ID Design Press, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2018 Sep 25; 6(9):1674-1677.
https://doi.org/10.3889/oamjms.2018.390
eISSN: 1857-9655
Clinical Science

High Il-1β Serum as a Predictor of Decreased Cognitive Function in Mild Traumatic Brain Injury Patients

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Citation: Samatra DPGP, Pratiwi NMD, Widyadharma IPE. High Il-1β Serum as a Predictor of Decreased Cognitive Function in Mild Traumatic Brain Injury Patients. Open Access Maced J Med Sci. 2018 Sep 25; 6(9):1674-1677. https://doi.org/10.3889/oamjms.2018.390

Keywords: IL-1β serum; Cognitive dysfunction; Traumatic brain injury

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Received: 05-Jul-2018; **Revised:** 06-Sep-2018; **Accepted:** 07-Sep-2018; **Online first:** 24-Sep-2018

Funding: This study was financially supported by a grant from the Research and Development Faculty of Medicine, Udayana University

Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Traumatic brain injury (TBI) exerts a significant impact on society with regards to physical, affective, and cognitive impairment. The consequent cognitive sequelae include a problem in memory, attention, concentration, and processing speed. Following traumatic brain injury, inflammatory response developed, characterised by increased interleukin 1-β (IL-1β) levels in the blood. IL 1-β at pathophysiological concentration has been reported to cause an inhibition of the expression of long-term potentiation (LTP) in the areas CA1, CA3, and dentate gyrus of the hippocampus.

AIM: This study aims to determine whether high IL-1β serum is a predictor of decreased cognitive function in mild TBI.

METHODS: This is a prospective cohort study conducted at the emergency room, surgical and neurologic ward at Sanglah Hospital from November 2017 until January 2018. As many as thirty-five mild TBI with normal IL-1β serum (< 0.0565 pg/ml) and thirty-five of those with high IL-1β serum (≥ 0.0565 pg/ml) subjects were included within the corresponding period. The decrease of cognition after trauma was measured seven days later.

RESULTS: This study demonstrated that group with high IL-1β serum levels were at higher risk of suffering from cognitive impairment after TBI when compared with the group with normal IL-1β serum levels (RR = 2.6; 95% CI 1.49-4.55, p < 0.001).

CONCLUSION: Mild TBI with high serum IL-1β levels were more than twice likely to experience decreased cognitive function than those with normal IL-1β levels.

Introduction

Traumatic brain injury (TBI) is a neuro-emergency situation which has a significant primary impact (i.e. cost of treatment) and also secondary impact (i.e. loss of productivity) in the patient. There are various TBI complications including physical, affective, and cognitive impairment. Furthermore, cognitive impairment comprises memory dysfunction, poor concentration and thinking process [1]. Meanwhile, physical impairment may occur as a headache, dizziness, and lethargy, whereas affective impairment includes emotional disturbance such as irritability, anxiety disorder, and depression. Those impairments may potentially affect the ability of patients to do work as usual and their role in society [2]. TBI is the third leading cause of death related to traumatic cases in the U.S.; it is estimated that 1.7 million American citizens suffered from TBI every year [3].

The resulting inflammatory response after TBI occurs both locally at the injured area (so-called neuroinflammation) and systemically. After the initial injury, complement is activated which subsequently followed by neutrophil, lymphocyte, and monocyte infiltration via blood-brain barrier. Also, secretion of pro-inflammatory cytokines and mediators, prostaglandin, reactive agents, and other inflammatory molecules also occur simultaneously. These processes subsequently lead to increased chemokine and adhesion molecule expressions, enabling immune cells and microglia to infiltrate brain parenchyma which initiates secondary brain injury [4] [5].

Interleukin 1-β (IL-1β) is an inflammatory marker that can be potentially used as a predictor of

TBI. IL-1β is produced by the central nervous system as a response to several stimuli, such as administration of peripheral lipopolysaccharides, TBI, acute stress, anorexia, and administration of β-α adreno-receptor agonists. In the brain, IL-1β levels are particularly high in the hippocampus and hypothalamic area. High IL-1β levels to the extent of its pathophysiologic concentration (0.1-10 ng/mL) as found in post-mortem tissue and cerebrospinal fluid in a chronic disease like Alzheimer have been reported to inhibit long-term potentiation (LTP) in CA1, CA3, and dentate gyrus of the hippocampal area [6].

A study conducted by Coogan et al., [6] also found that chronic high IL-1β levels were found to inhibit LTP induction process. Furthermore, another study by Ross et al., [7] concluded that IL-1β at 1 and 10 ng/mL could decrease the post-synaptic excitatory potential by 25% in CA1 area of the rat hippocampus. However, further studies are required to profile IL-1β levels increment if it is to be used as a predictor of cognitive function in TBI.

Therefore, this study aims to determine whether high IL-1β serum is a predictor of decreased cognitive function in mild TBI.

Material and Methods

This was an analytic observational prospective cohort study, with consecutive non-random sampling method. This study had been approved by the Ethical Committee for Human Study, Faculty of Medicine, Udayana University and all of the investigators had ensured that the study adhered to the WMA Declaration of Helsinki [8]. Also, every patient who participated in this study had agreed and signed informed consent paper.

This study was conducted at the emergency room, surgical and neurologic ward at Sanglah Hospital from November 2017 until January 2018. During the corresponding period, as many as thirty-five subjects suffering from mild TBI with normal IL-1β serum (< 0.0565 pg/mL) and thirty-five mild TBI subjects with high IL-1β serum (≥ 0.0565 pg/mL) were included.

The cognitive state examination pre-TBI, depression, and cognitive evaluation post-TBI were done using Short Form of the Informant Questionnaire on Cognitive Decline in the Elderly (Short IQCODE), Hamilton Rating Scale for Depression, and Indonesian Version of Montreal Cognitive Assessment (MoCA-INA) questionnaire, respectively. Mild TBI was diagnosed based on the subject's history, physical and neurological examinations and confirmed by non-contrast CT scan. IL-1β levels were measured during admission, i.e. at the onset of initial brain injury, before 24 hours using ELISA-based Quantikine HS Human IL-1/beta-1F2 Immunoassay (R&D system, USA). The protocol was conducted according to the procedure written at the packaging.

The collected data were subsequently analysed using IBM SPSS version 20 for Windows (IBM Inc, USA). Data were analysed in two phases, i.e. descriptive and analytical phases. Analytical statistics were performed in order to obtain the relative risk of cognitive impairment incidence post mild TBI between two groups, along with test for significance using Chi-square test. *P* value of < 0.05 was considered significant with confidence interval of 95%.

Results

70 subjects were involved in this study, whom further divided into two groups (normal vs. high IL-1β), each with 35 subjects. IL-1β serum levels from all subjects were within 0.028 to 2.315 pg/mL. An ROC curve was then determined in order to define the ability of IL-1β serum levels as a predictive factor of cognitive impairment. The obtained AUC of 86.9% (95% CI 78.5%-95.3%, p < 0.001) was considered adequate statistically (Figure 1). The results of ROC coordinate had showed that IL-1 β cut-off point of ≥ 0.0565 pg/mL which was used in this study had a 88.9% sensitivity and 64.7% specificity.

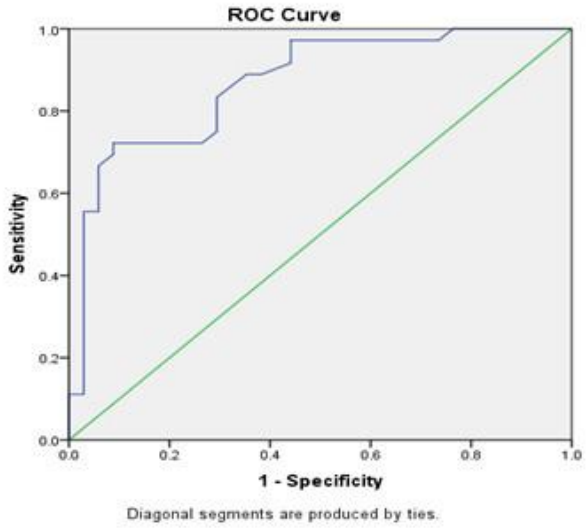

Figure 1: ROC of IL-1β serum levels toward cognitive decline with 86.9% AUC

Accordingly, all subjects were divided into two groups, i.e. those with high IL-1β as defined by serum levels of ≥ 0.0565 pg/mL and low IL-1β defined by serum levels of < 0.0565 pg/mL.

The characteristics of subjects based on IL-1β levels were presented at the Table 1.

Table 1: Subject's baseline characteristics

Variables	Normal IL-1β value	High IL-1β value	p
	n (%)	n (%)	
Gender			
Male	16 (45.7)	27 (77.1)	0,007[a]
Female	19 (54.3)	8 (22.9)	
Age			
17-25 years old	15 (42.9)	15 (42.9)	1,000[a]
26-35 years old	20 (57.1)	20 (57.1)	
Education			
Middle School	32 (91.4)	32 (91.4)	1,000[b]
Bachelor degree	3 (8.6)	3 (8.6)	

[a]*Chi-square test;* [b]*Fisher's Exact test.*

As many as 16 (45.7%) male and 19 female (54.3%) subjects had normal IL-1β levels, whereas 27 male (77.1%) and 8 female (22.9%) subjects had high IL-1β serum levels. Within normal IL-1β group, 15 (42.9%) subjects were of late adolescents and 20 (57.1%) were of early adults, while in high IL-1β group, 15 (42.9%) subjects were of late adolescents category and 20 (57.1%) subjects were of early adults (p = 1).

Similarly, education levels within group were alike, i.e. 32 (91.4%) vs. 32 (91.4%) subjects from normal and high IL-1β serum groups, respectively, graduated from middle school, whereas as many as 3 (8.6%) subjects from both groups graduated from university.

Table 2: Bivariate analysis of serum IL-1β levels with Cognitive Function

Variables		Cognitive Function		RR (IK 95%)	P
		Decreased n (%)	Normal n (%)		
Serum IL-1β levels	Normal	10 (28.6%)	25 (71.4%)	2.60 (1.49-4.55)	<0.001
	High	26 (74.3%)	9 (25.7%)		

The incidence of cognitive function impairment in mild TBI subjects with normal serum IL-1β levels was 28.6%, significantly lower when compared with those of high serum IL-1β group (74.3%). Accordingly, subjects with high serum IL-β levels were more prone to suffer from the decreased cognitive function as opposed to a normal group (RR 2.60; 95% CI 1.49-4.55, p < 0.001).

Table 3: Bivariate analysis of other variables with cognitive function impairment

Other Variables	Cognitive Function		RR (IK 95%)	p
	Decreased n (%)	Normal n (%)		
Male	26 (72.2)	17 (50.0)	1.63	0.056[a]
Female	10 (27.8)	17 (50.0)	(0.94-2.82)	
Late adolescent	11 (30.6%)	19 (55.9%)	0.59	0.032[a]
Early adult	25 (69.4%)	15 (44.1%)	(0.35-0.99)	
Middle School	33 (91.7%)	31 (91.2%)	1.03	1.000[b]
Bachelor Degree	3 (8.3%)	3 (8.8%)	(0.45-2.38)	

[a]*Chi-square Test;* [b]*Fisher's Exact Test.*

Further analyses revealed that decreased cognitive function was more commonly found among males (72.2%) across all groups. Indeed, males were more likely to suffer from decreased cognitive function than females, despite statistically non-significant (RR = 1.63; 95% CI 0.94-2.82, p = 0.056). In regards to age group, fewer late adolescent suffered from decreased cognitive function as opposed to early adult (30.6% vs. 69.4%, respectively; RR 0.59, 95% CI 0.35-0.99, p = 0.032). Furthermore, with respect to education levels, decreased cognitive function did not differ significantly in middle school- vs. university graduates (RR = 1.03, 95% CI 0.45-2.38, p = 1.00).

Discussion

This study showed that there were 27 males (77.1%) and 8 females (22.9%) who suffered from TBI had high serum IL-1β levels. These results were in accordance to a study conducted at Hasan Sadikin Hospital during the 2008-2010 period, in which as many as 79.8% males and 20.2% females from 3,578 subjects suffered from TBI [9]. This significant proportional difference of sex-based TBI was not unfamiliar, as males ride 4.5 times more frequently than females and tend to engage in physical conflict, thus potentially result in head injuries [10].

In normal serum IL-1β group, as many as 15 subjects were of late adolescent (42.9%), and 20 subjects were of early adult (57.1%). In this study, age was focused on these two groups since according to Indonesian national health statistics, TBI occurs most often among 15-44 years old age group. The decreased cognitive function was found more commonly among early adult with statistical significance. The result was apparently by another study which found that older subjects demonstrated a greater cognitive decline than younger one over a 5-year period [11]. Herein, we demonstrated a higher incidence of an acute decrease in cognitive function in older individuals shortly after TBI. These results may in part be explained by the age-related difference in synaptic plasticity and cortical volume. It is still to be determined, however, if the cognitive decline persists over a longer period, and if there is any difference in the status and rate of meaningful cognitive recovery among different age groups.

In both normal and high serum IL-1β groups, decreased cognitive function did not seem affected by educational level. This is contrary to the common belief and clinical findings that a higher educational level may be protective to cognitive decline post-TBI, with one of the most important factors is having higher cognitive reserve [12]. Our study results may be limited by the scarcity of subjects who had attained university degree (3 subjects in each group), thus providing inadequate power to the results.

In this study, serum IL-1β levels among all subjects were within 0.028 pg/mL to 2.315 pg/mL. Furthermore, AUC derived from ROC method was 86.9% (95% CI 78.5%-95.3%, p < 0.001). Statistically, AUC of 86.9% had an adequate diagnostic value

(Figure 1). ROC coordinate showed that IL-1β cut-off point of ≥ 0.0565 pg/mL used in this study had 88.9% sensitivity and 64.7% specificity. In our study, IL-1β levels among all groups were markedly lower than previous studies. Several reasons might account for this discrepancy, i.e. firstly, we included relatively younger subjects (15-44 years old) as opposed to a study with a wide age range (18-74 years old) [13]. IL-1β is not specific for TBI. Thus various diseases, including infection or metabolic/degenerative can obscure the result. Secondly, even when there are comorbidities, IL-1β levels can still surprisingly detected at minute levels, ranging from 0.5 pg/mL in the hip fracture to 1.39 pg/mL in subjects with congestive heart failure [14]. Given the wide variations of IL-1β levels, it should be ideally measured periodically and assessed for its elevation/decline rather than its absolute levels per se.

Most importantly, this study found a markedly increased risk of experiencing decreased cognitive function among subjects with high IL-1β levels. Our study thus confirmed the previous findings, for instance, one which was conducted by Coogan et al., [6] that abnormally high IL-1β levels had been shown to inhibit LTP. IL-1β at 1 and 10 ng/mL can decrease the post-synaptic excitatory potential by 25% in CA1 area of the rat hippocampus, thus potentially affecting memory formation, or even its storage and retrieval.

In conclusion, mild TBI with high serum IL-1β levels was more than twice likely to experience decreased cognitive function than those with normal IL-1β levels.

Acknowledgement

This study was financially supported by a grant from the Research and Development Faculty of Medicine, Udayana University. Authors in this study thanked all of the patients who participated in this study, as well as to Putri Rossyana Dewi, M.D. and Andreas Soejitno, M.D. for their assistance in translating this manuscript into English.

References

1. Borgaro SR, Prigatano GP, Kwasnica C, Rexer JL. Cognitive and affective sequelae in complicated and uncomplicated mild traumatic brain injury. Brain Inj. 2003; 17:189-98. https://doi.org/10.1080/0269905021000013183 PMid:12623495

2. Schretlen DJ, Shapiro AM. A quantitative review of the effects of traumatic brain injury on cognitive functioning. Int Rev Psychiatry. 2003; 15:341-9. https://doi.org/10.1080/09540260310001606728 PMid:15276955

3. Faul M, Xu L, Wald MM, Coronado VG. Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations and Deaths 2002-2006. U.S. Department of Health and Human Services: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2010. https://doi.org/10.15620/cdc.5571

4. Liao Y, Liu P, Guo F, Zhang ZY, Zhang Z. Oxidative burst of circulating neutrophils following traumatic brain injury in human. PLoS One. 2013; 8:e68963. https://doi.org/10.1371/journal.pone.0068963 PMid:23894384 PMCid:PMC3722225

5. Lozano D, Gonzales-Portillo GS, Acosta S, et al. Neuroinflammatory responses to traumatic brain injury: aetiology, clinical consequences, and therapeutic opportunities. Neuropsychiatr Dis Treat. 2015; 11:97-106. PMid:25657582 PMCid:PMC4295534

6. Coogan AN, O'Neill LA, O'Connor JJ. The P38 mitogen-activated protein kinase inhibitor SB203580 antagonizes the inhibitory effects of interleukin-1beta on long-term potentiation in the rat dentate gyrus in vitro. Neuroscience. 1999; 93:57-69. https://doi.org/10.1016/S0306-4522(99)00100-1

7. Ross FM, Allan SM, Rothwell NJ, Verkhratsky A. A dual role for interleukin-1 in LTP in mouse hippocampal slices. J Neuroimmunol. 2003; 144:61-7. https://doi.org/10.1016/j.jneuroim.2003.08.030 PMid:14597099

8. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2000; 284:3043-5. https://doi.org/10.1001/jama.284.23.3043

9. Zamzami NM, Fuadi I, Nawawi M. Angka Kejadian dan Outcome Cedera Otak di RS Hasan Sadikin Bandung Tahun 2008-2010. Jurnal Neuroanestesia Indonesia. 2013; 2:6.

10. Munivenkatappa A, Agrawal A, Shukla DP, Kumaraswamy D, Devi BI. Traumatic brain injury: Does gender influence outcomes? Int J Crit Illn Inj Sci. 2016; 6:70-3. https://doi.org/10.4103/2229-5151.183024 PMid:27308254 PMCid:PMC4901830

11. Marquez de la Plata CD, Hart T, Hammond FM, et al. Impact of age on long-term recovery from traumatic brain injury. Arch Phys Med Rehabil 2008;89:896-903. https://doi.org/10.1016/j.apmr.2007.12.030 PMid:18452739 PMCid:PMC2600417

12. Schneider EB, Sur S, Raymont V, et al. Functional recovery after moderate/severe traumatic brain injury: a role for cognitive reserve? Neurology. 2014;82:1636-42. https://doi.org/10.1212/WNL.0000000000000379 PMid:24759845 PMCid:PMC4211893

13. Tasci A, Okay O, Gezici AR, Ergun R, Ergungor F. Prognostic value of interleukin-1 beta levels after acute brain injury. Neurol Res. 2003; 25:871-4. https://doi.org/10.1179/016164103771953998 PMid:14669533

14. Di Iorio A, Ferrucci L, Sparvieri E, et al. Serum IL-1beta levels in health and disease: a population-based study. 'The InCHIANTI study'. Cytokine. 2003; 22:198-205. https://doi.org/10.1016/S1043-4666(03)00152-2