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Accumulation of amyloid in cognitive impairment after mild traumatic brain injury

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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.

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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

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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

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