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Research Article

ROLE OF P53 GENE ARG72PRO AND SERUM ELECTROLYTES IN OUTCOME OF TRAUMATIC BRAIN INJURY AMONG SUDANESE PATIENTS

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ABSTRACT

Background: Traumatic brain injury (TBI), defined as an alteration in brain functions caused by an external force, [(1)] is responsible for high morbidity and mortality around the world, TBI is an extremely important cause of mortality and morbidity in the developed world. The candidate genes affecting TBI outcomes including apolipoprotein E (APO E), P53, angiotensin I-converting enzyme (ACE), D2 subtype of the dopamine receptor (DRD2), atechol-O- methyltransferase (COMT), BCL-2, neuroglobin (NGB) and IL-1β. Also some biochemical changes may occur in patients with TBI, such like electrolytes and blood glucose. **Materials and methods:** This is a cross-sectional study that had been conducted at the National Center for Neurological Sciences (NCNS) during January 2016 to March 2016, Blood specimens were obtained from 51 TBI patients treated at NCNS, and processed for biochemical profile and molecular genotyping of p53 gene Arg/pro. **Results:** Molecular screening of P53 gene codon 72 at exon 4 showed that the most common allele was arginine (Arg/arg). In the present study measurement of sodium and potassium revealed that, sodium level < 135mmol/l was detected in 3.9% and >145 was 15.7% of TBI patients, potassium level <3.5 was detected in 25.5% of TBI patients.

INTRODUCTION

Traumatic brain injury (TBI), defined as an alteration in brain functions caused by an external force, is responsible for high morbidity and mortality around the world [(1)]. Numerous studies have consistently demonstrated biochemical changes following TBI. Few biochemical markers had been investigated as prognostic markers for outcome in TBI. These markers also show some changes in patients of trauma as a component of metabolic response to injury or infection [(2)].

TBI is an extremely important cause of mortality and morbidity in the developed world [(3)]. Several studies from South Africa (SA)Taiwan and India showed that, higher rates in developing countries accounted for primarily by road traffic accidents or motor vehicle accidents[(4)]. The overall incidence of TBI is therefore probably higher than officially reported, even in the developed world. South Africa does not have a TBI databank, and contemporaneous studies on the overall incidence and prevalence of TBI are lacking [(5)]. A study in 2007 found injury-related mortality rates in SA to be 6 times higher, and the incidence of road traffic injuries to be doubled, that of the global rate [(6)].

TBI is characterized by two injury phases, primary and secondary. The primary brain injury includes cerebral contusions, extra-axial hematomas (epidural, subdural, and subarachnoid hemorrhages), and diffuse axonal injury, is the direct injury to the brain cells incurred at the time of the initial impact [(7)]. This results in a series of, biochemical processes which then result in secondary brain injury. The secondary brain injury is caused by a dynamic interplay between ischaemic, inflammatory and cytotoxic processes. Studies with microdialysis techniques have shown that one of the most significant factors causing secondary brain injury is the excessive release of excitotoxins such as glutamate and aspartate that occurs at the time of the primary brain injury. These excitotoxins act on the N-methyl-D-aspartate channel,

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altering cell wall permeability with an increase in intracellular calcium and sodium and activation of calcineurin and calmodulin. This ultimately, leads to destruction of the axon [8, 9]. Potassium is also released from the cells and absorbed by the astrocytes, in an attempt to restrict the ionic imbalance causing swelling of the cells and ultimately cell death[10]. Hyperglycemia contributes to secondary brain injury by worsening intracellular acidosis as it provides a substrate for continued anaerobic metabolism. Whether prevention of hyperglycemia, particularly in sever TBI, improves outcomes is yet to be conclusively established [11]. It has been demonstrated that decreased brain tissue oxygenation is predictive of poor outcome following TBI, and brain oxygenation is strongly linked to systemic oxygenation [12].

Clinical outcomes following TBI are determined by multiple genetic elements and acquired environmental risk factors. TBI trigger a series of pathophysiological processes including neuroinflammation, oxidative stress, exocitotoxicity, apoptotic cell death, neurodegeneration, reparative processes, synaptic plasticity, and neurotransmitter alterations [13, 14]. Additionally, genetic factors have been implicated in almost all these processes to some extent and are therefore responsible for the variable individual responses to TBI [13- 15]. An individual's genetic predisposition to the injury may influence the variability of the initial response, the recovery process, susceptibility to the secondary injury, and response to rehabilitation. Genetic association studies are useful tools in investigating possible relationships between gene polymorphisms and disease outcome [16]. The candidate genes affecting TBI outcomes including apolipoprotein E (APO E), P53, angiotensin I-converting enzyme (ACE), D2 subtype of the dopamine receptor (DRD2), atechol-O- methyltransferase (COMT), BCL-2, neuroglobin (NGB) and IL-1β [17].

Programmed cell death is a genetic mechanism by which the cells are eliminated during development, and physiological mechanism by which cells are normally removed in the adult animal [18]. Apoptosis is now recognized as an important factor in secondary brain injury [19].

P53 is a tumor suppressor and its 19 kb gene (TP53) is situated on chromosome 17p13.1. It consists of 11 exons resulting in a transcript of 2,629 bp and a protein of 393 amino acids. In half of all human cancers, the tumor suppressor p53 is damaged by somatic mutation in tumor cells [20]. This protein is at the centre of cell regulatory pathways, influencing transcription and activity of several replication and transcription factors, and is known as the guardian of the genome. In case of UV-radiation, protooncogene activation or DNA damage, p53 is activated. P53 acts through several pathways when reacting to cellular stress. Apoptosis, cell cycle arrest at the G1 checkpoint, and cellular senescence are all mechanisms triggered by activated p53 [21], thereby preventing cancer growth [22]. The P53 gene is important in the regulation of apoptosis; this gene exhibits a common polymorphism that results in either proline or arginine at amino acid 72 [23]. Arg72Pro was first discovered in 1986 as a difference in electrophoretic mobility of two versions of p53 [24]. Since then, this SNP has been implicated in risk of cancer, hepatitis C and schizophrenia, in outcome for patients with traumatic brain injury, in placental weight and in ageing [25- 32]. In short, the Arg72 form is more efficient in apoptosis induction, whereas the Pro72 form induces more G1 arrest and is better at activating p53 dependent DNA repair [26]. Arg/Arg genotype of the Arg72Pro polymorphism in p53 is associated with an increased likelihood of a poor outcome at discharge from the surgical intensive care unit following TBI [23].

MATERIAL AND METHOD

This is a cross sectional hospital based study done at the National Center of Neurological sciences (NCNS) in Khartoum state between January 2016 to March 2016. Fifty one traumatic brain injury patients whom were admitted and diagnosed in NCNS during the above mentioned period were included in this study. The data were collected by using predesigned interview questionnaire. Venous blood sample were collected from all participants, in sterile containers that contains EDTA and lithium heparin for DNA extraction, and electrolytes respectively. Verbal and written consent from each participant was obtained. The following variables concerning each case was recorded (age, gender, residence, tribe, blood genotyping of p53 gene at codon 72 variants and biochemical parameters).

DNA extraction from blood samples

The DNA extraction was done by using guanidine chloride method[33], 2 ml from each TBI blood was placed into Falcon tube (15 ml), 10 ml from red cell lysis buffer was added, then tubes gently were mixed by using vortex mixer, after that the tubes were centrifuged at 6000 RPM for 10 minutes, this step was repeated until clear pallet was obtained, then 2 ml from White cell lysis buffer, 1 ml from guanidine chloride, 350 µl of ammonium acitate and 20 µl of proteinase K were added, tubes were vortexed and then incubated at 37 C for overnight, after incubation the tubes were vortexed and 2 ml from pre chilled chloroform was added, the tubes were mixed by using vortex mixer, after that the tubes were centrifuged at 6000 RPM for 10 minutes, then the supernatant was transferred into a new Falcon tube (15 ml), 8 ml of pre chilled ethanol was added to each tube with gentle mixing to precipitate the DNA, for completion of DNA precipitation the tubes were incubated at -20 C for 2 hours, after incubation the tubes were centrifuged at 6000 RPM for 10 minutes, then the ethanol was poured in to disposal bottle, after that 4 ml of 70% alcohol was added and after that the tubes were centrifuged at 6000 RPM for 10 minutes, the 70% alcohol was poured into disposal bottle, and after that the tubes were blotted on filter paper, and then left to air dry, after completion of drying 100 µl of Elution buffer was added, then after that the tubes were incubated at 4 C for completion of DNA elution. 18µl of readymade MM was added into each PCR tube, all reagents were placed in a frozen-cryo-rack. To avoid contamination, separate area for PCR was prepared, and all work material needed for PCR was carefully handled. According to the international PCR protocol all the steps were been followed.

Primers for p53 gene codon 72 arg/pro was obtained from the published data, 5 tcc ccc ttg ccg tcc caa 3 forward primer and 5 ctg gtg cag ggg cca cgc 3, reverse primer were used for amplification of arginine allele at codon 72, and, 5 gcc aga ggc tgc tcc ccc 3 forward primer and,5 cgt gca agt cac aga ctt 3 primer were used for amplification of prolin allel at codon 72. Each of the forward and reverse primers were prepared by

adding10µl of each stock primer (100 µM) to 90µl deionized water, the solution was mixed carefully using vortex mixer. Using 2% Agarose gel electrophoresis amplified PCR product were visualized.

RESULT

A total of 51 traumatic brain injury (TBI) patients were included in the present study. Male were 46 constituting 90.2%, and female where 5 constituting 9.8%.The most affected age group ranging from 21 to 30 years constituting 51.4%, followed by the age group ranging from 31 to 40 years constituting 30.7% . Results of this study indicated that 31.4% of the patients were come from Khartoum state.

43 of the patients had experienced good outcome, and 7 of the patients had poor outcome according to Glasgow coma score (GCS) (table 2). Molecular screening of P53 gene codon 72 at exon 4 showed that the most common allele was arginine (Arg/Arg) variant which encountered in 81.8% of the patients followed by Arginine/Proline (Arg/pro) and Pro/pro in 11.4% and 6.8% respectively (table 3). Biochemical profile results were displayed in (table 4, 5).

Cross tabulation of P 53 gene codon 72 and outcome showed that all the patients with Arg/Arg allele constituting 14.2% had poor outcome according to (GCS), and 100% of the patients with Arg/Pro and Pro/Pro alleles were survive (table 6).

Table 1 shows the types frequency a of TBI in patients

Type of TBI	Frequency	Percent (%)	Type of TBI	Frequency	Percent (%)
Brain edema	3	5.9	EDH+ SDH+ HC	1	2.0
Heamorrhge Contusion	12	23.5	SAH + edema	2	3.9
Ltercerebral heamorrhge	1	2.0	HC + SAH	4	7.8
Axonal injury	2	3.9	Bullet injury	1	2.0
Extradural heamatoma	9	17.6	SDH + contusion	3	5.9
Edema + contusion	4	7.8	SAH	3	5.9
			Total	51	100.0

EDH= Extradural heamatoma, SAH= subarachnoid hemorrhages, HC= Hemorrhagic Contusion, SDH= subdural heamatoma

Table 2 shows the frequency of outcome in traumatic patients

Outcome	Frequency	Percent (%)
Discharge	43	86.0
Death	7	14.0
Total	50	100.0

Table 3 shows the frequency of p53 gene alleles in traumatic patients

Allele	Frequency	Percent (%)
Arg/Pro	5	11.4
Arg/Arg	36	81.8
Pro/Pro	3	6.8
Total	44	100.0

Table 4 shows the frequency of sodium results in traumatic patients

Results (mmol/L)	Frequency	Percent (%)
<135 mmol/L	2	3.9
135 – 145 mmol/L	41	80.4
>145 mmol/L	8	15.7
Total	51	100.0

Table 5 shows the frequency of potassium results in traumatic patients

Results (mmol/L)	Frequency	Percent (%)
<3.5 mmol/L	13	25.5
3.5 – 5.0 mmol/L	38	74.5
Total	51	100.0

Table 6 shows the cross-tabulation of p53 gene variants and outcome in TBI patients

P53	Outcome		Total
	Discharge	Death	
Arg/Pro	5	0	5
Arg/Arg	30	5	35
Pro/Pro	3	0	3
Total	38	5	43

According to the type of TBI, frequency of hemorrghic contusion was 23.5%, followed by subdural hemorrhage and epidural hemorrhage in 17.6% and 11.7% of the patients respectively (table 1). The results of TBI outcome showed that

Cross tabulation of P53 gene with the types of TBI showed that 11 Arg/Arg variant were identified in hemorrhagic contusion followed by 7 in subdural hemorrhage, Arg/Pro and Pro/Pro alleles were identified in only one of extradural hemorrhage, and axonal injury respectively (table 7). Cross tabulation results of P53 gene with age groups and sex were displayed in table (8). Crosstabs of Na and K with outcome and sex where displayed in table (9, 10).

Table 7 shows p53 variants in types of TBI

Type of TBI	P 53			Total
	Arg/Arg	Arg/Pro	Pro/Pro	
Brain edema	3	0	0	3
Heamorrhge Contusion	11	0	0	11
Ltercerebral heamorrhge	1	0	0	1
Axonal injury	1	0	1	2
Extradural heamatoma	3	1	0	4
Subdural heamatoma	7	1	0	8
Edema+contusion	2	1	1	4
Bullet injury	0	1	0	1
SDH + contusion	2	0	1	3
SAH	0	1	0	1
EDH+ SDH+ HC	0	1	0	1
SAH + edema	1	0	0	1
HC + SAH	4	0	0	4
Total	35	6	3	44

Table 8 shows the cross- tabulation of P53 gene and sex in TBI patient

P 53 gene	Sex		Total
	Male	Female	
Arg/Pro	4	1	5
Arg/Arg	32	4	36
Pro/Pro	3	0	3
Total	39	5	44

Table 9 shows the cross-tabulation of sodium and outcome in TBI patients

Sodium (mmol/L)	Outcome		Total
	Discharge	Death	
<135 mmol/L	1	1	2
135 – 145 mmol/L	38	2	40
>145 mmol/L	4	4	4
Total	43	7	50

Table 10 shows the cross-tabulation of potassium and outcome in TBI patients

Potassium (mmol/L)	Outcome		Total
	Discharge	Death	
<3.5 mmol/L	12	1	13
3.5 – 5.0 mmol/L	31	6	37
Total	43	7	50

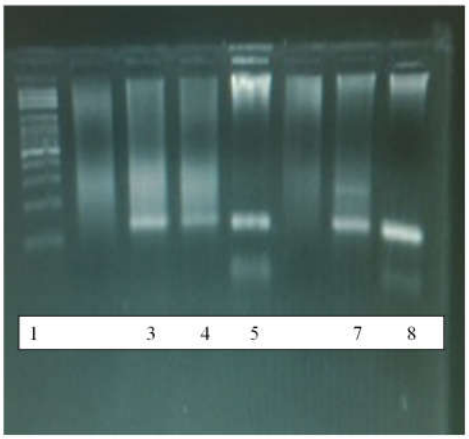

Figure 1 showed the gel electrophoresis of P 53 gene in traumatic brain injury patients

Lane 1 (DNA ladder100 bp), Lane (3, 4, 5, 8- Arg/Arg allele 140 bp) and lane (7 Arg/Pro allele 140/180 pb)

DISCUSSION

The main two types of traumatic brain injury are primary brain damage and secondary brain damage [34- 36]. Outcome from head injury is determined by two stages: the primary insult occurring at the time of impact [35]. The secondary insult (delayed non-mechanical damage) initiated at the moment of injury with delayed clinical presentation. Cerebral ischemia and intracranial hypertension refer to secondary insults and these types of injury are sensitive to therapeutic interventions [35, 36]. Moreover traumatic brain injury (TBI) is a major cause of mortality and disability in Europe and the United States (U.S), as well as in under developing countries, 2.5 million of people in U.S is suffering from bad outcome. Many head injured patients die or survive with severe brain damage, even after mild or moderate head injury [37, 38]. In Sudan the most common causes of TBI were Motor Vehicle Accidents, followed by assaults and falls. The presenting symptoms were mainly loss of consciousness [39]. In this study we aimed to investigate some biochemical profile and molecular screening of p53 gene as simple predictive markers for TBI outcome.

The results of this study showed that among the 51 TBI patients, male were 46 and females were 5 with male to female ratio 9:1.The male predominance in this study did not differ from study done by Arbab in Sudan and international one [39, 40]. The distribution of the ages of the studied cases revealed that 82% of the patients were under the age of 40 years; this finding did not differ from the international incidence of TBI age group in male and females [40]. In this study the most common type of TBI was the acute hemorrghic contusion in 23.5%.

The tumor suppressor gene p53 is up-regulated after DNA damage and can lead to DNA repair, cell growth arrest, or apoptosis [41]. Loss of heterozygosity in p53 tumor suppresser gene had been studied in different types of brain tumors [41], but little is known about p53 gene in TBI.

In the present study p53 gene Arg72pro alleles were investigated for the first time in TBI patients in Sudan. Our findings revealed that the most common allele in the TBI patients is the Arg/arg alleles; Napieralski *et al.* (1999) suggesting that p53 may play a role in the molecular response to TBI leading to cell death [42]. Tomasevic *et al.* (1999) compared the effects of brain injury in p53 knockout mice and their wild type (WT) littermates. At 7 days after injury, p53 (/) mice exhibited attenuated motor function deficits compared with their WT littermates [43]. Furthermore in this study our findings indicated that the Arg/Arg variant was found to be associated with the poor outcome of TBI patients, according to the (GCS) hence the all patients with poor outcome were having Arg/Arg alleles. These results did not differ from study done by Pascual Mart_nez-Lucas and his colleagues [40]. Several studies were investigated the role of p53 gene in CNS injury [41- 44]. Another studies showed that, the damage mediated by excitotoxicity, has been associated with increased production of reactive oxygen species [44- 47]. Other studies shown that one of the most significant factors causing secondary brain injury is the excessive release of excitotoxins such as glutamate and aspartate that occurs at the time of the primary brain injury. These excitotoxins act on the N-methyl-D-aspartate channel, altering cell wall permeability with an increase in intracellular calcium and sodium and activation of calcineurin and calmodulin. This ultimately, leads to destruction of the axon [8, 9]. Potassium is also released from the cells and absorbed by the astrocytes, in an attempt to restrict the ionic imbalance causing swelling of the cells and ultimately cell death [10]. The P53 gene is important in the regulation of apoptosis; this gene exhibits a common polymorphism that results in either proline or arginine at amino acid 72. Arg/Arg genotype of the Arg72Pro polymorphism in p53 is associated with an increased likelihood of a poor outcome at discharge from the surgical intensive care unit following TBI [48]. The results of Martinez were matched with our findings in this study. Moreover p53 gene has been investigated in different types of cancer, however different studies in Sudan that investigated P53 Codon 72 Polymorphism and cancer in Sudan, showed significant differences in frequency and genotype association between different types of cancer. Breast and cervical carcinoma showed excess of homozygous Arg genotype as compared to controls, while in Burkit lymphoma and oral cancer the most dominant genotype was Arg/pro [48- 51]. Recently Gassoum *et al* was investigated p53 gene in meningioma among sudanese patients, their findings showed excess of homozygote Arg allele [33].

In traumatic brain injury, correction of hyponatremia are clinically significant in neurology, hyponatremia may lead to neurological symptoms [52, 53]. Small Changes in K ions can severely affect nerve conduction, heart rhythm and muscle contraction [54].

In the present study measurement of sodium and potassium revealed that, sodium level < 135mmol/l was 3.9% and >145

mmol/l was 15.7% of TBI patients, potassium showed <3.5 was 25.5% of TBI patients. Study from India showed that, Seventeen of 50 patients of TBI Group had Na levels of 135mmol/L or lower, and hypernatremia (Na^+ level more than 145 mmol/L) 7/50 in TBI group, and moderate hypokalemia (K^+ levels below 3.6 mmol/L) was present in 10/50 patients in TBI group [(54)]. Another study showed, K^+ levels were lower in TBI patients [(55)]. The findings of the above mentioned two studies were not differing from our electrolyte results. Xing Wu reported that, the serum potassium level in TBI patients was 3.2 mmol/L, 2.8 mmol/L and 1.9 mmol/L in (mild, moderate and severe TBI patients). Serum sodium level in severe hypokalaemia patients was 162 mmol/L, which was significantly higher than that of the mild hypokalaemia group mmol/L] and moderate hypokalaemia group mmol/L] ($p < 0.001$) [(55)].

CONCLUSION

From the present, the most common allele of p53 gene was the Arg/arg allele. The poor outcome of TBI was associated with the Arg/arg allele. Sodium imbalance was associated with poor outcome of TBI.

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