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Accumulation of amyloid in cognitive impairment after mild traumatic brain injury

Shun-Tai Yang [a], Ing-Tsung Hsiao [b,c,d], Chia-Ju Hsieh [b,c,d], Yung-Hsiao Chiang [e], Tzu-Chen Yen [b,c,d], Wen-Ta Chiu [f], Kun-Ju Lin [b,c,d,*,1], Chaur-Jong Hu [g,h,i,**,1]

[a] Department of Neurosurgery, Shuang Ho Hospital, Taipei Medical University, Taipei, Taiwan
[b] Department of Medical Imaging and Radiological Sciences, College of Medicine, Chang Gung University, Taiwan
[c] Healthy Aging Research Center, Chang Gung University, Taoyuan, Taiwan
[d] Department of Nuclear Medicine and Molecular Imaging Center, Chang Gung Memorial Hospital, Taiwan
[e] Department of Neurosurgery, Taipei Medical University Hospital, the Ph.D. Program for Neural Regenerative Medicine, Graduate Institute of Neural Regenerative Medicine, Taipei Medical University, Taipei, Taiwan
[f] Graduate Institute of Injury Prevention and Control, College of Public Health and Nutrition, Taipei Medical University, Taipei, Taiwan
[g] Department of Neurology, Shuang Ho Hospital, Taipei Medical University, Taipei, Taiwan
[h] Department of Neurology, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan
[i] Department of Neurology, National Defense Medical Center, Taipei, Taiwan

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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.

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

* Correspondence to: K.-J. Lin, Department of Nuclear Medicine and Molecular Imaging Center, Chang Gung Memorial Hospital, Taiwan.
** Correspondence to: 291, Jhongjheng Rd, Jhonghe District, New Taipei City, 23561, Taiwan. Tel.: +886 2 22490088x86112.
E-mail addresses: lin4857@cgmh.org.tw (K.-J. Lin), chaurjongh@tmu.edu.tw (C.-J. Hu).
[1] KJ Lin and CJ Hu contribute this work equally.

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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 concussive mild head injury [27,28]. A study on postmortem brains from long-term survivors of a single TBI showed that both neurofibrillary tangles, or tauopathy, and Aβ-plaques were more abundant and widely distributed in TBI cases than in those of age-matched controls. That study indicated that some people who experience even a single TBI may develop long-term neuropathological changes, both tauopathy and amyloidopathy, which are similar to those observed in neurodegenerative diseases [6].

The application of biomarkers to AD diagnosis and clinical research has progressed rapidly. Those biomarkers include Aβ and Tau in cerebro-spinal fluid, structural MRI analysis, and brain metabolism with fluorodeoxyglucose-positron emission tomography (PET). A major advance is the quantitation of brain Aβ burden by using PET with new tracers (amyloid-PET) which has become the most effective approach for the early diagnosis of AD pathology [29–31]. Many novel therapeutic approaches have been developed for either cleaning Aβ or diminishing its downstream events [32].

In summary, epidemiological, pathological and animal studies have documented that Aβ accumulation could be accelerated by TBI, and that TBI increased the risk of AD onset. The inhibition of Aβ accumulation in TBI animals improved their cognitive function; however, TBI with long-term or delayed effects on Aβ accumulation, particularly among mTBI patients, requires further study. Therefore, this pilot study aims to explore the effect of mTBI on the accumulation of Aβ by examining the Aβ accumulation among the individuals with prior mTBI.

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 are 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′-CTCGGACAT GGAGGACGTG-3′ (P1; upstream), 5′-CTTACGCAGGTGGGAGG-CGAGAC-3′ (P2; downstream) for restriction enzyme HhaI, and 5′-CTGCGGGTGCTCGCCTCCCACCTGTGCA-AGC-3′ (P3; upstream), 5′-GAATTCGCCTCGGC-CTGGTAC-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 ^{18}F-Florbetapir and amyloid PET image acquisition have been described by our group [31,33]. In brief, all subjects received ^{18}F-Florbetapir PET scan using the Biograph mCT PET/CT System (Siemens Medical Solutions, Malvern, PA, USA) in a 3-dimentional acquisition mode. After injection of 378 ± 13 MBq of ^{18}F-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 mm^3.

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

Table 1
Demographic information and cognitive function of the participants.

	Control $n = 10$	mTBI without dementia $n = 21$	mTBI with dementia $n = 6$	*P*
Sex (male, female)	2, 8	9, 12	4, 2	
Age (*SD*) (years) (±*SD*)	50.6 ± 6.8	53.70 ± 7.9	60.0 ± 7.5	0.063
Education (years) (±*SD*)	12.8 ± 1.69	13.05 ± 2.31	11.17 ± 3.37	0.237
MMSE score ± *SD*	29.4 ± 1.4	29.3 ± 1.1	20.5 ± 4.8	<0.001*
AD8 score ± *SD*	0.3 ± 0.5	1.6 ± 1.6	3.3 ± 2.5	0.002*
Glasgow coma scale (±*SD*)	–	14.7 ± 0.6	14.8 ± 0.4	0.674
Initial loss of consciousness (%)	–	28.6%	83.3%	0.035*
Age of mTBI (years) ± *SD*	–	47.7 ± 10.5	54.2 ± 9.4	0.132
Duration between mTBI and amyloid PET (years) ± *SD*	–	6.10 ± 4.70	6.99 ± 5.18	0.693
Amyloid accumulation score 0	4	6	0	
Amyloid accumulation score 1	6	12	2	
Amyloid accumulation score 2	0	3	3	
Amyloid accumulation score 3	0	0	1	
Mean amyloid accumulation score	0.60 ± 0.52	0.86 ± 0.66	1.83 ± 0.75	0.002*

* Indicates $p < 0.05$.

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

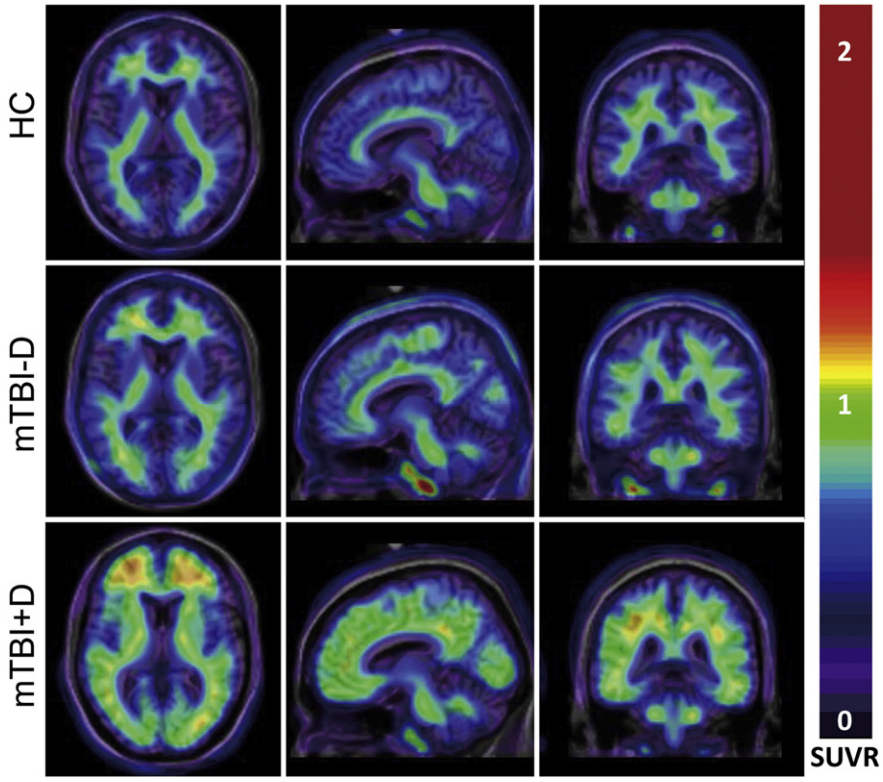

Fig. 1. ^{18}F-Florbetapir PET images in 3 subjects representative of range of tracer binding. Top subject was HC, middle was mTBI without dementia (mTBI − D), and bottom was mTBI with dementia (mTBI + D). All images were acquired with same acquisition time period, spatially normalized and overlay to the Montreal Neurological Institute MRI template in the same manner, scaled to same SUVR maximum, and were shown at identical sagittal plane for comparison.

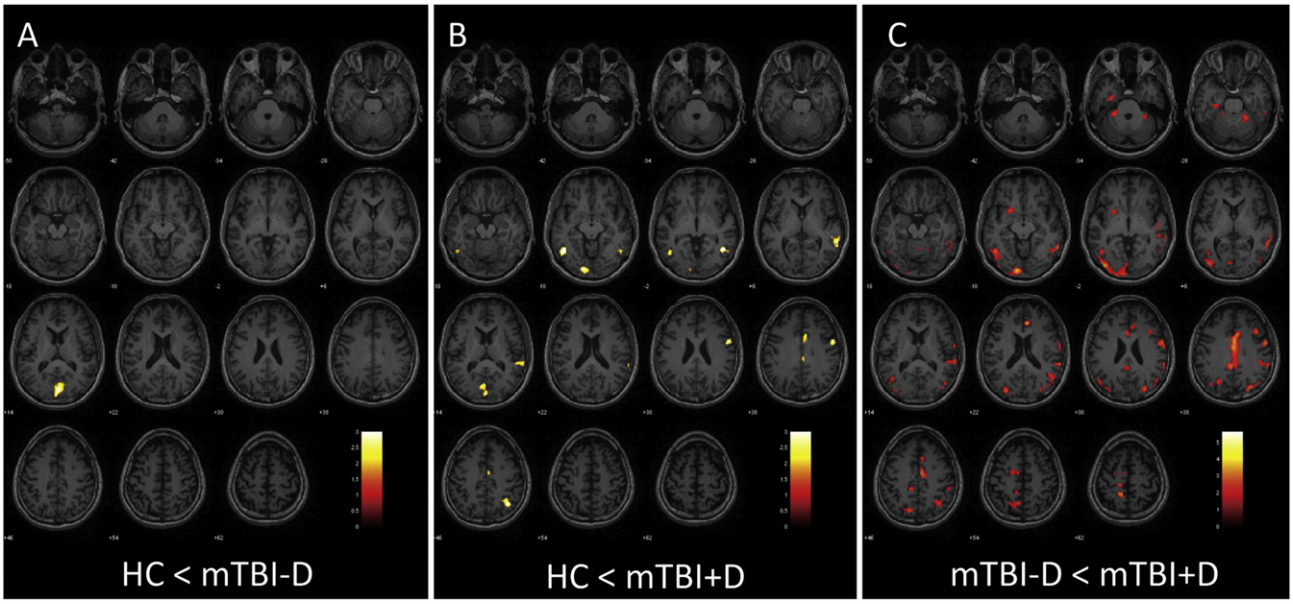

Fig. 2. Comparison of (A) mTBI without dementia (mTBI − D) vs. HC, (B) mTBI with dementia (mTBI + D) vs. HC, and (C) mTBI + D vs. mTBI − D shown in transverse views. Highlighted areas indicate regions with significant increased amyloid burden of increased ^{18}F-Florbetapir SUVR normalized to whole cerebellum at threshold of $p < 0.05$ (uncorrected, and clusters consisting of a minimum of 100 contiguous voxels).

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 ILCO 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 ^{18}F-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 cunenus 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 left putamen were noted when compare 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.

Brain region	HC (10)	mTBI without dementia (21)	mTBI with dementia (6)
Striatum	1.06 ± 0.08*	1.12 ± 0.06	1.23 ± 0.15*
Frontal	1.05 ± 0.07	1.08 ± 0.08	1.15 ± 0.20
Anterior cingulate	1.09 ± 0.11	1.08 ± 0.09	1.15 ± 0.21
Posterior cingulate	1.19 ± 0.09	1.21 ± 0.10	1.27 ± 0.13
Occipital	1.11 ± 0.07*	1.17 ± 0.06	1.25 ± 0.11*
Parietal	1.01 ± 0.08*	1.07 ± 0.06	1.17 ± 0.14*
Precuneus	0.99 ± 0.06*	1.04 ± 0.04	1.14 ± 0.16*
Temporal	1.00 ± 0.05	1.03 ± 0.07	1.12 ± 0.15
Average (all regions)	1.07 ± 0.07	1.10 ± 0.05	1.17 ± 0.19

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.

Table 3
APOE genotyping results.

	Genotype distribution						Allele frequency	*P*	Correlation with amyloid PET index
	ε2ε2	ε2ε3	ε2ε4	ε3ε3	ε3ε4	ε4ε4	ε4		
Control (10)	0	0.200 (2)	0	0.700 (7)	0.100 (1)	0	0.050	–	
mTBI without dementia (21)	0	0.143 (3)	0.048 (1)	0.571 (12)	0.238 (5)	0	0.143	0.140	
mTBI with dementia (6)	0	0.333 (2)	0	0.167 (1)	0.500 (3)	0	0.250	0.049	
All (37)									<0.05[a]

[a] Spearman correlation between ApoE4 allele frequency and amyloid PET SUVR index.

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 chromotomography 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 amyloipathy 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.

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References

[1] DeKosky ST, Ikonomovic MD, Gandy S. Traumatic brain injury-football, warfare, and long-term effects. N Engl J Med 2010;363:1293–6.
[2] Basso A, Previgliano I, Servadei F. World Health Organization (WHO). Neurological disorders-public health challenges; 2006 164–73.
[3] Chiu WT, Chu SF, Chang CK, Lui TN, Chiang YH. Implementation of a motorcycle helmet law in Taiwan and traffic deaths over 18 years. JAMA 2011;306:267–8.
[4] Lin JW, Lin CM, Tsai JT, Hung KS, Hung CC, Chiu WT. Neurotrauma research in Taiwan. Acta Neurochir Suppl 2008;101:113–7.
[5] Baumann CR, Werth E, Stocker R, Ludwig S, Bassetti CL. Sleep–wake disturbances 6 months after traumatic brain injury: a prospective study. Brain 2007;130:1873–83.
[6] Johnson VE, Stewart W, Smith DH. Widespread tau and amyloid-beta pathology many years after a single traumatic brain injury in humans. Brain Pathol 2012;22:142–9.
[7] Masel BE, DeWitt DS. Traumatic brain injury: a disease process, not an event. J Neurotrauma 2010;27:1529–40.
[8] Van Den Heuvel C, Thornton E, Vink R. Traumatic brain injury and Alzheimer's disease: a review. Prog Brain Res 2007;161:303–16.
[9] Mortimer JA, van Duijn CM, Chandra V, Fratiglioni L, Graves AB, Heyman A, et al. Head trauma as a risk factor for Alzheimer's disease: a collaborative re-analysis of case–control studies. EURODEM Risk Factors Research Group. Int J Epidemiol 1991;20(Suppl. 2):S28–35.
[10] Nemetz PN, Leibson C, Naessens JM, Beard M, Kokmen E, Annegers JF, et al. Traumatic brain injury and time to onset of Alzheimer's disease: a population-based study. Am J Epidemiol 1999;149:32–40.
[11] Wang HK, Lin SH, Sung PS, Wu MH, Hung KW, Wang LC, et al. Population based study on patients with traumatic brain injury suggests increased risk of dementia. J Neurol Neurosurg Psychiatry 2012;83:1080–5.
[12] Mirra SS, Heyman A, McKeel D, Sumi SM, Crain BJ, Brownlee LM, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. Neurology 1991;41:479–86.
[13] Jack Jr CR, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 2010;9:119–28.
[14] Selkoe DJ. Alzheimer's disease: genotypes, phenotypes, and treatments. Science 1997;275:630–1.
[15] Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 1993;261:921–3.

[16] Hu CJ, Sung SM, Liu HC, Chang JG. Association of apolipoprotein E genotype and intronic polymorphism of the presenilin-1 gene with Alzheimer's disease in elderly Taiwan Chinese. J Neurol Sci 1998;157:158–61.
[17] Takeda M, Martínez R, Kudo T, Tanaka T, Okochi M, Tagami S, et al. Apolipoprotein E and central nervous system disorders: reviews of clinical findings. Psychiatry Clin Neurosci 2010;64:592–607.
[18] Chuang YF, Hayden KM, Norton MC, Tschanz J, Breitner JC, Welsh-Bohmer KA, et al. Association between APOE epsilon4 allele and vascular dementia: the Cache County study. Dement Geriatr Cogn Disord 2010;29:248–53.
[19] Brichtova E, Kozak L. Apolipoprotein E genotype and traumatic brain injury in children-association with neurological outcome. Childs Nerv Syst 2008;24:349–56.
[20] Chiang MF, Chang JG, Hu CJ. Association between apolipoprotein E genotype and outcome of traumatic brain injury. Acta Neurochir 2003;145:649–54.
[21] Mayeux R, Ottman R, Maestre G, Ngai C, Tang MX, Ginsberg H, et al. Synergistic effects of traumatic head injury and apolipoprotein-epsilon 4 in patients with Alzheimer's disease. Neurology 1995;45:555–7.
[22] Galimberti D, Scarpini E. Alzheimer's disease: from pathogenesis to disease-modifying approaches. CNS Neurol Disord Drug Targets 2011;10:163–74.
[23] Lenzlinger PM, Morganti-Kossmann MC, Laurer HL, McIntosh TK. The duality of the inflammatory response to traumatic brain injury. Mol Neurobiol 2001;24:169–81.
[24] Zhang X, Chen Y, Jenkins LW, Kochanek PM, Clark RS. Bench-to-bedside review: apoptosis/programmed cell death triggered by traumatic brain injury. Crit Care 2005;9:66–75.
[25] Chen XH, Siman R, Iwata A, Meaney DF, Trojanowski JQ, Smith DH. Long-term accumulation of amyloid-beta, beta-secretase, presenilin-1, and caspase-3 in damaged axons following brain trauma. Am J Pathol 2004;165:357–71.
[26] Uryu K, Laurer H, McIntosh T, Praticò D, Martinez D, Leight S, et al. Repetitive mild brain trauma accelerates Abeta deposition, lipid peroxidation, and cognitive impairment in a transgenic mouse model of Alzheimer amyloidosis. J Neurosci 2002;22:446–54.
[27] Yoshiyama Y, Uryu K, Higuchi M, Longhi L, Hoover R, Fujimoto S, et al. Enhanced neurofibrillary tangle formation, cerebral atrophy, and cognitive deficits induced by repetitive mild brain injury in a transgenic tauopathy mouse model. J Neurotrauma 2005; 22:1134–41.
[28] McKee AC, Cantu RC, Nowinski CJ, Hedley-Whyte ET, Gavett BE, Budson AE, et al. Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. J Neuropathol Exp Neurol 2009;68:709–35.
[29] Mintun MA, Larossa GN, Sheline YI, Dence CS, Lee SY, Mach RH, et al. [^{11}C]PIB in a nondemented population: potential antecedent marker of Alzheimer disease. Neurology 2006;67:446–52.
[30] Koivunen J, Pirttilä T, Kemppainen N, Aalto S, Herukka SK, Jauhianen AM, et al. PET amyloid ligand [^{11}C]PIB uptake and cerebrospinal fluid beta-amyloid in mild cognitive impairment. Dement Geriatr Cogn Disord 2008;26:378–83.
[31] Lin KJ, Hsu WC, Hsiao IT, Wey SP, Jin LW, Skovronsky D, et al. Whole-body biodistribution and brain PET imaging with [^{18}F]AV-45, a novel amyloid imaging agent—a pilot study. Nucl Med Biol 2010;37:497–508.
[32] Mangialasche F, Solomon A, Winblad B, Mecocci P, Kivipelto M. Alzheimer's disease: clinical trials and drug development. Lancet Neurol 2010;9:702–16.
[33] Yao CH, Lin KJ, Weng CC, Hsiao IT, Ting YS, Yen TC, et al. GMP-compliant automated synthesis of [(18)F]AV-45 (Florbetapir F 18) for imaging beta-amyloid plaques in human brain. Appl Radiat Isot 2010;68:2293–7.
[34] Hsiao IT, Huang CC, Hsieh CJ, Hsu WC, Wey SP, Yen TC, et al. Correlation of early-phase ^{18}F-florbetapir (AV-45/Amyvid) PET images to FDG images: preliminary studies. Eur J Nucl Med Mol Imaging 2012;39:613–20.
[35] Mielke MM, Savica R, Wiste HJ, Weigand SD, Vemuri P, Knopman DS, et al. Head trauma and in vivo measures of amyloid and neurodegeneration in a population-based study. Neurology 2014;82:70–6.
[36] Hong YT, Veenith T, Dewar D, Outtrim JG, Mani V, Williams C, et al. Amyloid imaging with carbon 11-labeled Pittsburgh compound B for traumatic brain injury. JAMA Neurol 2014;71:23–31.
[37] Kawai N, Kawanishi M, Kudomi N, Maeda Y, Yamamoto Y, Nishiyama Y, et al. Detection of brain amyloid β deposition in patients with neuropsychological impairment after traumatic brain injury: PET evaluation using Pittsburgh Compound-B. Brain Inj 2013;27:1026–31.
[38] McKee AC, Stern RA, Nowinski CJ, Stein TD, Alvarez VE, Daneshvar DH, et al. The spectrum of disease in chronic traumatic encephalopathy. Brain 2013;136(Pt 1): 43–64.