chronic traumatic encephalopathy (CTE) [27]. For example, frontotemporal dementia is seen more often in those with TBI than in those without a TBI history [28, 29]. However, the manner by which TBI affects risk for other types of dementia or cognitive impairment is beyond the scope of this study because it was performed in an MCI/AD cohort. In addition, this study did not control for other possible confounding factors that might affect the AAO of

cognitive impairment as well such as alcoholism, hypertension, stroke and type 2 diabetes mellitus [30-33].

Our study demonstrated TBI as a risk factor associated with an earlier AAO of cognitive impairment. Even a history of mTBI was shown to significantly accelerate the AAO of cognitive impairment. Lastly, mTBI was shown to acclerate the AAO in patients with MCI. The cognitive symptoms seen in people with a TBI history may be associated with a common sequelae of head injury: namely depression [7, 34], which was not investigated further in the current study. The quantification information regarding how TBI assoicates with an earlier AAO of cognitive impairment may be useful for clincans to make a more accurate prognosis or take appropriate preventative or therapeutic measures for TBI patients. The roles of moderate or severe TBIs on cogntion impairments are worthy to be studied with a larger sample in the future. Finally, the observed association between TBI and AAO of cognitive impairment need further confirmation by studies investigating biomarker changes and studies assesssing pathological changes at autopsy.

Conflict of Interest Statement

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Fig1. An earlier AAO was found in participants with a TBI history.

The AAOs were compared between participants with and without (none) a TBI history. AAO: age at onset; None: participants without TBI; TBI: participants with a history of traumatic brain injury

Fig2. The AAO varied with changes in the severity of TBI.

The AAOs were compared among three groups of participants (none, mTBI, and sTBI). AAO: age at onset; None: participants without TBI; mTBI: mild TBI; TBI: moderate or severe TBI

Fig3. mTBI was associated with an earlier AAO in participants with MCI.

The effects of mTBI on AAO were studied among participants with cognitive symptoms (MCI or AD). The participants were divided into four subgroups (MCI, MCI + mTBI, AD and AD + mTBI). AAO: age at onset; MCI: mild cognitive impairment; mTBI: mild TBI; AD: Alzheimer's disease
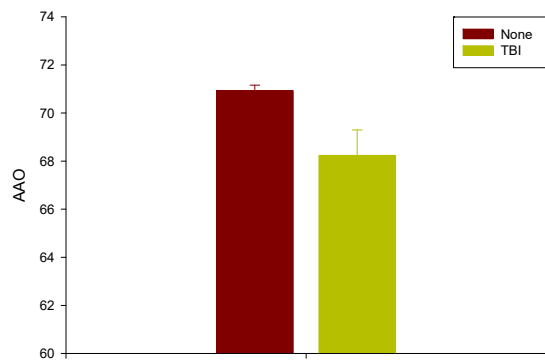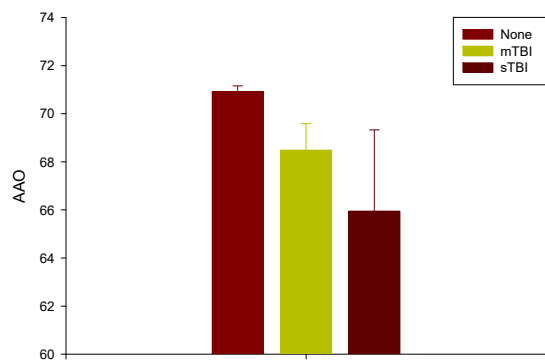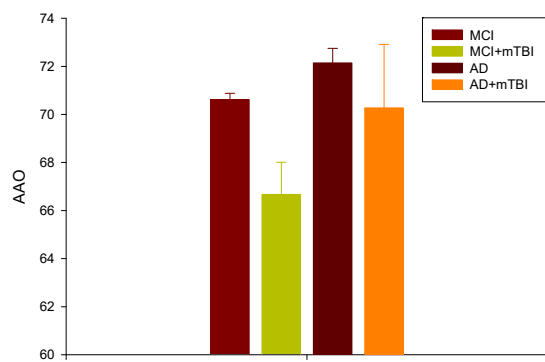
Figure 1.

Figure 2.

Figure 3.

Table1. Demographic and clinical information was shown for the ADNI participants.

Participant group	TBI (n=81)	Non-TBI (n=1197)
Gender (male: female)	58 (71.6%): 23 (28.4%)	677 (56.56%): 520 (43.44%)
Education (mean ± SD)	16 ± 3	16 ± 3
MCI: AD (baseline diagnosis group)	45 (81.82%): 10 (18.18%)	935 (82.89%): 193 (17.11%)
APOE ε4 genotype (+/-)	37 (45.68%): 44 (54.32%)	646 (53.97%): 551 (46.03%)
MMSE Total Score	27.3 ± 2.8	26.5 ± 2.7

No significant difference was found between the TBI and non-TBI groups for any of the variables. TBI: traumatic brain injury; mean ± SD: mean ± standard deviation; MCI: mild cognitive impairment; AD: Alzheimer's disease; *APOE* ε4: Apolipoprotein epsilon 4; MMSE: mini-mental status examination

Table 2. The AAOs of cognitive impairment were shown for different groups.

Group	AAO	95% CI	N	p
None	70.9 ± 0.2	70.5 - 71.4	1197	
TBI	68.2 ± 1.1	66.2 - 70.3	62	0.013 (versus the Non-TBI group)
mTBI	68.5 ± 1.1	66.3 - 70.7	56	0.032 (versus the Non-TBI group)
sTBI	66.0 ± 3.4	59.3 - 72.6	6	
MCI	70.6 ± 0.3	70.1 - 71.1	935	
mTBI + MCI	66.5 ± 1.3	63.1 - 69.1	45	0.016 (versus the MCI group)
AD	72.3 ± 0.6	71.1 - 73.5	193	
mTBI + AD	70.2 ± 2.6	65.1 - 73.5	10	

AAO: age at onset; TBI: traumatic brain injury; mTBI: mild TBI; sTBI: moderate or severe

TBI; AAOs were shown as mean ± standard error; CI: confidence interval; MCI: mild

cognitive impairment; AD: Alzheimer's disease