ORIGINAL ARTICLE

Is IL-8 level an indicator of clinical and radiological status of traumatic brain injury?

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ABSTRACT

BACKGROUND: Since understanding the fact that traumatic brain injury includes an inflammatory process, the number of studies of cytokines has increased. The objective of this study was to analyze and discuss the association of interleukin (IL)-8 level with the clinical and radiological status of patients with head trauma.

METHODS: Patients who were admitted to our hospital due to head trauma were included in the study. Findings of clinical and laboratory examinations were analyzed. Data regarding patient age, gender, available clinical findings, Glasgow Coma Scale (GCS) score, trauma cause, brain tomography findings, and biochemical laboratory test results were recorded. The patients were divided into 3 groups according to their GCS score: Group I: GCS ≥13, Group II: GCS = 9–12, and Group III: GCS = 3–8.

RESULTS: A total of 23 (76.7%) patients were male and 7 (23.3%) were female. Overall, 17 (56.7%) patients were admitted due to a fall, 8 (26.7%) due to a traffic accident, and 5 (16.7%) due to assault. Each group comprised 10 patients. As the GCS score increased, the IL-8 level decreased. The mean IL-8 level was 1.2 pg/mL in Group I, 6.6 pg/mL in Group II, and 4.7 pg/mL in Group III; however, there was no statistically significant difference between the groups (p=0.147). Moreover, the IL-8 level was significantly greater in patients who demonstrated an abnormal tomography finding (p=0.023).

CONCLUSION: IL-8 may be a beneficial indicator for monitoring the clinical and radiological status of traumatic brain injury. Nonetheless, studies of larger cohorts in which IL-8 levels are measured at all stages of brain injury and follow-up of long-term prognosis are warranted.

Keywords: Glasgow Coma Scale; interleukin; traumatic brain injury.

INTRODUCTION

Traumatic brain injury (TBI) is a mechanical injury caused by externally induced trauma and may cause temporary or permanent neurological effects. Moreover, TBI is a clinical state with important public health outcomes and often causes lifelong physical, cognitive, and psychosocial function disorders.[1] In Turkey, traffic accidents and falling are the most common etiologies of head trauma. Head trauma is classified into mild, moderate, and severe trauma according to its severity, as assessed by the Glasgow Coma Scale (GCS). GCS score is calculated on the basis of clinical findings of patients.[2]

Brain injury is characterized into 2 stages following trauma. Primary damage is induced by the mechanical forces that rapidly affect the skull and brain, whereas secondary damage occurs as a result of effects of ischemia, hypoxemia, and increased intracranial pressure. Secondary damage progressively emerges minutes or hours after primary damage, and the observed brain damage worsens with oxidative stress and inflammation. Reportedly, inflammation and cerebral inflammatory response related to TBI are mediated within minutes of trauma.[3–5]

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Experimental and clinical studies have demonstrated that neuroinflammation following TBI may exert damaging or benefiting effects during the acute and delayed phases. Future anti-inflammatory neuroprotective treatments should aim at decreasing neurotoxic, disruptive effects while conferring beneficial, neurotropic effects of inflammation to ensure regeneration and repair following damage.[6,7]

Previous studies have demonstrated that the excreted interleukins (IL) determined the clinical course of brain damage. IL-10 produced by macrophages and microglia showed anti-inflammatory and immunosuppressant effect, whereas IL-8 excreted by monocytes and endothelial cells induced both regeneration and degeneration.[8,9]

In the present study, we aimed to examine the association of GCS scores of patients with TBI due to various mechanical traumas with laboratory and brain tomography findings and serum IL-8 levels. Moreover, we discussed the potential of IL-8 as an inflammatory indicator of clinical and radiological status of brain damage.

MATERIALS AND METHODS

Clinical and laboratory examination data of patients who were admitted to our hospital, due to head trauma were retrospectively analyzed. This study was approved by the Ethics Committee of Clinical Research (Ref no:2018/160). Patient data regarding age; gender; available clinical findings; GCS score calculated based on clinical findings at the time of admittance; trauma cause; computed brain tomography (CBT) findings; presence of additional trauma findings; biochemical laboratory test results (leukocytes, Hb, pO2, ALT, AST, LDH, ALP, CRP, sedimentation, and IL-8); and administered treat-

Table 1. Laboratory data of patients groups according to GCS scores

	Group I (GCS ≥13)	Group II (GCS 9–12)	Group III (GCS 3–8)	p
	Median (IQR)	Median (IQR)	Median (IQR)	
IL–8 (pg/mL)	1.2 (0.4–6.8)	6.6 (4.6–10.6)	4.7 (1.1–10.9)	0.147
Hb (g/dL)	14.9 (13.8–15.8)	12.4 (12.2–13.4)	14.1 (12.0–14.8)	0.051
WBC (K/mm³)	8750 (6800–11400)	20650 (15125–28000)	19200 (14800–25600)	0.0002
Glucose (mg/dl)	133.0 (111.2–158.5)	166.0 (126.5–208.2)	166.5 (143.0–369.7)	0.128
AST (U/L)	27.5 (21.7–34.0)	40.0 (30.0–124.2)	41.5 (27.0–120.0)	0.077
ALT (U/L)	21.0 (14.0–36.2)	24.5 (14.7–58.0)	28.5 (17.0–68.5)	0.551
ALP (U/L)	101.5 (78.7–175.5)	106.0 (79.5–304.2)	153.5 (108.5–300.0)	0.191
LDH (U/L)	322.5 (309.7–457.5)	699.5 (356.7–1446.0)	646.5 (560.0–842.0)	0.004
pO2 (mmHg)	75.7 (69.4–77.7)	83.5 (65.6–97.9)	70.9 (51.7–89.1)	0.426

IL: Interleukin; GCS: Glasgow Coma Scale; IQR: Interquartile range; WBC: White blood cells; Hb: Hemoglobin AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; LDH: Lactate dehydrogenase.

Table 2. Laboratory data of patient groups according to trauma type

	Falling down	Traffic accident	Assault	p
	Median (IQR)	Median (IQR)	Median (IQR)	
IL–8 (pg/mL)	5.4 (1.2–7.4)	5.5 (0.9–10.9)	1.2 (0.8–9.7)	0.657
Hb (g/dL)	14.0 (12.9–15.6)	12.3 (12.0–13.5)	14.7 (12.8–15.2)	0.238
WBC (K/mm³)	15300 (8750–22950)	18800 (12675–27400)	13100 (10250–17100)	0.143
Glucose (mg/dl)	150.0 (129.0–241.0)	166.5 (123.0–307.7)	149.0 (109.5–173.0)	0.271
AST (U/L)	32.0 (23.0–106.0)	40.0 (29.5–123.7)	31.0 (26.5–31.5)	0.105
ALT (U/L)	20.0 (14.5–56.0)	29.0 (19.5–62.5)	26.0 (19.0–38.5)	0.714
ALP (U/L)	131.0 (86.0–258.5)	106.0 (100.0–225.7)	102.0 (69.0–263.0)	0.883
LDH (U/L)	648.0 (322.5–766.5)	606.5 (370.7–767.2)	416.0 (321.0–1052.5)	0.380
pO2 (mmHg)	76.7 (68.3–85.9)	73.0 (55.9–85.6)	78.2 (60.8–97.9)	0.464

IL: Interleukin; IQR: Interquartile range; WBC: White blood cells; Hb: Hemoglobin; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; LDH: Lactate dehydrogenase.

ment were recorded. The patients were divided into 3 groups according to their GCS scores: Group I: GCS ≥ 13; Group II: GCS = 9–12; and Group III: GCS = 3–8. The association of GCS score with hematological and radiological laboratory data was analyzed.

Statistical Analysis

SPSS-20.0 statistics program was used. Since the subgroup sample numbers were low in descriptive statistics, median and interquartile values were used. In groups with more than 4 samples, 25th and 75th percentile values were presented, whereas in groups with less than 4 samples, only 25th percentile value was presented. Non-parametric Kruskal–Wallis H test was used for the comparison of continuous variables, and Fisher's exact test was used for the comparison of categorical variables. A $p<0.05$ was considered statistically significant.

RESULTS

A total of 30 patients were included in the study [23 (76.7%) males and 7 (23.3%) female]. Overall, 10 patients showed GCS scores of ≥13 (Group I), 10 showed GCS scores between 9 and 12 (Group II), and 10 showed GCS scores between 3 and 8 (Group III). Moreover, 17 (56.7%) patients were admitted to the emergency services due to falling, 8 (26.7%) due to traffic accidents, and 5 (16.7%) due to assault. Median values of Hb, WBC, glucose, AST, ALT, ALP, LDH, pO2, and IL-8 in the 3 groups according to GCS scores are presented in Table 1. WBC and LDH values were significantly low in Group I than in groups II and III. Furthermore, IL-8 levels increased as GCS decreased, although this change was not statistically significant.

Median values of Hb, WBC, glucose, AST, ALT, ALP, LDH, pO2, and IL-8 according to types of trauma (falling, traffic accident, or assault) are presented in Table 2. There was no statistically significant difference between trauma type and the laboratory finding.

CBT requested based on clinical findings following trauma revealed pathological findings in 21 (70%) patients but not in 9 (30%) patients. Median IL-8 levels and presence of abnormal CBT findings showed a significant association: IL-8 levels were significantly higher in patients with abnormal CBT findings. However, there was no statistically significant difference among CBT findings (traumatic subarachnoid bleeding, linear fracture, edema, contusion, chronic infarct, pneumocephalus, subdural hematoma, epidural hematoma, depression fracture, or intraparenchymal hematoma) (Table 3).

Table 3. Association between of computed brain tomography findings and IL-8 levels

	IL–8* (pg/mL) Median (IQR)	p
computed brain tomography		
Normal (n=9)	1.2 (0.4–4.5)	0.023
Abnormal (n=21)	6.6 (2.4–11.2)	
Traumatic subarachnoid bleeding		
Yes (n=3)	12.8 (4.5–)	0.088
None (n=27)	4.9 (1.2–6.6)	
Linear fracture		
Yes (n=3)	6.6 (6.6–)	0.223
None (n=27)	4.5 (1.2–7.4)	
Edema		
Yes (n=6)	5.6 (1.9–8.0)	0.834
None (n=24)	5.1 (1.2–7.2)	
Contusion		
Yes (n=2)	15.3 (6.6–)	0.167
None (n=28)	4.7 (1.2–7.2)	
Chronic infarct		
Yes (n=1)	5.4	0.954
None (n=29)	4.9 (1.2–7.4)	
Pneumocephalus		
Yes (n=1)	6.6	0.641
None (n=29)	4.9 (1.2–7.4)	
Subdural hematoma		
Yes (n=7)	2.5 (0.8–33.8)	0.805
None (n=23)	6.6 (1.2–7.4)	
Epidural hematoma		
Yes (n=2)	20.2 (6.6–)	0.143
None (n=28)	4.7 (1.2–7.2)	
Depression fracture		
Yes (n=1)	6.6	0.641
None (n=29)	4.9 (1.2–7.4)	
Intraparenchymal hematoma		
Yes (n=2)	9.5 (6.6–)	0.224
None (n=28)	4.7 (1.2–7.2)	

*Interquartile Range values are shown besides median values. The 75th percentile of the IQR was left blank when the number of patients was 3 or less. When a subgroup consisted of one patient only median value was given.
IL: Interleukin; IQR: Interquartile range.

DISCUSSION

Post-traumatic inflammatory response forms a link in the chain of events causing secondary tissue damage, which continue following physical damage occurring immediately after head trauma. Endothelial damage, which emerges with the infiltration of neutrophils into the tissue, cellular adhesion, excretion of molecules, production of inflammatory mediators, and disruption of superficial anticoagulant mechanisms, triggers the neuroinflammatory cascade. Cytokines determine the inflammatory response developing after trauma.[10,11] Increasing number of studies have discussed and demonstrated the association between clinical status and neuroin-

flammation in TBI by measuring levels of various indicators in plasma and cerebrospinal fluid (CSF).[12–15]

IL-8 is a member of the CXC chemokine receptor family, and CXCL8 is secreted by glial cells, macrophages, and endothelium cells. IL-8 is an important mediator of chemotaxis and neutrophil activation during acute inflammation.[16] Moreover, IL-8 is excreted from astrocytes during brain damage.[13] Yousefzadeh-Chabok et al.[14] analyzed IL-6, IL-8, and IL-10 levels in serum samples collected within the first 6 hours of trauma from 44 TBI patients with GCS scores of ≤8 and compared these values with GCS scores measured after 6 months of trauma; they have shown that increase in serum IL-6 and IL-8 levels was associated with brain damage observed in the late phase and have proposed that these 2 cytokines are indicators of poor prognosis in TBI. In a study by Gopcevic et al.,[15] IL-8 levels, as an indicator of cranial inflammation, were measured in samples collected from the jugular catheter and CSF of 20 patients with severe isolated head trauma, of which 10 died. They emphasized that IL-8 levels were lower in survivors and that IL-8 levels were significantly correlated with GCS score, age, and Acute Physiology and Chronic Health Evaluation score, which defines disease severity based on changes in physiological parameters; moreover, IL-8 levels in the central venous blood may be a more important indicator of early damage.

Our study contributes to the literature discussing the importance of inflammatory indicators in TBI by analyzing the association of IL-8 levels with GCS score and CBT findings. We observed that as GCS score decreased, IL-8 levels increased, although this increase was not statistically significant. Moreover, IL-8 levels varied with type of mechanical trauma causing brain damage. To the best of knowledge, we demonstrated for the first time that IL-8 levels were significantly increased in patients who exhibited abnormal tomography findings. However, there was no association between IL-8 levels and different tomography findings, which may be attributed to the low number of patients included in our study.

In our study, although the association between serum IL-8 levels and GCS score did not reach a level of statistical significance, it tended to be negative. In our literature review, we yielded no studies comparing CBT results as radiological findings and serum IL-8 levels as clinical findings in patients with TBI. Significant increase in IL-8 levels in patients with pathological findings on CBT indicates that IL-8 level increased with the severity of TBI.

Our study has some limitations. This is a retrospective and single-center study, which results in a certain weakness of methodology and limited ability to generalize the result to other centers or circumstances, and the number of patients was low. Moreover, long-term prognosis of was not monitored, and changes in the IL-8 levels were not compared between TBI and other clinical conditions inducing non-traumatic brain injury.

In conclusion, although serum IL-8 level may be a beneficial inflammatory indicator of clinical and radiological status of patients with TBI, further studies are warranted that include a larger cohort in which intermittent IL-8 measurements are performed at all stages of TBI and long-term prognosis is followed up.

Conflict of interest: None declared.

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ORİJİNAL ÇALIŞMA - *ÖZET*

IL-8 seviyesi travmatik beyin hasarının klinik ve radyolojik durumunda bir gösterge midir?

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AMAÇ: Travmatik beyin hasarının enflamatuvar bir süreci de içerdiği anlaşılması üzerine içerisinde sitokinlerin yer aldığı çalışmalar artmıştır. Bu çalışmada amaç kafa travması geçiren hastalarda interlökin (IL)-8 düzeyinin klinik durum ve radyolojik bulgularla ilişkisinin araştırılması ve tartışılmasıdır.
GEREÇ VE YÖNTEM: Hastane verilerinden kafa travması nedeniyle başvurmuş hastaların klinik bulguları ve yapılmış olan laboratuvar sonuçları incelendi. Hastaların yaşı, cinsiyeti, mevcut klinik bulguları, Glaskow Koma Skoru (GKS), travma nedeni, beyin tomografi sonuçları, biyokimyasal laboratuvar incelemeleri ile ilgili tüm verileri kaydedildi. Hastalar GKS'ye göre üç gruba ayrıldı; Grup I: GKS ≥13; Grup II: GKS = 9–12; Grup III: GKS = 3–8.
BULGULAR: Çalışmada yer alan hastaların 23'ü (%76.7) erkek, 7'si (23.3) kadındı. Hastaların 17'si (%56.7) düşme, 8'i (%26.7) trafik kazası ve 5'i (%16.7) darp nedeniyle başvurmuş idi. Üç grupta 10'ar hasta yer almaktaydı. GKS arttıkça IL-8 değerlerinin daha düşük olduğu gözlendi. Gruplar için ortalama IL-8 düzeyleri Grup I = 1.2 pg/mL, Grup II = 6.6 pg/mL ve Grup III = 4.7 pg/mL olarak tespit edildi, ancak istatistiksel olarak anlamlı fark saptanmadı (p=0.147). IL-8 değerlerinin tomografi bulguları anormal olan hastalarda anlamlı olarak yükseldiği gözlendi (p=0.023).
TARTIŞMA: Travmatik beyin hasarında ortaya çıkan klinik ve radyolojik durumunu izlemekte IL-8'in yararlı bir belirteç olabileceği düşünülmekle birlikte, beyin hasarının tüm aşamalarında IL-8 ölçümlerinin değerlendirildiği ve uzun dönem prognoz takiplerinin kaydedildiği, daha geniş hasta serileriyle yapılmış çalışmalara gereksinim bulunmaktadır.
Anahtar sözcükler: Glaskow Koma Skoru; interlökin; travmatik beyin hasarı.

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