Accumulation of amyloid in cognitive impairment after mild traumatic brain injury

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ARTICLE INFO

Article history:
Received 3 September 2014
Received in revised form 2 December 2014
Accepted 22 December 2014
Available online 30 December 2014

Keywords:
Mild traumatic brain injury
Amyloid PET
Alzheimer disease
Cognitive impairment
Genetics
Neurodegenerative diseases

ABSTRACT

Recent epidemiology studies have indicated that traumatic brain injury (TBI) can increase the risk of developing neurodegenerative diseases such as Alzheimer’s disease (AD). Amyloid-β (Aβ) plaques and neurofibrillary tangles are pathological indicators of AD. The accumulation of Aβ is considered the first step of AD pathophysiology. Compelling studies have supported the hypothesis that TBI accelerates the formation and accumulation of Aβ. These findings could link TBI with AD, although the research that reported these findings had limitations, particularly regarding mild TBI (mTBI) patients. The effects of mTBI on Aβ-accumulation remain uncertain because of a lack of mTBI pathology data. Using amyloid-positron emission tomography (amyloid-PET), researchers can help to determine whether mTBI increases the accumulation of Aβ, which might be involved in the pathophysiological mechanisms of mTBI in AD, and could be a target for the treatment of neurodegenerative diseases associated with TBI. In this study, we recruited 27 mTBI patients with mTBI in mean 6 years before this study (21 mTBI patients without cognitive impairment, 6 mTBI patients with cognitive impairment, and 10 controls. All of them underwent mini-mental state examination, apolipoprotein E (APOE) genotyping, and amyloid-PET. The results show an increase of amyloid accumulation and allele frequency of APOE4 in the mTBI patients with cognitive impairment. These findings indicate that amyloid accumulation is an important indicator of cognitive impairment, and amyloid-PET should be a safe and useful tool for diagnosing amyloid-related cognitive impairment. APOE allele might play a role in the occurrence of cognitive impairment after mTBI. The contribution of mTBI to the amyloid accumulation requires further study, and mTBI patients should be recruited for longitudinal research with repeated amyloid-PET studies.

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1. Introduction

Traumatic brain injury (TBI) has become a critical health care concern because of its high incidence and mortality rates, and long-term complications [1], The World Health Organization (WHO) listed TBI as a high-priority research field. In Taiwan, more than 100 000 people, most of whom are young, suffer from TBI, and the annual financial loss is approximately US$350 million [2-4].

Headache, vertigo, balance impairment, and migraine are typical symptoms following TBI. Some of these symptoms are free after the acute stage, but they can also occur unpredictably with a time lag [5]. Many studies have shown that TBI patients are at a high risk of developing neurodegenerative diseases, such as Alzheimer’s disease (AD), Parkinsonism, and motor neuron disease. The pathophysiologic mechanism of all of these disorders could be attributed to complications from TBI [6,7]. Evidence has increasingly supported the association between TBI and AD [8]. A study on community-dwelling elderly adults and a collaborative
reanalysis of case–control studies showed that TBI increases the risk of developing AD [9]. Another analysis of over 1200 TBI survivors showed that the time until the onset of AD was markedly reduced from 18 to 10 years in patients who sustained TBI [10]. In an analysis on data from Taiwan’s longitudinal Health Insurance Database, TBI increases the risk of developing AD by 1.49 times in 5 years after diagnosis [11]. The pathological markers of AD include extracellular senile plaques and intracellular neurofibrillary tangles. Amyloid-β (Aβ) and Tau proteins are the main components of senile plaques and tangles, respectively [12]. Compelling evidence has shown that the accumulation of Aβ or senile plaque formation is the earliest change of AD pathophysiology [13]. All of the genes responsible to familial AD, including amyloid precursor protein, presenilin-1 and presenilin-2, are involved in the metabolism of Aβ [14]. The apolipoprotein E (APOE) gene contains three genetic polymorphisms (alleles; ε2, 3, 4), and APOE4 has been associated with the increased risk of AD development and earlier onset in a gene-dose dependent manner [15]. In our previous study, APOE4 carriers conferred a fivefold increase in the risk of developing AD [16]. In addition, APOE4 has been associated with numerous brain injury conditions, such as the risk of developing vascular dementia [17,18].

In a recent large-scale study, APOE4 was associated with poorer long-term outcomes of TBI, although it was not associated with acute TBI severity [19]. These findings are comparable with those from our previous study, which showed that APOE4 is a predictor for poor outcomes of TBI [20]. The mechanisms were speculated to be attributed to various effects of the different APOE alleles on inflammatory and cellular repair processes, as well as the different statuses of amyloid deposition after TBI in distinct genotypes. The results of in vitro and in vivo experiments have shown that Aβ confers neurotoxicity; Aβ has thus become the main target for new treatment development [21,22].

TBI results in dramatic biochemical, molecular, and cellular changes that contribute to subsequent neuronal damage and death. Brain damage by TBI is a consequence of direct (i.e., related to the immediate mechanical disruption of brain tissue) or primary injury, and indirect (i.e., secondary or delayed) mechanisms. The secondary mechanisms include an acute inflammatory process, which further induces the breakdown of the blood–brain barrier, brain edema and swelling, infiltration of leukocytes, and the recruitment of additional immunocompetent cells, as well as the release of numerous interleukins and chemotactic factors. Subsequently, apoptosis occurs in the damaged brain after TBI [23,24]. Furthermore, an increase in amyloid burden has been observed in both TBI patients and animals. Several studies have reported that downregulation of the key enzyme for amyloid production markedly decreased the amyloid burden and damage size, and improved the TBI outcome in animals [25,26]. A progressive tauopathy or chronic traumatic encephalopathy has been described in selected cohorts with a history of repetitive mechanical disruption of brain tissue) or primary injury, and indirect (i.e., secondary or delayed) mechanisms. The secondary mechanisms include an acute inflammatory process, which further induces the breakdown of the blood–brain barrier, brain edema and swelling, infiltration of leukocytes, and the recruitment of additional immunocompetent cells, as well as the release of numerous interleukins and chemotactic factors. Subsequently, apoptosis occurs in the damaged brain after TBI [23,24]. Furthermore, an increase in amyloid burden has been observed in both TBI patients and animals. Several studies have reported that downregulation of the key enzyme for amyloid production markedly decreased the amyloid burden and damage size, and improved the TBI outcome in animals [25,26]. A progressive tauopathy or chronic traumatic encephalopathy has been described in selected cohorts with a history of repetitive injury/dementia, and Aβ has thus become the main target for new treatment development [21,22].

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2. Method

2.1. Participants

Based on information obtained from the Taiwan-TBI database, TBI patients who fit the inclusion criteria and have received treatment for acute TBI at Taipei Medical University (TMU) Hospital or TMU-Shuang Ho Hospital were listed as candidates for this study. The inclusion criteria for the mTBI participants were a Glasgow coma score (GCS) of 13–15, loss of consciousness (if present) of less than 30 min, and post-traumatic amnesia (if present) of less than 24 h. Controls were volunteers who underwent physical examination in these two hospitals. The mTBI participants and controls were excluded if they had a history of neurological disease, psychiatric disturbance, additional closed-head injuries with loss of consciousness for less than 5 min, head injury within the past year, a learning disorder, attention deficit hyperactivity disorder (ADHD), or substance abuse. The participants were informed by mail or telephone. Finally, 27 mTBI patients, including 6 mTBI with cognitive impairment/dementia (mTBI + D), 21 patients mTBI without cognitive impairment/dementia (mTBI – D), and 10 controls (HC) participated in this study. All of them were volunteers, and their informed consent was provided in writing.

2.2. Questionnaire screening

After providing written informed consent, the participants underwent the AD8 questionnaire and Mini-Mental Status Examination (MMSE). Cognitive impairment is defined as both AD8 equal to or over 2 points, and MMSE score less than 26 points. We grouped the participants based on whether they had cognitive impairment, in terms of mTBI — D or mTBI + D.

2.3. Laboratory study (APOE genotyping)

APOE genotyping was conducted using the PCR-RFLP method. There are two pairs primers, 5’-CTCCGACAT GGGAGGACGTG-3’ (P1; upstream), 5’-CCTACCGAGGTGGAG-GGAGAC-3’ (P2; downstream) for restriction enzyme HhaI, and 5’-CCTCCGCGGTGGAGGAG-3’ (P3; upstream), 5’-GAATTCCGTGAGCCTGGCC-3’ (P4; downstream) for restriction enzyme CfoI.

2.4. Amyloid-PET

All of the participants visited Chang Gung Memorial Hospital (Linkou, Taiwan) for amyloid-PET examination. The details of radiosynthesis of 18F-Florbetapir and amyloid PET image acquisition have been described by our group [31,33]. In brief, all subjects received 18F-Florbetapir PET scan using the Biograph mCT PET/CT System (Siemens Medical Solutions, Malvern, PA, USA) in a 3-dimensional acquisition mode. After injection of 378 ± 13 MBq of 18F-Florbetapir, a single 10-min PET scan was acquired 50 min post injection. Each PET image was then reconstructed using the 3-D OSEM algorithm (4 iterations, 24 subsets; Gaussian filter: 2 mm; zoom: 3) with CT-based attenuation correction, scatter and random corrections as provided by the manufacture. The reconstructed images were with a matrix size of 400 × 400 × 148 and a voxel size of 0.68 × 0.68 × 1.5 mm³.

All image data were proceed and analyzed using PMOD image analysis workstation (version 3.3, PMOD Technologies Ltd, Zurich, Switzerland). Each PET image was co-registered to the corresponding MR image, and the individual MR image was spatially normalized to...
Montreal Neurological Institute (MNI) MRI template. The spatial normalization parameters were then applied to the MRI matched PET images. A total of 7 volumes of interest (VOIs) including whole cerebellum, bilateral frontal, precuneus, parietal, occipital, striatum, posterior cingulate, and temporal were selected based on the automated anatomic labeling (AAL) atlas with some modification [34]. The whole cerebellum was applied as the reference region for calculating standardized uptake value ratio (SUVR) for each VOI. The average SUVR from 7 cortical VOIs and a global cortical SUVR were computed for further analysis.

In addition to VOI analysis, voxel-wise analysis was performed by Statistical Parametric Mapping 5 (SPM5). Voxel-wise two-sample t-test for group comparison among HC, mTBI without dementia (mTBI − D) and mTBI with dementia (mTBI + D) subjects were computed in amyloid SUVR images. Due to a relatively small sample size of our study, SPM analysis were examined using a more stringent threshold of two-tailed p < 0.05 with uncorrected statistics and an extent voxels of 100 here. We also developed a visual scoring system for the data analysis, in which a score of 0 or 1 indicated definitely or equivocally negative amyloid accumulation, and 2 or 3 indicated equivocally positive or definitely positive amyloid accumulation. The scorer was blind to the clinical information.

### 3. Results

The participants in this study comprised 10 controls without mTBI (HC), 21 mTBI patients without dementia (mTBI − D), and 6 mTBI patients with dementia (mTBI + D). The mean MMSE scores were 29.4, 29.3, and 20.5 in the controls, mTBI − D patients, and mTBI + D subjects respectively. The mean amyloid accumulation score was 0.60 ± 0.52 in controls, 0.86 ± 0.66 in mTBI − D patients, and 1.83 ± 0.75 in mTBI + D patients. The differences were statistically significant (p < 0.05).

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### Table 1

Demographic information and cognitive function of the participants.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>mTBI without dementia</th>
<th>mTBI with dementia</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>10</td>
<td>21</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Sex (male, female)</td>
<td>2, 8</td>
<td>9, 12</td>
<td>4, 2</td>
<td></td>
</tr>
<tr>
<td>Age (SD) (years)</td>
<td>50.6 ± 6.8</td>
<td>53.70 ± 7.9</td>
<td>60.0 ± 7.5</td>
<td>0.063</td>
</tr>
<tr>
<td>Education (years)</td>
<td>12.8 ± 1.69</td>
<td>13.05 ± 2.31</td>
<td>11.17 ± 3.37</td>
<td>0.237</td>
</tr>
<tr>
<td>MMSE (±SD)</td>
<td>29.4 ± 1.4</td>
<td>29.3 ± 1.1</td>
<td>20.5 ± 4.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AD8 score (±SD)</td>
<td>0.3 ± 0.5</td>
<td>1.6 ± 1.6</td>
<td>3.3 ± 2.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glasgow coma scale</td>
<td>–</td>
<td>14.7 ± 0.6</td>
<td>14.8 ± 0.4</td>
<td>0.674</td>
</tr>
<tr>
<td>Initial loss of consciousness (%)</td>
<td>–</td>
<td>28.6%</td>
<td>83.3%</td>
<td>0.035*</td>
</tr>
<tr>
<td>Age of mTBI (years)</td>
<td>–</td>
<td>47.7 ± 10.5</td>
<td>54.2 ± 9.4</td>
<td>0.132</td>
</tr>
<tr>
<td>Duration between mTBI and amyloid PET (years)</td>
<td>–</td>
<td>6.10 ± 4.70</td>
<td>6.99 ± 5.18</td>
<td>0.693</td>
</tr>
</tbody>
</table>

**Notes:**
- Amyloid accumulation score 0: 4
- Amyloid accumulation score 1: 6
- Amyloid accumulation score 2: 0
- Amyloid accumulation score 3: 0
- Mean amyloid accumulation score: 0.60 ± 0.52
- Age of mTBI: 47.7 ± 10.5
- Duration between mTBI and amyloid PET: 6.10 ± 4.70

* Indicates p < 0.05.

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![Fig. 1](image-url)  
**Fig. 1:** 18F-Florbetapir PET images in 3 subjects representative of range of tracer binding. Top subject was HC, middle was mTBI without dementia (mTBI − D), and bottom was mTBI with dementia (mTBI + D). All images were acquired with same acquisition time period, spatially normalized and overlay to the Montreal Neurological Institute MRI template in the same manner, scaled to same SUVR maximum, and were shown at identical sagittal plane for comparison.
patients, respectively. The mean AD8 scores were 0.3, 1.6, and 3.3 in the controls, mTBI − D patients, and mTBI + D patients, respectively. The clinical manifestations of mTBI were recorded, including the initial loss of consciousness (ILOC), Glasgow coma scale (GCS), age of mTBI onset, and duration between mTBI and amyloid PET (Table 1). These findings indicate that ILOC could be a risk factor for the further development of dementia. The OR of ILOC for the mTBI with dementia group was 12.5 (95% CI 1.20–130.62, p = .035).

The mean amyloid accumulation score of mTBI + D, 1.83 ± 0.75, is higher than those of the mTBI − D, 0.86 ± 0.65, and the control (HC) group, 0.60 ± 0.52 (Table 1). The difference in mean amyloid accumulation scores was nonsignificant between the mTBI − D and the HC group. These data could be comparable with the cognitive performance results, which did not reach the statistical significance for the difference between the HC and mTBI − D. However, the mTBI − D still contained more amyloid in the brain. There were 3 cases with a score of 2 among the mTBI − D, but none of the HC received a score greater than 1.

Example amyloid images of controls (HC), mTBI − D, and mTBI + D were shown in Fig. 1. The levels of amyloid burden as shown by 18F-Florbetapir PET images were similar among HC and mTBI − D subjects with little uptake of radioactivity over brain cortex area. Inversely, mTBI + D subjects show relative high uptake of radioactivity over cortical regions including bilateral striatum, frontal, temporal and parietal regions. When look into the voxelwise comparison among the three groups, significant increased amyloid burden was shown at right cuneus between HC and mTBI − D subjects (Fig. 2A). Additional regions including bilateral superior temporal, left cuneus, right parietal, and right cingulate were highlighted between HC and mTBI + D subjects (Fig. 2B). More amyloid burden in bilateral precuneus, bilateral parietal, and right putamen were noted when compared between mTBI − D and mTBI + D subjects (Fig. 2C), suggesting a possible increased amyloid burden in mTBI + D group as compared to HC and mTBI − D (Table 2).

Apolipoprotein E genotyping is also a risk factor for mTBI patients with dementia. The allele frequency of APOE4 was significantly higher in the mTBI with dementia group than in the control group (P = .049). The linear regression analysis between ApoE4 and average amyloid SUVR showed significant correlation for all subjects. However, there was no significant correlation for individual groups (Table 3).

4. Discussion and conclusion

In this pilot study, we recruited 10 patients without mTBI or dementia, 21 mTBI patients without cognitive impairment, and 6 mTBI patients with cognitive impairment. No substantial side effects or complications of amyloid PET were observed. Compared with the control group, the subjective cognitive performance (i.e., the MMSE) of the mTBI groups, the difference between the mTBI without cognitive impairment group and the controls was nonsignificant, 29.4 vs. 29.3, which could possibly be attributed to the ceiling effect of the MMSE. MMSE might be not adequately sensitive enough to detect extremely mild cognitive impairment, especially for people with prior high cognitive function. However, this finding could be comparable with previous studies, either in case–control studies or cohort studies on health care database analysis [35]. Although the clinical manifestations were similar among the mTBI − D and mTBI + D groups, the ILOC appears to be a risk factor for the subsequent development of dementia in mTBI patients (5/6 vs. 6/21, OR 12.5, 95% CI 1.20–130.62). ILOC usually indicates greater severity of TBI; therefore, it is speculated that the occurrence of dementia after mTBI depends partially on the severity of the involved TBI.

The amyloid PET examination showed that amyloid accumulation increased in the mTBI patients with dementia (mTBI + D). The difference in amyloid accumulation was nonsignificant between the mTBI

### Table 2

Regional amyloid PET SUVR in HC, mTBI with and without dementia subjects.

<table>
<thead>
<tr>
<th>Brain region</th>
<th>HC (10)</th>
<th>mTBI without dementia (21)</th>
<th>mTBI with dementia (6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Striatum</td>
<td>1.06 ± 0.08&lt;sup&gt;*&lt;/sup&gt;</td>
<td>1.12 ± 0.06</td>
<td>1.23 ± 0.15&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Frontal</td>
<td>1.05 ± 0.07</td>
<td>1.08 ± 0.08</td>
<td>1.15 ± 0.20</td>
</tr>
<tr>
<td>Anterior cingulate</td>
<td>1.09 ± 0.11</td>
<td>1.08 ± 0.09</td>
<td>1.15 ± 0.21</td>
</tr>
<tr>
<td>Posterior cingulate</td>
<td>1.19 ± 0.09</td>
<td>1.21 ± 0.10</td>
<td>1.27 ± 0.13</td>
</tr>
<tr>
<td>Occipital</td>
<td>1.11 ± 0.07</td>
<td>1.17 ± 0.06</td>
<td>1.25 ± 0.11&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Parietal</td>
<td>1.01 ± 0.08&lt;sup&gt;*&lt;/sup&gt;</td>
<td>1.07 ± 0.06</td>
<td>1.17 ± 0.14&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Temporal</td>
<td>0.99 ± 0.06&lt;sup&gt;*&lt;/sup&gt;</td>
<td>1.04 ± 0.04</td>
<td>1.14 ± 0.16</td>
</tr>
<tr>
<td>Precuneus</td>
<td>1.00 ± 0.05&lt;sup&gt;*&lt;/sup&gt;</td>
<td>1.03 ± 0.07</td>
<td>1.12 ± 0.15</td>
</tr>
<tr>
<td>Average</td>
<td>1.07 ± 0.07&lt;sup&gt;*&lt;/sup&gt;</td>
<td>1.10 ± 0.05</td>
<td>1.17 ± 0.19</td>
</tr>
</tbody>
</table>

Significant increased amyloid uptake at striatum, occipital, parietal, and precuneus regions in mTBI with dementia as compare to HC subjects.

* p < 0.05 one way ANOVA with Dunn’s multiple comparison test.
patients without dementia (mTBI − D) and the control group. These data could be comparable with the cognitive performance results, which did not reach the statistical significance for the difference between the control group and the mTBI patients without dementia. However, the mTBI − D patients still contained more amyloid in the brain.

A postmortem study documented the specificity of amyloid PET with [11C]PIB tracer for amyloid deposition by using [3H]PIB autoradiography [36]. In that report, they also recruited the 15 patients with moderate to severe TBI, patient, GCS ranged 3–10, and the amyloid PET examinations were conducted in a short period after the TBI, in between 2 days and about 1 year. The mean age of that study is younger than that of this study. Their results support increase of amyloid accumulation following TBI. Our findings also indicate that amyloid PET is a reliable tool that can facilitate diagnosing amyloid-related dementia, particularly in surveying the amyloid burden in the brain even among the patients with mTBI after a long period following the injury. A recent small-scale study showed that amyloid accumulation was not associated with the severity of injury, initial chromatography findings, elapsed time from the injury, or neuropsychological test scores [37]. Further study using methods that are more sensitive or precise in analyzing amyloid PET data might be necessary to identify the effect of mTBI on amyloid accumulation and cognitive dysfunction. Both amyloipahty and tauopathy appear in neurodegeneration-related dementia, such as AD and CTE (chronic traumatic encephalopathy). The real pathomechanisms of dementia after TBI are still unclear. Therefore, further survey of Tau, in addition to amyloid accumulation, should be warranted [38].

APOE4 frequency was high in the mTBI patients with dementia. This might indicate that APOE was involved in the occurrence of dementia in the mTBI patients, which supports the findings of our previous report [20]. Since there are many factors contributing to the accumulation of amyloid in the brains with or without TBI, the results of this study may only support APOE4 to be one of the many contributing factors.

The limitations of this study are detailed as follows. First, the number of participants was small. Because this is a pilot study and the amyloid PET examination was introduced into clinical use only recently, the participants and people were unfamiliar with this tool, particularly regarding the concern of isotope exposure. The findings of this study could alleviate safety concerns and might be accepted by mTBI patients soon in the future. Second, the methods for cognitive evaluation and amyloid PET analysis might not be adequately sensitive to differentiate the amyloid burden between mTBI − D and control groups. Third, the mean age of mTBI + D is larger than the other groups although it is not statistically different. It has been well documented that the accumulation of amyloid increases along with the aging, although TBI might accelerate the rate of amyloid accumulation. This piece of data certainly raises the concern about the age effects on the amyloid accumulation. Larger scale of study remains necessary. Fourth, there is lack of direct evidence of mTBI on the amyloid accumulation in this study and further survey of the increase rate of amyloid accumulation among control and mTBI groups might be helpful. Therefore, a second amyloid PET examination remains necessary to clarify this concern.

This is the first report regarding the amyloid accumulation focusing on the patients with a single event of mild traumatic injury (mTBI), which usually did not show significant abnormality in conventional neuro-image examinations and was considered as a benign disease. All of the findings indicate that amyloid accumulation is a critical indicator of cognitive impairment after mTBI, and that amyloid-PET should be a safe and useful tool for diagnosing amyloid-related cognitive impairment or dementia. APOE allele and initial loss of consciousness might play a role in the occurrence of cognitive impairment after mTBI. The contribution of mTBI to the onset of cognitive impairment or amyloid accumulation requires further study. The 37 patients who participated in this study could be recruited for a second amyloid PET in 2–3 years, and the rates of increase in amyloid accumulation could be compared among the three groups to understand the impacts of mTBI on the amyloid accumulation. A higher number of cases is also critical.

Conflict of interest

There is no conflict of interest for this work.

Acknowledgment

This study was supported by Ministry of Science and Technology, Taiwan, ROC, NSC 100–2314–B–182A–091–MY3 (KJ Lin) and Ministry of Health and Welfare, Taiwan, ROC, DOH101–TD–PB–111–NSC017 (CJ Hu).

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