Neurology Asia 2014; 19(1) : 69 – 77

Cognitive impairments in mild traumatic brain injury and genetic polymorphism of apolipoprotein E: A preliminary study in a Level I trauma center

[1]Vigneswaran Veeramuthu *MEd Psych*, [1]Devaraj Pancharatnam *MSurg*, [1]Anada Raj Poovindran *BSc*, [2]Nur Atikah Musthapha *DipOT*, [3]Wong Kum Thong *FRCPath*, [2]Mazlina Mazlan *MRehabMed*, [1]Vicknes Waran *FRCS(SN)*, [1]Dharmendra Ganesan *FRCS (NeuroSurg)*

[1]Division of Neurosurgery, Department of Surgery, [2]Department of Rehabilitation Medicine, and [3]Department of Pathology, University Malaya Medical Center, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

Abstract

The complex pathophysiology of traumatic brain injury, its cascading effects and a varied outcome suggest that factors such as genetics may permeate and modulate the neurocognitive outcomes in patients with mild traumatic brain injury (mTBI). This study was conducted to determine the relationship between genetic polymorphism of apolipoprotein E, and neurocognitive and functional outcomes in mTBI. Twenty-one patients with mTBI were recruited prospectively. The severity of the injury was established with the Glasgow Coma Score (GCS). Other assessments included the CT Scan of the head on admission, Disability Rating Scale, Chessington Occupational Therapy Neurological Assessment (COTNAB) and Glasgow Outcome Scale (GOS). The Spearmen correlation analysis of ApoE allele status and the cognitive and functional assessments saw some association with the Sensory Motor Ability - Coordination (-0.526, $p<0.05$), Communication Ability (-0.651, $p<0.05$), and the Employability (Return to Work) at 1st month (0.455, $p<0.05$). Notably, the deficits of specific attributes of visuospatial and sensory motor function were seen with greater impairment consistently observed in patients with ApoE e4 allele. In conclusion, the preliminary findings support the possible relationship that exists between ApoE e4 and neurocognitive impairment in mTBI, despite good functional recovery in 6 months post injury.

INTRODUCTION

In a nation with a high incidence of traffic-related accidents[1], traumatic brain injury (TBI) and its associated disabilities and impairments are common and widespread. These traumatic brain injuries are considered to be one of the leading factors in continuous neurological impairments[2] and a substantial number of patients do complain of long term cognitive deficits even in mild head injuries.[3]

Apolipoprotein E (ApoE) is an important factor that is involved in lipid transportation in human central nervous system (CNS). The ApoE gene has 3 common alleles, namely, e2, e3, and e4 with corresponding isoforms (e2, e3, and e4).[4] Each isoform play different roles in the neuronal and synaptic repair, remodeling and regeneration in response to traumatic brain injury.[5-6] The allele e2 and e3 serves as neuroprotectors[7,8] and whereas the e4 is alleged to be destructive in nature.[8] The e4 isoform is believed to provide less neuroprotection and a lower ability for brain tissue recovery and functional restoration in comparison to the other isoforms.[5] Those with e4 allele are also likely to be unable to avoid secondary damage, remove injury-induced degeneration products or repair damaged tissues.[9] Hence, as a combined effect of these mechanism, the e4 carriers are more likely to experience more severe injuries and be at risk of neurological and cognitive decline.[10,11] There are many studies that lend support to the proposition that the genetic polymorphism of ApoE could possibly influence the degree of brain injury severity, length of recovery period , functional and cognitive outcomes, hence, the altered quality of life and return to work abilities.[12,13]

We embarked on this study to elucidate why some patients with similar injuries perform better than others in mild TBI (mTBI). One of the causal

Address correspondence to: Vigneswaran Veeramuthu, Division of Neurosurgery, Level 5 Neurosurgical Ward, University Malaya Medical Center, Faculty of Medicine, University of Malaya, Kuala Lumpur 50603, Malaysia. Tel: +603-79674251, Fax: +603-79678841, Email: vicveera@gmail.com

factors known to influence the outcomes in TBI is the genetic predisposition of patients with ApoE e4 allele.[14] The current study aimed to determine the relationship between genetic polymorphism of ApoE, particularly e4, and neurocognitive and functional outcomes in mTBI.

METHODS

The study patients were recruited prospectively for the purpose of this study at a tertiary care hospital with Level I trauma facilities. In order to match the general population of TBI patients, the mechanism of injury was strictly limited to motor vehicle accidents. The injury severity of the patients was established with the Glasgow Coma Scale (GCS). All patients who were selected had a GCS score between 13 to 15. The CT scan of the head was done upon the arrival of the patient at the emergency department. They were subsequently admitted to the ward for observation. Consent from the legal representative of the patients was sought before other study protocols were executed. Thereafter, blood sample of the patients were taken for genetic screening purposes. Upon discharge, the patients were given a follow up date at 1 and 6 month post injury where they were reassessed functionally by the rehabilitative physicians and occupational therapists.

All patients who were successfully recruited into this study were literate, proficient in either English or Malay, and had no co-morbid ailments or psychiatric history which may preclude the cognitive and functional assessment. The patients were selected from a cohort of potentially eligible patients (n = 94) who sustained mTBI and were seen at the emergency department between September 2011 and July 2012. Of these 94 patients with mTBI, 31 patients were excluded, due to previous history of head trauma, mechanism of injury other than motor-vehicle accidents, substance abuse, and co-morbid ailments. Eighteen were not contactable, 22 refused participation in any form of functional or cognitive assessments, and/ or genetic screening. This left only 23 patients with mTBI, subsequently reduced to 21 due to loss of follow up.

Cognitive and functional assessment

The neurocognitive and functional outcomes were measured using the Chessington Occupational Therapy Neurological Assessment (COTNAB)[15], Disability Rating Scale[16], and Glasgow Outcome Scale (GOS).

COTNAB

The COTNAB is a fully validated battery of tests for the assessment of perceptual and functional deficits in neurological patients including stroke and brain injury.[17-19] The COTNAB consist of four modules: Visual Perception (VP), Constructional Ability (CA), Sensory Motor Ability (SMA) and Ability to Follow Instruction (AFI).The VP module contains the Overlapping Figure Test, Hidden Figures Test and the Sequencing Ability Test. The CA module has 3 sets of test, namely, 2D Construction, 3D Construction Test and also Block Printing Test. The SMA module consist of 3 tests, i.e. Stereognosis / Tactical Discrimination Test, Dexterity Test, and the Coordination Test. The fourth COTNAB module is the AFI module, consisting of Written Instruction Test, Verbal Instruction Test and Spoken Instruction Test. All patients were assessed with COTNAB at 6th month post injury. The overall performance and time taken by the patients to complete each tasks were documented.

The COTNAB assessment is a recommended tool to be performed by occupational therapist and in this study, it was performed by a trained senior occupational therapist looking after brain injury patients for the last 10 years. The lab in which the test was conducted was at the Occupational Therapy lab in the Department of Rehabilitation Medicine, University Malaya Medical Centre, a tertiary centre with reputable research portfolio.

DRS

The DRS is a measure used to assess a wide range of functional disability ranging from the level of consciousness to the disability in more complex areas including feeding, toileting, grooming, independence at home and employability (employment status). It is a widely used tool in assessing the functional disability among patients with head injuries.[20-23]The score range are from 0 (no disability) to 29 (severe or complete disability). The DRS was administered at one month (1) and six (6) month post injury as the patients comes for rehabilitation or follow-up visits.

GOS

The GOS was used to establish the outcome at discharge in patients recruited in this study. The scale is divided into five categories: death (Grade 1), vegetative state (Grade 2), severe disability (Grade 3), moderate disability (Grade 4), and good recovery (Grade 5).

APOE genotyping

5ml of EDTA blood were taken from study patients. The DNAs were extracted using phenol-chloroform extraction method. The extracted DNAs were used to amplify the region of interest in APOE gene using conventional PCR method. Upon which, the genotypes (e2e2, e2e3, e2e4, e3e3, e3e4, e4e4) were determined by sequencing the purified PCR product.

Statistical analysis

The data collected were analyzed using both descriptive and inferential statistics. The distribution of the demographics, allele status, functional outcomes and all cognitive test scores were analyzed using mean and percentage. The interrelationships between the variables were assessed using the non-parametric Spearmen correlation test due to the small sample size and wide distribution of test scores. Both p value of <0.01 (two-tailed test) and <0.05 (one-tailed test) were used in this study to determine any possible relationship between the variables. IBM/SPSS 21.0 was used for the purpose of statistical analysis in this study.

RESULTS

Demographics

The demographics of the study patients are presented in Table 1. No significant differences were observed between potentially eligible patients with mTBI (n=94) and study patients (n=21) in terms of age and sex. The study patients were aged between 13 and 62 years, with the mean age being at 31.5 years (SD 13.46). The subjects were mainly male (90.5%) who consists of 11 (52.3%) Malays, 3 (14.3%) Chinese and 5 (23.8%) Indians. There were 2 (9.5%) female patients recruited into this study. They were of Malay (4.8%) and Indian (4.8%) origin ethnically. The average mean of years of education among the patients were 12.00 (SD 2.02) year. Most of the patients recruited for this study had the GCS score of 13 (42.8%), 14 (23.8%) and 15 (33.3%). The majority type of injuries shown in the CT scan are subarachnoid hemorrhages (42.8%), subdural hemorrhages (38.4%), and intraparenchymal bleeds (19.1%). Most of this patients (90.5%) were treated conservatively and two (9.5%) required surgical intervention as the GCS dropped. Notably, one of these 2 patients who required a surgical intervention was positive for e4 allele status (e4 e4).

APOE genotypes

The genotyping were divided into two categories: ApoE e4 positive (e2e4, e3e4, e4e4) and ApoE e4 negative (e2e3, e3e3). The majority (66.7%) of the study sample possessed e3e3 genotypes, followed by e2e3 (19.0%), e2e4 (4.8%), e3e4 (4.8%) and e4e4 (4.8%). The ApoE e4 positive category accounts for 14.3 percent of the study sample, similar in representation of the overall prevalence of the genotype in Malaysia.[24]

Visual perception

The 3 subtest within Visual Perception module of the COTNAB assessment yielded a varied result. The Overlapping Figures test scores indicated that out of the 21 patients, 10 (47.6%) had either below average or borderline scores, with 1 (4.8%) of them testing positive for e4 allele status. The Hidden Figures test saw 4 (19.0%) patients with below average/borderline performance and 1 (4.8%) patient with impaired performance. The Sequencing test overall performance showed more patients falling into below average - borderline (38.1%) and impaired (23.8%) scores. All ApoE e4 positive (14.3%) patients performed poorly in this test in comparison to the ApoE e4 negative group. Most of patients with below average to severely impaired scores in the aforementioned tests fell within the 19 to 49 age subgroup.

Constructional activity

The 2D Construction task resulted in mostly normal scores with 17 (81.0%) performing within the normal limits and 4 (19.0%) impaired performances. All study patients had a normal overall performance score for the 3D Construction test. In contrast, many of these patients had a poorer performance in the Block Printing test (47.7% below average scores, 23.8% impaired scores. It is notable that all 3 (14.3%) patients with e4 positive allele status were performing poorly in this task as well.

Sensory motor ability

The Dominant Stereognosis and Tactical Discrimination (D-STD) test indicated 8 (38.1%) patients had borderline/ below average scores and 3 (14.3%) had impaired/ severely impaired scores. The mTBI patients showed further decreased overall performance in Non-Dominant STD (ND-STD) test as only 3 (14.3%) performed within the normal limits, where the remaining 18 (85.7%) either had a below average or impaired score.

Table 1: Demographics of Patients with Mild Traumatic Brain Injury

Demographic [n (%)] **Total**	**Patient** **N=21 (%)**
Gender:	
Male	19 (90.5)
Female	2 (9.5)
Age: Mean ± standard deviation	31.56 ± 13.46
Age categories:	
13−18 years	2 (9.5)
19−49 years	15(71.4)
50−65 years	4(19.1)
Ethnicity:	
Malay	12(57.1)
Chinese	3 (14.3)
Indian	6 (28.6)
Education: Mean ± standard deviation	12.00 ± 2.02
Level of Education	
Primary	13 (61.9)
College/ Diploma	6 (28.6)
Tertiary	2 (9.5)
Glasgow Coma Scale (Admission)	
15/15	7 (33.3)
14/15	5 (23.8)
13/15	9 (42.8)
Glasgow Outcome Score (Upon Discharge)	
5	19 (90.5)
4	2 (9.5)
Type of Injury (s)Based on CT Scan Report*:	
Contusion	2 (9.5)
Subarachnoid Haemorrhage	9 (42.8)
Subdural Haemorrhage	8 (38.4)
Intracerebral Haemorrhage	2 (9.5)
Intraparenchymal Haemorrhage	4 (19.1)
Basal Skull Fracture	1 (4.8)
Tentorial Bleed	1 (4.8)
Concussion	3 (14.3)
MCA Dissection	1 (4.8)
Intervention:	
Surgical	2 (9.5)
Conservative	19 (90.5)

*The total types of injuries does not equate to n=21 as many patients had multiple injuries.

Table 2: Distribution of demographic and APOE ε4 allele status in COTNAB overall performance scores in patients with mTBI

Modules and Subtest	Normal Limits [N(%)]							Below Average/Borderline [N(%)]							Impaired/Severly Impaired [N(%)]							Unable/Unwilling [N(%)]						
	Gender		Age			APOE ε4 Status		Gender		Age			APOE ε4 Status		Gender		Age			APOE ε4 Status		Gender		Age			APOE ε4 Status	
	M	F	13-18	19-49	50-65	+	-	M	F	13-18	19-49	50-65	+	-	M	F	13- 18	19-49	50 -65	+	-	M	F	13-18	19-49	50-65	+	-
Visual perception (n=21)																												
Overlapping figures	9(42.9)	2(9.5)	2(9.5)	6(28.7)	3(14.3)	2(9.5)	9(42.9)	10(47.6)	-	-	9(42.9)	1(4.8)	1(4.8)	9(42.9)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hidden figures	14(66.7)	2(9.5)	1(4.8)	12(57.1)	3(14.3)	2(9.5)	14(66.7)	4(19.0)	-	1(4.8)	2(9.5)	1(4.8)	1(4.8)	3(14.3)	1 (4.8)	-	-	1(4.8)	-	-	1(4.8)	-	-	-	-	-	-	-
Sequencing	8 (38.1)	-	1(4.8)	6(28.6)	1(4.8)	1(4.8)	7(33.3)	6(28.6)	2(9.5)	1(4.8)	5(23.8)	2(9.5)	2(9.5)	6(28.6)	5(23.8)	-	-	4(19.0)	1(4.8)	-	5(23.8)	-	-	-	-	-	-	-
Contructional cctivity (n= 21)																												
2D construction	16(76.2)	1(4.8)	2(9.5)	12(57.1)	13(61.9)	2(9.5)	15(71.4)	-	-	-	-	-	-	-	3(14.3)	1(4.8)	-	3(14.3)	1(4.8)	1(4.8)	3(14.3)	-	-	-	-	-	-	
3D construction	19(90.5)	2(9.5)	2(9.5)	15(71.4)	4(19.0)	3(14.3)	18(85.7)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Block printing	6(28.6)	-	-	5(23.8)	1(4.8)	-	6(28.6)	9(42.9)	1(4.8)	2(9.5)	6(28.6)	2(9.5)	2(9.5)	8(38.1)	4(19.0)	1(4.8)	-	4(19.0)	1(4.8)	1(4.8)	4(19.0)	-	-	-	-	-	-	
Sensory motor ability (n= 21)																						-	-	-	-	-	-	-
Stereognosis &																												
- Dominant	9(42.9)	1(4.8)	-	6(28.6)	4(19.0)	1(4.8)	9(42.9)	7(33.3)	1(4.8)	1(4.8)	7(33.3)	-	2(9.5)	6(28.6)	3(14.3)	-	1(4.8)	2(9.5)	-	-	3(14.3)	-	-	-	-	-	-	-
Tacticle discrimination																												
- Non-Dominant	3(14.3)	-	-	2(9.5)	1(4.8)	-	3(14.3)	5(23.8)	1(4.8)	-	3(14.3)	3(14.3)	1(4.8)	5(23.8)	11(52.4)	1(4.8)	1(4.8)	5(23.8)	-	2(9.5)	10(47.6)	-	-	-	-	-	-	-
Dexterity																												
- Dominant	6(28.6)	-	-	4(19.0)	2(9.5)	-	6(28.6)	5(23.8)	1(4.8)	1(4.8)	3(14.3)	2(9.5)	-	6(28.6)	8(38.1)	1(4.8)	1(4.8)	8(38.1)	-	3(14.3)	6(28.6)	-	-	-	-	-	-	-
- Non-Dominant	11(52.4)	-	1(4.8)	7(33.3)	3(14.3)	1(4.8)	10(47.6)	2(9.5)	2(9.5)	-	3(14.3)	1(4.8)	-	4(19.0)	6(28.6)	-	1(4.8)	5(23.8)	-	2(9.5)	4(19.0)	-	-	-	-	-	-	-
- Bilateral	4(19.0)	-	-	3(14.3)	1(4.8)	1(4.8)	3(14.3)	2(9.5)	1(4.8)	-	-	3(14.3)	-	3(14.3)	13(61.9)	1(4.8)	2(9.5)	12(57.1)	-	2(9.5)	12(57.1)	-	-	-	-	-	-	-
Coordination																												
- Dominant	15(71.4)	2(9.5)	1(4.8)	12(57.1)	4(19.0)	1(4.8)	16(76.2)	1(4.8)	-	-	1(4.8)	-	-	1(4.8)	3(14.3)	-	1(4.8)	2(9.5)	-	2(9.5)	1(4.8)	-	-	-	-	-	-	-
- Non-Dominant	18(85.7)	2(9.5)	2(9.5)	14(66.7)	4(19.0)	3(14.3)	17(80.9)	-	-	-	-	-	-	-	1(4.8)	-	-	1(4.8)	-	-	1(4.8)	-	-	-	-	-	-	-
Ability to follow instruction (n=21)																												
Written instruction	12(57.1)	1(4.8)	1(4.8)	9(42.9)	3(14.3)	1(4.8)	12(57.1)	2(9.5)	-	-	2(9.5)	-	-	2(9.5)	3(14.3)	-	1(4.8)	1(4.8)	1(4.8)	2(9.5)	1(4.8)	2(9.5)	1(4.8)	-	3(14.3)	-	-	3(14.3)
Visual instructions	15(71.4)	2(9.5)	2(9.5)	12(57.1)	3(14.3)	3(14.3)	14(66.7)	3(14.3)	-	-	2(9.5)	1(4.8)	-	3(14.3)	1(4.8)	-	-	1(4.8)	-	-	1(4.8)	-	-	-	-	-	-	-
Spoken instructions	6(28.6)	1(4.8)	1(4.8)	3(14.3)	3(14.3)	1(4.8)	6(28.6)	3(14.3)	-	-	2(9.5)	1(4.8)	2(9.5)	1(4.8)	9(42.9)	1(4.8)	1(4.8)	9(42.9)	-	-	10(47.6)	1(4.8)	-	-	1(4.8)	-	-	1(4.8)

Further poor performances were still noted in subsequent Dominant Dexterity (DD) test with 6 (28.6%) below average/borderline and 9 (42.9%) impaired/severely impaired scores. Notably, all 3 (14.3%) patients with e4 positive allele status had impaired/ severely impaired performance in this test. The Non-Dominant Dexterity (N-DD) test further yielded 10(47.6%) below average and impaired performances. The Bilateral Dexterity (BD) test saw similar scores repeated, with 17(80.9%) below average or impaired performances. The majority of the positive e4 allele patients had impaired or severely impaired performances in both the tests.

The Dominant Coordination (DC) test however saw the reversal in the performance scores as 17 (80.9%) performed within the normal limits, whereas only 1(4.8%) was within borderline score and 3(14.3%) with impaired performance. Two (66.6%) of the ε4 positive patients had impaired performance in this DC test. The Non-Dominant Coordination (N-DC) test had similar positive performance with 20 (95.2%) normal limit scores and only 1(4.8%) impaired performance. All e4 allele positive patients performed within the normal limits.

Ability to follow instruction

The overall performance in the Written Instruction (WI) test yielded 2 (9.5%) borderline, 3 (14.3%) impaired scores. There were however 3 (14.3%) patients who were not able to complete the test as seen in Table 2. Most of the sample performed well (17, 80.9%) in the Visual Instruction (VI) test with only 3 (14.3%) borderline and 1 (4.8%) severely impaired performance. None of the latter was positive for e4 allele status. The overall performance in the Spoken Instruction (SI) test indicated that 10 (47.6%) patients with mTBI had impaired performance, and 2 (9.5%) patients with borderline scores were positive for e4 allele status.

Disability Rating Scale

The results at 1st month post injury showed 90.5% of the mTBI patients being completely independent and only 9.5% required some assistance in special environment, faced challenges in communicating, feeding and unable to return to work/unemployed. Reassessment at 6th month post injury yielded completely normal scores for all patients.

The Spearman correlation resulted in all negative correlation between e4 allele status and

Table 3: Spearman correlation analysis of test performance, allele status, age, Glasgow Coma Scale (GCS) and Glasgow Outcome Scale (GOS) Scores

Test	Subtests	Allele Status	Age	GCS	GOS
COTNAB	DC Overall Performance	-0.526*			
	D-STD Overall Performance		-0.566**		
	ND-STD Overall Performance		-0.466*		
	BD Overall Performance		-0.517*		
	WI Overall Performance			0.439*	
DRS	Communication ability -1st month	-0.651**	-0.524*		
	Employment status -1st month	-0.455*			
	Feeding Ability -1st month		-0.505*	0.441*	
	Level of functioning – 1st month		-0.452*		
	Employment status – 6th month				0.689**
	Level of functioning – 6th month				0.689**

DC = Dominant Coordination Test
D-STD = Dominant - Stereognosis and Tactical Discrimination Test
ND-STD = Non Dominant - Stereognosis and Tactical Discrimination Test
BD = Bilateral Dexterity Test
WI = Written Instruction Test
** significant at $p < 0.01$
* significant a $p < 0.05$

DC test overall performance (rs = -0.526, p < 0.05), communication ability at first month (rs = -0.651, p < 0.01) and employment status at 1st month (rs = -0.455, p < 0.05). The patients' age also resulted all negative correlation with COTNAB subtests such as overall performance in D-STD test (rs = -0.566, p < 0.01), ND-STD (rs = -0.466, p < 0.05), BD (rs = -0.517, p < 0.05). The age of the patients also negatively correlated with the DRS scores such as Communication Ability at 1st month (rs = -0.524, p < 0.05), Feeding (rs = -0.505, p < 0.05) and Level of Functioning at 1st month (rs = -0.452, p < 0.05). The GCS scores upon admission correlated with the overall performance in WI test(rs = 0.439, p < 0.05), and Feeding Ability at 1st month (rs = 0.441, p < 0.05). The GOS score at discharge showed significant correlation with Level of Functioning at 6th month post injury (rs = 0.689, p < 0.01) and employment status at 6th month (rs = 0.689, p < 0.01).

DISCUSSION

This preliminary study was designed to specifically examine the relationship between the genetic polymorphism of ApoE and outcomes (neurocognitive and functional) in mild head injuries. The novelty of this study lies in the selection of patient group and the assessment tools used to measure transient cognitive decline in patients with mTBI, affecting their overall functionality. Existing local study in its preliminary findings concluded that there were no clear association between ApoE e4 allele status and cognitive decline.[25] Their within-person comparison of neuropsychological performance however saw significant decline in 3 measures, namely the divided attention, recognition of faces and recall of actions in patients with at least one e4 allele.[25] It is also important to note that the severity of injury in patients selected for their study were not homogenous with a mixture of mild and moderate head injuries.

There are methodological differences and limitations in this present study which may have influenced our findings. As noted by previous studies, neurocognitive outcome in mTBI is influenced by various factors including age, level of education, sex, mechanism of injury, presence of intracranial lesion, posttraumatic amnesia, posttraumatic seizures, length of lost of consciousness, and the presence of alcohol.[26-28] Although we have ensured that all these factors were taken into account while analyzing the data, the fact that we had an extremely sample size limits the generalizability of the findings. Besides that, the wide age range in the study sample could have been better controlled. The presence of intracranial lesion as previously noted is also a crucial factor in assessing neurocognitive outcome in patients with mild traumatic brain injury. The differences between patients with or without intracranial lesion/s were not measured in this study.

We also limited our patient selection criteria to mild head injuries only in order to control the differences in outcomes influenced by the severity of the injury (GCS scores). This yielded in a positive result where some degree of association was seen. Most of the patients who had at least a single e4 allele performed poorly in most of the subtests in COTNAB in exception of the N-DC subtest (SMA module) and AFI test module at 6th month after injury. This supports the findings of Liberman *et al*. on the acute effects of CNS trauma and the role of ApoE. They concluded that the presence of e4 allele in patient with mTBI results in a wide array of negative cascading effects ranging from neuroinflammatory reactions to nerve regeneration[29] which influences neurocognitive outcomes from the initial acute period to months and years after the actual insult to the brain.

Perceptual dysfunction, visuospatial impairment, and sensory motor deficit are among the minimally studied areas in mTBI.[30] This study found that patients with mTBI who possess e4 allele were more likely to perform poorly in visual perception related tasks in comparison to those without e4 allele. The notion that patients with mTBI tend to develop visuospatial and sensory motor deficits is supported by a number of studies conducted in recent years.[31,32] It is also notable that patients who tend develop such complications fall within the 19-49 years old age group in agreement with other literatures on the said deficits.[29,33] The sensory motor deficits observed in this study were within the areas of stereognosis / tactical discrimination (dominant and non- dominant), and dexterity (dominant, non- dominant and bilateral) where most of the patients' performance showed plausible deficit. The severity of the deficits within this domain was more evident in patients who possessed the e4 allele. Similarly, Ariza et al., (2006) for instance noted that the patients with mTBI in their study carrying e4 allele were significantly worse on motor speed, fine motor coordination, visual scanning, attention and mental flexibility and significant neurobehavioral disturbances than the group with the e4 allele.[9]

The motor response speed (motor planning and execution) deficits were also seen in most of the patients with mTBI in this study, as observed by other studies[30,34] with the e4 positive allele group performing the tasks much slower in comparison to those without e4 allele. The complex information processing and reconstructing capabilities as assessed by the SI subtest in the AFI module yielded an overall poor score among most of the patients, including those with ApoE e4 allele. These patients exhibited impaired ability to understand and execute photographic instruction to assemble complex instruction. Similar patterns were observed in other studies.[35-37]

Although the mixed level of significance observed in this study (ApoE allele status, COTNAB and DRS scores) cannot be generalized, it however provides room for some important empirical notations to be made. The e4 allele status was negatively correlated with the overall performance in DC subtest, with most of the patients presenting impaired scores. In contrast, the initial influence of the e4 allele on communication and employment status (ability to return to school, work or premorbid condition) at the 1st month post injury was not observed at the 6th month post injury functional reassessment, therefore undermining the consistency of ApoE e4's long term effect on functional outcomes in patients with mTBI .

In conclusion, although the functional outcome in mTBI may improve over time, the cognitive impairment seems to persist in various forms. The important findings as previously stated within the specific attributes of visuospatial and sensory motor domain of cognitive functions possibly modulated by ApoE e4 warrants further investigation. Larger sample size and comprehensive assessment tools should be considered in future studies.

ACKNOWLEDGEMENT

This project is partially funded by the High Impact Research Grant of University of Malaya (UM.C/625/1/HIR-MOHE/12).We would like to acknowledge the staff of the Neurosciences Ward and Neurorehabilitation Unit of University Malaya Medical Centre for their kind support in patient registration and coordination. We would also like to thank Dr Vairavan Narayanan FRCS (Neurosurg) for advising on the preparation of the manuscript.

DISCLOSURE

Conflict of Interest**:** None

REFERENCES

1. Hejar AB, Zulkifli NAM, Law TH, Subramaniam K. *Proceedings of the Eastern Asia Society for Transportation Studies* 2005; 5:1867-74.
2. World Health Organization. *Neurological Disorders: Public Health Challenges*. 2006. Geneva, Switzerland.
3. Andersson EE, Emanuelson I, Bjourklund R, Stalhammar DA. Mild traumatic brain injuries: The impact of early intervention on late sequelae. A randomized controlled trial. *Acta Neurochirgica (Wein)* 2007; 149:151-60.
4. Millar K, Nicoll JAR, Thornhill S, Murray GD, Teasdale GM. Long term neuropsychological outcome after head injury: relation to APOE genotype. *J Neurol, Neurosurg Psychiatry* 2003; 7:1047-52.
5. Horaburgh K, McCarron MO, White F, Nicol JA. The role of apolipoprotein E in Alzheimer's disease. Acute brain injury and cerebovascular disease: evidence of common mechanisms and utility of animal models. *Neurobiol Aging* 2000; 21:245-55.
6. Gennarelli TA, Graham DI. Neuropathology of the head injuries. *Semin Clin Neuropsychiatry* 1998; 3:160-75.
7. Corder EH, Saunders AM, Risch, NJ, *et al*. Protective effects of apolipoprotein E type 2 allele for late onset of Alzheimer disease. *Nat Genet* 1995; 7(2):180-4.
8. Moran LM, Taylor HG, Ganesalingam K, *et al*. Apolipoprotein E4 as a predictor of outcomes in pediatric mild traumatic brain injury. *J Neurotrauma* 2009; 26:1489-95.
9. Ariza M, Pueyo R, Matarin MM, *et al*. Influence of APOE polymorphism on cognitive and behavioral outcome in moderate and severe traumatic brain injury. *J Neurol Neurosurg Psychiatry* 2006; 77:1191-3.
10. Liaquat I, Dunn LT, Nicol JAR, Teasdale GM, Norrie JD. Effect of apolipoprotein E genotype on hematoma volume after trauma. *J Neurosurg* 2002; 96:90-6.
11. Jainh Y, Sun X, Xia Y, Tang W, Cao Y, Gu Y. Effect of APOE polymorphisms on early response to traumatic brain injury. *Neurosci Lett*, 2006; 408:155-8.
12. Brichtova E, Kozak L. Apolipoprotien E genotype and traumatic brain injury in children – association with neurological outcome. *Childs Nerv Syst* 2008; 24:349-56.
13. Adamson MM, Hutchinson JB, Shelton AL, Wagner AD, Taylor JL. Reduced hippocampal activity during encoding in cognitively normal adults carrying the APOE ϵ4 allele. *Neuropsychologia* 2011; 49:2248-455.
14. Freidman G, Froom P, Sazlon L, *et al*. Apolipoprotien E- ε4 genotype predicts a poor outcome in survivors of traumatic brain injury. *Neurology* 1999; 52:244-8.
15. Tyerman R, Tyerman A, Howard P, Chessington HC. Occupational OT Neurological Assessment Battery (COTNAB), 1986. Nottingham Rehab Ltd, Nottingham.
16. Wilde EA, Whiteneck GG, Bogner J, *et al*.

Recommendations for the use of common outcome measures in traumatic brain injury research. *Arch Phys Med Rehabil* 2010; 91(11).
17. Laver AJ, Huchinson S. The performance and experience of normal elderly people on the Chessington Occupational Therapy Neurological Assessment Battery (COTNAB). *Br J Occup Ther* 1994; 57(4):137-42.
18. Sloan RL, Downie C, Hornby J, Pentland B. Routine screening of brain-damaged patients: a comparison of the Rivermead Perceptual Assessment Battery and the Chessington Occupational Therapy Neurological Assessment Battery. *Clin Rehabil* 1991; 5(4):265-72.
19. Stanley M, Buttfield J, Bowden S, Chessington WC. Occupational Therapy Neurological Assessment Battery: Comparison of performance of people aged 50–65 years with people aged 66 years and over. *Aust Occup Therap J* 1995; 42:55-65.
20. Hall KM, Hamilton BB, Gordon WA, Zasler ND. Characteristics and comparisons of functional assessment indices: Disability Rating Scale, Functional Independence Measure, and Functional Assessment Measure. *J Head Trauma Rehabil* 1993; 8:60-74.
21. Bowers D, Kofroth L. Comparison: Disability Rating Scale and Functional Independence Measure during recovery from traumatic brain injury. *Arch Phys Med Rehabil* 1989; 70:A58.
22. Gourvier WD, Blaton PD, LaPorte KK, Nepomuceno C. Reliability and validity of the Disability Rating Scale and the Levels of Cognitive Functioning Scale in monitoring recovery from severe head injury. *Arch Phys Med Rehabil* 1987; 68(2):94-7.
23. Hall K, Cope DN, Rappapot M. Glasgow Outcome Scale and Disability Rating Scale: comparative usefulness in following recovery in traumatic head injury. *Arch Phys Med Rehabil* 1985; 66(1):35-7.
24. Anada RP, Ganesan D, Ramahsamay N, Wong KT. A prevalence study of single nucleotide polymorphisms in the promoter of the apolipoprotein E gene in different ethnic groups in Malaysia. *Neurol Asia* 2012; 17(4):341-6.
25. Shadli RM, Peiter MS, Yaacob MJ, Rashid FA. APOE genotype and neuropsychological outcome in mild to moderate traumatic brain injury: A pilot study. *Brain Injury* 2011; 25(6):596-603.
26. Ponsford J, Draper K, Schonberger M. Functional outcome 10 years after traumatic brain injury: its relationship with demographic, injury severity, cognitive and emotional status. *J Intl Neuropsychol Soc* 2008; 14:233-42.
27. Belanger HG, Curtiss G, Demery JA, Lebowitz BK, Vanderploeg RD. Factors moderating neuropsychological outcomes following mild traumatic brain injury: a meta-analysis. *J Intl Neuropsychol Soc* 2005; 11(3):215-27.
28. Skandsen T, Finnanger TG, Andersson S, Lydersen S, Brunner JF, Vik A. Cognitive impairment 3 months after moderate and severe traumatic brain injury: A prospective follow-up study. *Arch Phys Med Rehabil* 2010; 91:1904-13.
29. Liberman JN, Stwart WF, Wesnes K, Troncoso J. Apolipoprotien E ϵ4 and short term recovery from predominantly mild brain injury, *Neurology* 2002; 58:1038-44.
30. Sosnov JJ, Broglio SP, Ferrara MS. Cognitive and motor function are associated following mild traumatic brain injury**.** *Exp Brain Res* 2009; 187:563-71.
31. Proto D, Pella RD, Hill BD, Gouvier WD. Assessment and rehabilitation of acquired visuospatial and proprioceptive deficits associated with visuospatial neglect. *Neurorehabilitation* 2009; 24:145-57.
32. McKenna K, Cooke DM, Fleming J, Jefferson A, Ogden S. The incidence of visual perceptual impairment in patient with severe traumatic brain injury. *Brain Injury* 2006; 20 (5):507-18.
33. Savage RC. The developing brain after TBI: Predicting long term deficits and services for children, adolescents and young adults. *Neurotrauma Letters* 2009; 04.
34. Lachapelle J, Teasdale JB, Ptito A, and McKerral M. Deficits in complex visual information processing after mild TBI: Electrophysiological markers and vocational outcome prognosis. *Brain Injury* 2008; 22(3):265-74.
35. Gagnon I, Swaine B, Friedman D, Forget R. Visuo-motor response time in children with a mild head injury. *J Head Trauma Rehabil* 2004; 19:391-404.
36. Mathias JL, Beall JA, Bigler ED. Neuropsychological and information processing deficits following mild traumatic brain injury. *J Intl Neuropsychol Soc* 2004; 10:286-97.
37. Sterr A, Herron K, Hayward C, Montaldi D. Are mild head injuries as mild as we think? Neurobehavioral concomitants of chronic post-concussive syndrome. *BMC Neurology* 2006; (1):7.