The Association of *Apolipoprotein* E Allele 4 Polymorphism with the Recovery of Sleep Disturbance after Mild Traumatic Brain Injury

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Abstract-

Purpose: Mild traumatic brain injury (mTBI) is a major public health concern. The apolipoprotein E (*APOE*) gene contains three polymorphisms, and the *APOE4* polymorphism may affect several physiological states, such as the recovery from mTBI as well as sleep. This study aims to investigate the association between *APOE4* with the recovery of sleep disturbance after mTBI.

Methods: From May 2012 to Aug 2015, 189 mTBI patients completed baseline (1st week post-mTBI) and follow-up (6th week post-mTBI) sleep assessments that involved using the Pittsburgh Sleep Quality Index (PSQI). *APOE* genotypes were determined by sequencing the products of polymerase chain reaction from genomic DNA. Statistical analyses were performed using the Wilcox signed-rank or chi-square test.

Results: Thirty-five (18.5%) participants were *APOE4* carriers. At baseline, the demographic data and the severity of sleep disturbance were similar in both groups. *APOE4* carriers demonstrated significant improvement in the overall PSQI score (8.34±3.9 at baseline and 7.43±3.99 at follow-up, $p = 0.05$) and scores of several PSQI subscales, including sleep disturbance, sleep latency, daytime dysfunction caused by sleepiness, and overall sleep quality, which was similar to *APOE4* noncarriers.

Conclusion: *APOE4* is not associated with the recovery of sleep disturbance after mTBI.

Key Words: mild traumatic brain injury, sleep, Apolipoprotein E4

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o-2 105-0046.indd 13 2017/6/22 下午2:46

INTRODUCTION

Mild traumatic brain injury (mTBI) is a major public health concern affecting people globally. According to the survey conducted by World Health Organization, the incidence of hospital-treated mTBI is approximately 100–300/100,000 people; however, if mTBI cases not treated at hospitals are considered, the real incidence would be more than 600/100,000 people [1]. A latest population-based study conducted in New Zealand demonstrated that the incidence may be up to 749/100,000 people [2]. mTBI is defined as minimal changes in consciousness (Glasgow Coma Scale, 13–15) and full neurological recovery or minimal neurological deficit. More than direct damage, mTBI probably results in indirect and delayed effects to the brain, including inflammation and breakdown of the blood–brain barrier, thus triggering brain oedema and swelling, leukocyte infiltration, lactic acid accumulation, immunocompetent cell recruitment, and apoptosis in the damaged brain (reviewed by Laskowski et al[3]). These pathological events can be long-lasting and explain why patients sustaining repetitive mTBIs typically develop long-term neuropathological changes similar to those observed in neurodegenerative diseases[4].

Clinically, mTBI may cause neurological sequelae in many aspects, including changes in cognition and personality, psychiatric disorders, memory impairment, and sleep disturbance [5]. Posttraumatic hypersomnia, excessive daytime sleepiness, fatigue, insomnia, sleep architecture changes or reduced sleep quality, increased wake after sleep onset, decreased sleep efficiency, and alteration in sleep stage proportion are common presentations of sleep disturbance in patients with mTBI and affect their quality of life [6-8].

The gene encoding *Apolipoprotein E (APOE)* is located at chromosome 19q13.2. *APOE* is a component of plasma lipoproteins and synthesised in the liver, brain, spleen, kidneys, gonads, adrenals, and macrophages [9,10]. The *Apolipoprotein E (APOE)* gene is polymorphic and has three alleles: *APOE* ε2, ε3, and ε4, which produce three isoforms: *APOE2*, *E3*, and *E4*, respectively [11,12]. *APOE ε4 (APOE4)* is a crucial genetic risk factor for Alzheimer disease (AD) and modulates *APOE* levels and regulates pathological amyloid-β (Aβ) accumulation, and it is involved in neuronal repair and remodelling [13].

APOE4 has been identified as a risk factor for the poor outcome of traumatic brain injury (TBI)[14-16]. Sleep disturbance is one of the common sequlae of TBI and in our previous studies, we have demonstrated significant recovery from sleep disturbance 6 weeks after mTBI [17], and that a genetic polymorphism is associated with the recovery of sleep disturbance [18]. Meanwhile, *APOE* genotypes are associated with the progression of sleep/wake disturbances in patients with AD [19] and the association between *APOE4* allele is significantly associated with obstructive sleep apnoea/hypopnoea[20,21]. However, the association between *APOE* polymorphisms and the recovery of mTBI-related sleep disturbance is still unknown. We hypothesise that *APOE* polymorphism, which is associated with the outcome of TBI and sleep disturbance, respectively, is associated with the recovery of sleep disturbance after mTBI.

METHODS

Participants and study design

This study was approved by the Taipei Medical University-Joint Institutional Review Board (TMU-JIRB). From May 2012 to Aug 2015, the participants in the current study were recruited from the emergency department of three hospitals: Taipei Medical University Hospital, Taipei Municipal Wan Fang Hospital (Managed by Taipei Medical University), and Taipei Medical University Shuang Ho Hospital. The inclusion criteria were age between 20 and 70 years, Glasgow Coma Scale of 13–15 at the time of triage, loss of consciousness less than 30 minutes, no structural imaging findings on brain computed tomography, and nonrecent (within 1 year) any kind of TBI before this event. Individuals fulfilling one or more of the following criteria were excluded from this study: younger than 20 years, older than 70 years, and a history of neurological problems or psychiatric conditions. A total of 427 informed consent were obtained from the research nurse at emergency department; 189 (43.8%) of them completed 6-week assessments. There was no significant difference among the demographic data between drop-out and retained patients except the habit of smoking, which is significant higher in drop-put group (supplementary data).

o-2 105-0046.indd 14 2017/6/22 下午2:46

APOE genotyping

Genomic DNA was extracted using the Blood Genomic DNA Extraction Midiprep System (VIOGENE, Sunnyvale, CA, USA). An APOE DNA fragment containing rs429358 and rs7412 single-nucleotide polymorphisms (SNPs) was amplified using polymerase chain reaction (PCR) in the DNA Thermal Cycler (Perkin Elmer Cetus, Foster City, CA, USA) with forwards and reverse primers 5'-TCCAAGGAGCTGCAGGCGGCGCA-3'and 5'-ACAGAATTCGCCCCGGCCTGGTACACTGCCA-3', respectively. The PCR reaction mixture (25 μL) contained 1 μg of gDNA, 100 ng of primers, 0.4 mM each dNTP, 1X PCR buffer, and 1 unit of Taq polymerase (TOYOBO, Osaka, Japan). The reaction mixture was subjected to 35 cycles of 0.5 min at 94 °C for denaturation, 0.5 min at 61 °C for annealing, and 30 min at 72 °C for extension. All PCR products were sequenced at Tri-I Biotech (Tri-I Biotech Inc., New Taipei City, Taiwan), and the genotypes were determined using Sequencher 5.4®(Gene Codes Corporation, Ann Arbor, MI USA).

Outcome measure

Subjective sleep quality over the previous month was evaluated using the Pittsburgh Sleep Quality Index (PSQI), a 19-item, self-rated questionnaire [22]. The 19 items of the PSQI are categorised into seven subscales: sleep latency, sleep duration, daytime dysfunction caused by sleepiness, habitual sleep efficiency, sleep disturbance, subjective sleep quality, and sleeping medication. Each subscale is scored from 0 (no problem) to 3 (severe), and the scores are summed into an overall score ranging from 0 to 21. A higher score indicates a worse sleep problem. The Chinese version of the PSQI was administered to the study participants [23]. At both baseline and 6-week follow up, the written-form of PSQI was filled out by patients themselves.

Statistical analyses

Descriptive statistics (e.g. mean ± standard deviations, frequencies with percentage) were calculated for all variables. Nonparametric statistics were calculated using Wilcox signed-rank and chi-square tests for comparison of *APOE4* carriers with *APOE4* noncarriers. Statistical significance was set at $p < 0.05$, and statistical analyses were performed using R, Version 3.2.2. (Copyright© 2015, The R Foundation for Statistical Computing).

RESULTS

Table 1 presents the comparison of baseline demographic characteristics between groups. One hundred and thirteen (59.8%) were women. Most mTBIs were caused by traffic accident (47.6%), followed by falls (35.4%). Thirty-five (18.5%) participants were *APOE4* carriers. The *APOE4* carrier and noncarrier groups were similar in gender (women: 54.3% and 61.0%, respectively), age (42.2±14.7 and 40.1±15.2 years, respectively), and the rest of demographic data.

The average overall PSQI scores of all participants were 8.3±3.9 and 8.5±4.3 among *APOE4* carrier and noncarrier at baseline, respectively. There was no significant difference observed in the overall score and all subscale scores of the PSQI at baseline between the

Table 1. Demographic data of all participants and *APOE4* carriers and noncarriers

	All	*APOE4* carriers	*APOE4* noncarriers	*p*-value
Sample size	189	35	154	
Female (percentage)		19(54.29%)	94(61.04%)	0.52
Age (years)		42.20±14.76	40.14±15.15	0.39
Education (years)		13.71±3.25	13.92±2.92	0.97
Smoker (%)		7(20%)	40(25.97%)	0.54
GCS		15±0	14.93±0.38	0.34
Mode of injury				0.27
Traffic accident		20	70	
Falls		12	55	
Other		3	29	

GCS: Glasgow Cowa Scale

o-2 105-0046.indd 15 2017/6/22 下午2:46

Table 2. Overall and subscale scores of Pittsburgh Sleep Quality Index (PSQI) at baseline between *APOE4* carriers and noncarriers

Baseline	*APOE4* carriers	*APOE4* noncarriers	*p*-value
Overall PSQI	8.34±3.9	8.51±4.38	0.97
PSQI-1 (Duration of sleep)	1.26±1.22	1.29±1.23	0.83
PQSI-2 (Sleep disturbance)	1.49±0.66	1.34±0.65	0.33
PSQI-3 (Sleep latency)	1.54±0.78	1.40±1.02	0.34
PSQI-4 (Daytime dysfunction caused by sleepiness)	1.14±0.85	1.00±0.89	0.33
PSQI-5 (Sleep efficiency)	0.91±1.04	1.20±1.29	0.45
PSQI-6 (Overall sleep quality)	1.86±0.73	1.77±0.81	0.55
PSQI-7 (Use of sleep medication)	0.14±0.60	0.51±1.07	0.04*

* *p*-value <0.05

Table 3. Differences in overall and subscale scores of Pittsburgh Sleep Quality Index (PSQI) between baseline and the sixth week for *APOE4* carriers and noncarriers.

APOE4 carriers (n = 35)	*Baseline*	*Sixth week*	*p-value*
Overall PSQI	8.34±3.9	7.43±3.99	0.05
PSQI-1 (Duration of sleep)	1.26±1.22	1.49±1.20	0.92
PQSI-2 (Sleep disturbance)	1.49±0.66	1.17±0.51	<0.01*
PSQI-3 (Sleep latency)	1.54±0.78	1.31±0.90	0.08
PSQI-4 (Daytime dysfunction caused by sleepiness)	1.14±0.85	0.77±0.81	0.02*
PSQI-5 (Sleep efficiency)	0.91±1.04	1.14±1.31	0.91
PSQI-6 (Overall sleep quality)	1.86±0.73	1.43±0.81	<0.01*
PSQI-7 (Use of sleep medication)	0.14±0.60	0.11±0.53	0.50
APOE4 noncarriers (n = 154)	Baseline	Sixth week	*p*-value*
Overall PSQI	8.51±4.38	8.05±3.80	0.03
PSQI-1 (Duration of sleep)	1.29±1.23	1.29±1.18	0.45
PQSI-2 (Sleep disturbance)	1.34±0.65	1.19±0.62	<0.01
PSQI-3 (Sleep latency)	1.40±1.02	1.34±1.00	0.27
PSQI-4 (Daytime dysfunction caused by sleepiness)	1.00±0.89	0.94±0.80	0.19
PSQI-5 (Sleep efficiency)	1.20±1.29	1.16±1.23	0.30
PSQI-6 (Overall sleep quality)	1.77±0.81	1.58±0.83	<0.01
PSQI-7 (Use of sleep medication)	0.51±1.07	0.56±1.10	0.82

* *p*-value <0.05

Table 4. Differences of Pittsburgh Sleep Quality Index (PSQI) at baseline and the sixth week between *APOE4* carriers and noncarriers.

Difference	*APOE4* carriers	*APOE4* noncarriers	*p*-value
Overall PSQI	-0.91±3.11	-0.45±3.44	0.41
PSQI-1 (Duration of sleep)	0.23±0.91	0.00±1.24	0.22
PQSI-2 (Sleep disturbance)	-0.31±0.68	-0.15±0.69	0.24
PSQI-3 (Sleep latency)	-0.23±0.84	-0.06±0.98	0.16
PSQI-4	-0.37±1.00	-0.06±0.93	0.10
PSQI-5 (Sleep efficiency)	0.23±1.11	-0.05±1.32	0.20
PSQI-6 (Overall sleep quality)	-0.43±0.81	-0.19±0.79	0.10
PSQI-7 (Use of sleep medication)	-0.03±0.38	0.05±0.79	0.96

o-2 105-0046.indd 16 2017/6/22 下午2:46

APOE4 carrier and noncarrier groups except the use of sleep medicine, which is significantly higher among noncarrier (Table 2).

Both *APOE4* carriers and noncarriers exhibited improvement in overall PSQI scores between baseline and 6th weeks follow up (carrier: baseline 8.34±3.9, 6th week: 7.43±3.99, p=0.05; noncarrier: baseline 8.51±4.38, 6th week: 8.05±3.80, p=0.03). In the subscale of PSQI, both group demonstrated significant improvement in the aspect of "Sleep disturbance" and "Overall sleep quality", while carrier also significantly improved in "Daytime dysfunction caused by sleepiness" (Table 3). Comparing the differences of PSQI at baseline and the 6th week between *APOE4* carriers and noncarriers also showed no significant different (Table 4).

DISCUSSION

The current study demonstrated that the *APOE4* polymorphism is not associated with the recovery of sleep disturbance after mTBI. Both *APOE4* carriers and noncarriers exhibited significant improvement in sleep quality at the 6th week follow-up. To the best of our knowledge, it is the first report to investigate the association between *APOE4* with the recovery of sleep disturbance after mTBI.

The association between sleep disturbance and *APOE4* has been investigated. Some studies claim that *APOE4* carriers exhibit a higher probability of developing moderate-to-severe sleep-disordered breathing [20,24]. Besides, compared with noncarriers, *APOE4* carriers with mild cognitive impairment demonstrated a reduction in rapid eye movement sleep, which is associated with memory consolidation [25]. However, the underlying mechanism is ambiguous and the association was not consistent. Saarelainen et al. suggested the lack of association between *APOE4* and obstructive sleep apnea[26]. A meta-analysis pooled 8 studies together also fail to demonstrate the association[27]. The present study revealed that the quality of sleep measured by PSQI was identical between carriers and noncarriers 1-week and 6-week after mTBI, which also indicated the lack of association between *APOE4* and sleep disturbance after mTBI.

APOE4 has been found to be associated with overall recovery from TBI[28]. *APOE4* carriers have a twofold risk of an unfavourable outcome 6 months after head injury [29]. Considerably few *APOE4* carriers achieve favourable functional recovery [30], and *APOE4* negatively affects the outcome of rehabilitation and memory performance in patients with TBI [31,32]. For mTBI, Sundström et al found that *APOE4* affected the neuropsychological outcome after mild head injury, but Liberman et al argued that *APOE4* only affected the severity of acute injury but not the recovery pattern [28,33]. In addition, late cognitive decline to occur after TBI is not associated with the *APOE* genotype and TBI increased the risk for AD in *APOE4* noncarriers only[34,35], which hint *APOE4* is not consistently associated with the outcome after TBI. The present study revealed that the recovery of sleep disturbance was identical in both *APOE4* carrier and noncarrier groups, and there was no significant difference in all subscale of PSQI. It speculates that *APOE4* is not associated with the recovery of sleep disturbance after mTBI.

The current study has some limitations. The sample size is only 189 and only 18.5% were *APOE4* carriers, thus limiting the possibility of reaching high statistical power. Moreover, the drop-out rate is high, because mTBI is not a severe disease; hence, participants may be unwilling to revisit for follow-up after recovery from symptoms. Fortunately, there was no significant difference among the demographic data between drop-out and retained group. The present study recruited more female participants, which may be in contrast with the fact that male were in majority of mTBI patients. The use of the self-reported PSQI questionnaire may also have disadvantages such as overestimation, recall bias, social desirability bias, and errors in self-observation.

In conclusion, the current study showed that *APOE4* allele was not associated with the recovery of sleep disturbance 6 weeks after mTBI. A longer follow-up period may be required for further investigation about the *APOE4*-associated consequence after mTBI, such as cognitive decline and the risk of AD.

CONTRIBUTORSHIP STATEMENT

Hsun-Hua Lee: study design, data collection, drafting of the manuscript and its final approval

Chun-Ting Yeh: study design, data collection, drafting of

o-2 105-0046.indd 17 2017/6/22 下午2:46

the manuscript and its final approval
Ju-Chi Ou: study design, data analysis, drafting of the manuscript and its final approval
Hon-Ping Ma: acquisition of data and its final approval
Kai-Yun Chen: acquisition of data and its final approval
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Yao-Hsien Huang: acquisition of data and its final approval
Chaur-Jong Hu: study design, data collection, drafting of the manuscript and its final approval
Chien-Tai Hong: study design, data collection, drafting of the manuscript and its final approval

Statement of competing interests

All the authors have no conflict of interest to declare

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Data sharing statement

There is no additional data available

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o-2 105-0046.indd 18 2017/6/22 下午2:46

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o-2 105-0046.indd 19 2017/6/22 下午2:46