International Journal of Science Academic Research
Vol. 04, Issue 03, pp.5320-5324, March, 2023
Available online at http://www.scienceijsar.com

ISSN: 2582-6425

Research Article

ASSOCIATION BETWEEN C-REACTIVE PROTEIN LEVEL AND MORTALITY AMONG TRAUMATIC CEREBRAL HEMORRHAGIC CONTUSION SUDANESE PATIENTS, KHARTOUM, SUDAN

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Received 24th January 2023; **Accepted** 20th February 2023; **Published online** 30th March 2023

Abstract

C-reactive protein (CRP) has previously found to be a predictive biological inflammatory biomarker of secondary pathologies associated with Traumatic brain injury (TBI). The aim is to determine an association between CRP level with the mortality of traumatic cerebral hemorrhagic contusion patients. A case-control study was conducted on ninety Sudanese patients presented with traumatic cerebral hemorrhagic contusion at the National Center for Neurological Sciences (NCNS) Khartoum-Sudan. Non-Sudanese patients, and hemorrhagic contusion associated with other types of brain bleeding were excluded. Moreover, 90 individuals were selected as controls. The results showed that 95.6% of the patients presented with abnormal CRP level > 6 mg/L (P. value = 0.000). Patients with TBI are at a risk of 70.6 times of having high CRP compared to a healthy control. Almost 90 % of patients admitted with severe injury (GCS <8) had CRP level > 60 mg/L and 58.3% of the patients with multiple contusions showed CRP level > 60 mg/L compared to 35.5% of patient with a single cerebral contusion. Presence of brain edema was not associated with high levels of CRP. Fifty-nine percent of patients admitted 2 days after trauma have significantly (P. Value <0.05) high CRP levels (> 60 mg/L) compared to 40.0% and 25.6% admitted 1 and 3 days respectively. The number of deaths were 8 (8.9%). Almost 87.5% of them (n=7) had CRP > 60 mg/L. CRP can be considered as an important inflammatory biomarker predictor for morbidity and mortality among traumatic cerebral hemorrhagic contusion.

Keywords: Cerebral contusion, Traumatic brain injury, C-reactive protein, Biological biomarker, Mortality.

INTRODUCTION

Inflammation is an important part of the patho-physiology of brain trauma. Although the central nervous system (CNS) differs from the other organs because of the complete isolation from the blood stream mediated by the blood–brain barrier (BBB), the main steps characterizing the immune activation within the brain follows a scenario similar to that in other organs (Morganti-Kossmann, 2002). The key players in these processes are the numerous immune mediators released within minutes of the primary injury. They guide a sequence of events including expression of adhesion molecules, cellular infiltration, and additional secretion of inflammatory molecules and growth factors, resulting in either regeneration or cell death (Morganti-Kossmann, 2002). Recent evidence supported the dual, the beneficial, or the deleterious role of neuro-inflammation after brain trauma (Morganti-Kossmann, 2002). Trauma initiates local CNS as well as systemic immune activation. Numerous observational studies describe elevation of inflammatory markers that are associated with important clinical variables including neurologic outcome and mortality (Hinson, *et al.,* 2015). CRP which is an acute phase protein belongs to an ancient family of proteins called the pentraxins. It is produced by the liver and suggested to be produced by vascular smooth muscle cells and macrophages (Yasojima *et al.,* 1999). CRP level increase dramatically in a wide range of infections and immune related disorders and has been shown to be associated with TBI Pathogenesis and prognosis (Naghibi, 2017).

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Acute brain trauma is accompanied by acute and immediate inflammatory response so called acute phase response. During this phase hepatic synthesis of acute of several plasma proteins (acute phase proteins) such as CRP increases significantly. This inflammation is due to reaction to the tissue damage (Cederberg *et al.,* 2010). Recently CRP has been considered not only as a biochemical marker of inflammation, but also as a predictor of prognosis and outcome in TBI (Lee *et al.,* 2005). The relation of CRP levels to TBI was not well known. However; high concentration of CRP was reported to be associated with a poor outcome and an increased risk of death after ischemic stroke and aneurysmal subarachnoid hemorrhage. It binds with receptors expressed on the surface of dead or dying cells in order to activate the complement system. It also has a role in complex modulatory functions. It may directly participate in enhancing inflammation in cerebral vessels and brain injury through activation of complement cascade, initiation of leukocyte chemotaxis and expression of adhesion molecules through a positive feedback mechanism. It induces apoptosis through a caspase-dependent mechanism (Black *et al.,* 2004). The aim is to determine an association between CRP level with the morbidity mortality of traumatic cerebral hemorrhagic contusion patients.

MATERIALS AND METHODS

Study setting

This is a case-control study conducted at the National Center for Neurological Sciences (NCNS). Non-Sudanese patients, and hemorrhagic contusion associated with other type of brain bleeding were excluded. Demographic, clinical and laboratory data were collected from Nighty patients' records (cases) using

a questionnaire. Controls were selected from the community around the NCNC

Laboratory assay

Blood samples were collected from all participants in plain containers for CRP measurement. Serum was separated by centrifugation 2000 rpm for 5 minutes and then stored at -4 C until tested for CRP level. CRP level was measured in serum by Nyco-Carde Reder 2 system using Sandwich-form immunometric assay. Diluted sample was applied to membrane coated with immobilized CRP-specific monoclonal antibodies. When the sample flows through the membrane, the C-reactive proteins are captured by antibodies. CRP trapped on the membrane was bind the gold-antibody conjugate added, in a sandwich-type reaction. Unbound conjugate was removed from membrane by washing solution. A paper layer underneath the membrane absorbs excess liquid. In the presence of a pathological level of CRP in the sample, the membrane appears red-brown with color intensity proportional to the CRP concentration of the sample. The color intensity is measured quantitatively with the Nyco-Card Reader 2 device. Analytical specificity was tested using monoclonal antibodies specific to human CRP, no other human blood components are found to cross react with CRP in Nyco-Card CRP single test system.

Statistical analysis

Data analysis was carried out using Statistical Package for Social Sciences (SPSS) version 19. The descriptive statistic was used for demographic data. Chi-square test was used to assess the association between CRP with clinical and demographic data. Odd ratio was calculated to estimate the association between exposure and the outcome.

Ethical approval

The ethical approval was obtained from Ethical Review Board of NCNS.

RESULTS

A total of 90 patients were admitted the emergency department at the NCNS and diagnosed with traumatic brain hemorrhagic contusion. Moreover, 90 apparently healthy individuals were selected as control. Males constituted 93.3%, their ages ranged from 25 to 44 years, and 67.8 % of the patients were affiliated to Afro-asiatic tribes. Nearly 47.8% of the patients were admitted to hospital 3 days after trauma. The initial results of CT brain scan showed that 60% of the patients presented with frontal lobe injury. However, 14.4% of the patients had multiple injured sites. Brain edema was observed among 22.2 % of the patients (Figure 1). The Glasgow Coma Scale (GCS) was used to assess the initial conscious level, and accordingly, 11.1 % of the patients had severe brain injury, 30.0% had moderate injury, and 58.9 % had mild injury. The percentage of mortality among patients was 8.9%. The results of CRP showed that a significant increase in CRP in cases compared to controls (P. value = 0.000) (Figure 2). The Odd Ratio (OR) was calculated among patients and controls and found that patients who have TBI are 70.6 times more susceptible to have high CRP compared to controls (Odds =70.6) with a 95% confidence interval. In 50% of the patients in the age group between 45- 65, the CRP level was found to be 60mg/L. There was no significant association between genders or linguistic affiliation with CRP levels (Table 1). Moreover, 90 % of patients admitted with severe injury had CRP level > 60 mg/L. Although no statistically significant difference was found between high CRP levels and multiple contusions; 58.3% of the patients with multiple contusion showed CRP level > 60 mg/L. Presence of brain edema was not associated with high levels of CRP. Almost 59% of Patients admitted 2 days after trauma have significantly high CRP levels (> 60mg/L) (P. value <0.05) compared to 40.0% and 25.6% admitted 1 and 3 days respectively. The number of deaths were 8 (8.9%). Although there was no significant association between high CRP levels and mortality 87.5% of the deaths (n=7) had CRP > 60 mg/L (Table 2).

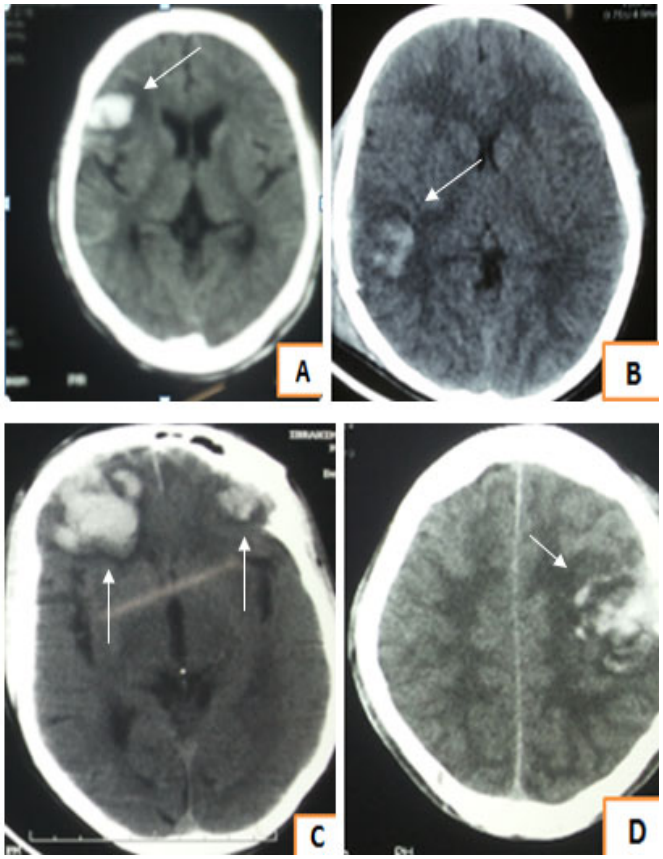
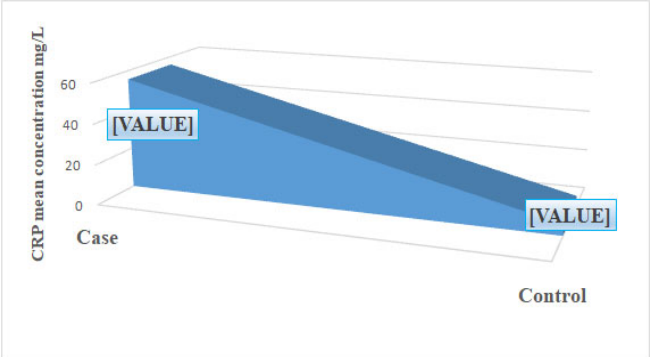


Figure 1. A: Patient with right frontal cerebral hemorrhagic contusion. B: Patient with right temporal hemorrhagic cerebral contusion and brain edema. C: Patient with multiple cerebral hemorrhagic contusion bilateral frontal. D: patient wit left parietal cerebral hemorrhagic contusion.



Significant elevation (P. value = 0.000) of CRP mg/L mean concentration among case compared to control; std deviation (42.45 and 0.78 respectively). Odd ratio 70.6 with 95% confidence interval.

Figure 2. CRP Circulatory Level In mg/L Among Cases and Controls

Table 1. The effect of demographic of the patients on CRP circulatory levels

Variables	CRP mg/L					Total n=90	value
	Less than 6	6-20	21-40	41-60	More than 60		
Age group years							
5-14	3 (15.8%)	5(26.3%)	3 (15.8%)	3 (15.8%)	5 (26.3%)	19 (21.1 %)	0.194
15-24	1(4.3%)	8(34.8%)	5(21.7%)	3 (13.0%)	6(26.1%)	23 (25.6 %)	
25-44	0(0.0%)	7(24.1%)	6(20.7%)	2 (6.9%)	14(48.3%)	29 (32.2%)	
45-65	0(0.0%)	2(14.3%)	2(14.3%)	3 (21.4%)	1(20.0%)	14 (15.6%)	
>65	0 (0.0%)	1(20.0%)	1(20.0%)	1(20.0%)	2 (40.0%)	5 (5.6%)	
Gender							
Male	3(3.6%)	22 (26.2%)	16 (19.0%)	9 (10.7%)	34 (40.5%)	84 (93.3%)	1.000
Female	1(16.7%)	1(16.7%)	1 (16.7%)	3 (50.0%)	0(0.0%)	16 (6.7%)	
Linguistic affiliation							
Afro-asiatic	1 (1.6%)	14 (23.0%)	11 (18.0%)	9 (14.8%)	26 (42.6%)	61(67.8%)	0.100
Niger-Congo	2 (25.0%)	1 (12.5%)	2 (25.0%)	0 (0.0%)	3(37.5%)	8 (8.9%)	
Nilo-Saharan	1 (4.8%)	8 (38.1%)	4 (19.0%)	3 (14.3%)	5 (23.8%)	21 (23.3%)	

Table 2. The effect of Clinical data on CRP mg/L circulatory levels

Variables	CRP mg/L					Total n=90	P. value
	Less than 6	6-20	21-40	41-60	More than 60		
GCS Score							
Mild injury (13-15)	3 (5.7%)	17 (32.1%)	11 (20.8%)	7 (13.2%)	15 (28.3%)	53 (58.9%)	0.089
Moderate injury (8-12)	1 (3.7%)	6 (22.2%)	5 (18.5%)	5 (18.5%)	10 (37.0%)	27 (30.0 %)	
Sever injury (<8)	0 (0.0%)	0 (0.0%)	1 (10.0%)	0 (0.0%)	9 (90.0%)	10 (11.1%)	
Brain edema							
Yes	1 (5.0%)	2 (10.0%)	3 (15.0%)	4 (20.0%)	10 (50.0%)	20 (22.2 %)	0.248
No	3 (4.3%)	21 (30.0%)	14 (20.0%)	8 (11.4%)	24 (34.3%)	70 (77.8 %)	
Time after trauma							
1 day	1 (4.0%)	3 (12.0%)	7 (28.0%)	4 (16.0%)	10 (40.0%)	25 (27.8%)	0.026
2 days	1 (4.5%)	2 (9.1%)	2 (9.1%)	4 (18.2%)	13(59.1%)	22 (24.4%)	
3 days	2 (4.7%)	18(41.9%)	8 (18.6%)	4 (9.3%)	11(25.6%)	43 (47.8%)	
Radiological variables							
Anatomical site of trauma							
Frontal lobe	3 (5.6%)	15 (27.8%)	11 (20.4%)	9 (16.7%)	16 (29.6%)	54 (60%)	0.832
Temporal lobe	0	2 (28.6%)	2 (28.6%)	0 (0.0%)	3 (42.6%)	7 (7.8 %)	
Parietal lobe	0	4 (30.8%)	3 (23.1%)	1 (7.7%)	5 (38.5%)	13 (14.4 %)	
Bifrontal lobe	0	1 (33.3%)	0 (0.0%)	0 (0.0%)	2 (66.7%)	3 (3.3 %)	
Others	1 (7.7%)	1 (7.7%)	1 (7.7%)	2 (15.4%)	8 (61.5%)	13 (14.4%)	
Number of injured sites							
Single site	3 (3.9%)	21 (27.6%)	16 (21.1%)	9 (11.8%)	27 (35.5%)	77 (85.6%)	0.481
Multiple sites	1 (8.3%)	2 (16.7%)	1 (8.3%)	1 (8.3%)	7 (58.3%)	13 (14.4%)	
Mortality							
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	7 (87.5%)	8 (8.9 %)	0.48
Alive	4 (4.9%)	23 (28.0%)	17 (20.7%)	11 (13.4%)	27 (32.9%)	82 (91.1%)	

GCS Glasgow coma scale

DISCUSSION

CRP has previously been found to be a predictive biomarker of secondary pathologies associated with TBI (Hergenroeder *et al.,* 2008). Our finding demonstrated that 95.6% of traumatic cerebral contusion patients presented with significant elevation of circulatory CRP level compared to normal healthy controls. Similar findings were reported previously by Sharma and his colleagues (Sharma *et al.,* 2017). Serum CRP level in adults marginally increases with age (Sesso *et al.,* 2007). Whereas, our study showed non-significant association between CRP circulatory levels and age of the patients, but the highest concentration of CRP level was found within 50% of the patients within the age group 45-65 years. Lee *et al* (2005). Demonstrated that serum levels of CRP are not significantly different in relation to the age of the head injured patients. Similarly, CRP level after trauma was not significantly different between males and females (Naghibi, 2017). In contrast, Maehira.*et al* (2002) indicated that CRP serum levels were related to gender in healthy subjects, and were higher in women than in men (Sesso *et al.,* 2007). With regards to ethnic differences in circulating CRP levels, Forourhi.*et al* (2001) demonstrated that South Asian women had nearly double the level of CRP when compared to European women (Forouhi *et al.,* 2001).

In the present study, the highest CRP level (>60 mg/L) was observed among Afro-asiatic linguistic affiliated patients. The reason for these discrepancies is unclear but may reflect the number and different selection method of the individuals in the studies and the level of adjustment for confounding factors. It is of interest to note that a significant difference in levels between Pakistani European and African Caribbean individuals were also demonstrated (Heald *et al.,* 2003). They indicated that ethnicity was not independently associated with CRP. The level of CRP was significantly lower in African-Caribbean individuals compared with whites (Heald *et al.,* 2003). Patel.*et al* (2006) observed that sex but not ethnicity was retained as an independent correlate of CRP. However, Albert *et al* (2004) demonstrated that even though multiple adjustments attenuated the difference between blacks and whites, it was still significant following adjustment for age, body mass index (BMI), history of hypertension, smoking status, alcohol use, exercise, history of myocardial infarction, estrogen use, education and low-density lipoproteins (LDL) (Albert *et al.,* 2004). Likewise, a multiple analysis adjusting for traditional risk factors, BMI, estrogen and statin use found that both gender and ethnicity were independently associated with CRP (Kalra *et al.,* 2005). Genetic factors were reported to be associated with ethnic differences in CRP levels, blood pressure, serum lipids levels, plasma glucose and insulin

sensitivity (Russell *et al.,* 2003; Piche *et al.,* 2005). CRP levels are related to estrogens but are only in whites and not Native Americans (LaMonte *et al.,* 2002). Both oral contraceptives and hormone replacement therapy influence CRP levels (Ridker *et al.,* 1999). Elevated CRP levels were reported during systemic inflammatory response syndrome, especially following trauma, and its production is related to the severity of organ dysfunction (Castelli *et al.,* 2004). A strong correlation between serum CRP level and severity of brain injury among TBI patients was also reported (Sharma *et al.,* 2017). CRP level was significantly correlated with severe trauma among TBI female patients. This relationship was not observed in women with mild trauma (Naghibi, 2017). Thus, it can be speculated that female sex hormones might have variable influences on the different levels of injury-induced inflammation (Naghibi, 2017). Our finding revealed that 90% of patients presented with severe injury had CRP level more than 60 mg/L. Elevated CRP level was reported previously as a marker for CT scan-evidence of brain edema among stroke and intracerebral hemorrhage patients (ICH) patients (Modreg *et al.,* 2008). In the present study, 58.3% of the patients with multiple contusions showed CRP level > 60 mg/L compared to 35.5% patients with a single cerebral contusion. However, Lee *etal*. (2005) stated that CRP can be used as a predictive marker in cases of diffuse brain injury where imaging studies are usually less optimal to reveal the severity of TBI. The peak of CRP is 48h after trauma, and persistently increased for approximately 5-7or even days19 (Sesso *et al.,* 2007). Our finding demonstrated a significant correlation between CRP level and time after trauma where 59.1% of the patients admitted 2 days after trauma presented with CRP level > 60 mg/L. Inflammatory processes and the immune response may vary throughout the 24 hours circadian period, environmental factors, may influence CRP levels as well as other inflammatory mediators, men and women, seasonal and diurnal variation in CRP (Rudnicka *et al.,* 2007). Elevated plasma level of CRP was associated with a worse outcome of acute ischemic cardio- and cerebrovascular disease (Brown *et al.,* 2002;Ridker *et al.,* 2002). Similarly, Belavic.*et al* (2015) reported a positive association between CRP and mortality. In contrast, other studies reported a negative association between elevated CRP levels and mortality (Naghibi 2017;Lee *et al.,* 2005). The present study has shown that 87.5% of the deaths presented with CRP >60 mg/L. Research on cardiovascular patients showed that elevated CRP was more associated with mortality hazards in men, but not in women (Doran *et al.,* 2013). Thus, the result of human and experimental studies describing the role of CRP in post-trauma functional outcome and mortality are conflicting. Possible reasons for the differences may be due to differences between populations, different times for CRP measurement and methods for CRP level measurement. While other confounding factors should be considered also.

Conclusion

In traumatic cerebral contusions, an increase in levels of CRP can be considered as an important inflammatory biomarker predictor where 90% of patients presented with severe injury had CRP more than 60mg/L. Patients with TBI are more than 70 times susceptible to have high CRP levels than the controls.

Conflict of interest: Non declared.

Acknowledgment: The authors acknowledge the staff of National Center for Neurological Science for their support.

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