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Serum adhesion molecules, outcome and neuro-psychological function in acute traumatic brain injury patients

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ABSTRACT

Background: Serum concentrations of adhesion molecules may be associated with secondary brain injury after acute traumatic brain injury (TBI).
Methods: Blood samples of 68 patients admitted within 24 h after TBI were obtained on admission and on Days 4 and 7 after TBI. Patients received neuro-psychological testing on discharge and at 3 months after TBI.
Results: Compared to controls, patients with acute TBI had markedly increased sICAM-1 and sVCAM-1 on presentation ($p = 0.002$ and $p = 0.021$, respectively), but markedly decreased sL-selectin and sE-selectin ($p = 0.009$ and $p \leq 0.001$, respectively). Outcome was assessed upon discharge using the Glasgow Outcome Scale (GOS). Good outcome was defined as GOS ≥ 4 and poor outcome as GOS ≤ 3. Motor deficits on admission ($p \leq 0.001$), Glasgow Coma Scale score on admission ($p = 0.002$), Injury Severity Score on admission ($p = 0.009$), neuro-surgical intervention ($p = 0.004$), post-traumatic seizure ($p = 0.04$), and sVCAM-1 level on admission ($p = 0.033$) were significant risk factors of outcome. A sVCAM-1 cut-off value of 752.5 ng/ml on admission had 80.0% sensitivity and 68.1% specificity for predicting outcome.
Conclusion: Serum adhesion molecules are not specific for predicting outcome in patients with TBI. However, higher mean levels of these molecules on admission may imply more severe inflammatory response causing secondary brain injury and worse neuro-psychological function. These molecules may be added as evaluation markers in clinical practice.

1. Introduction

Acute traumatic brain injury (TBI) is a major cause of mortality and disability among young individuals in many countries [1]. It is a disease process with an initial injury that induces biochemical and cellular changes, which in turn contribute to continuing neuronal damage and death over time. This continuing damage, known as secondary injury, involves the activation of multiple apoptotic and inflammatory pathways [2,3]. The extent of brain damage is determined by the severity of primary mechanical injury and the intensity of secondary bio-molecular injury cascades causing neuro-inflammation. This leads to cerebral edema, increased intracranial pressure, and delayed cellular destruction [4].

There is growing evidence that TBI elicits inter-dependent central nervous system (CNS) and systemic inflammatory and coagulation cascades that lead to secondary neuro-pathologic sequelae [5,6]. The vascular endothelium provides a critical interface for host inflammatory and coagulation responses to injury that are associated with the activation of resident microglia, astrocytes [7,8], and peripheral blood leukocytes [9,10], as well as the expression of inflammatory cytokines [11], adhesion molecules [12–14], and coagulation co-factors [6,15].

Abbreviations: TBI, traumatic brain injury; CNS, central nerve system; sICAM-1, soluble intercellular cell adhesion-molecule-1; sVCAM-1, soluble vascular cell adhesion molecule-1; sL-selectin, soluble leukocyte-selectin; sP-selectin, soluble platelet-selectin; sE-selectin, soluble endothelial-selectin; CT, computed tomography; MRI, magnetic resonance imaging; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; ISS, Injury Severity Score; WAIS, Wechsler Adult Intelligence Scale; CASI, Cognitive Ability Screening Instrument; WCST, Wisconsin Card Sorting Test; IQ, intelligence quotient.

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Injured endothelium promotes inflammation via initial tethering and rolling of marginalized cells along the vessel wall. This is mediated by soluble leukocyte-selectin (sL-selectin), soluble endothelial-selectin (sE-selectin), and soluble platelet-selectin (sP-selectin) that bind to circulating leukocytes. Subsequent adhesion to endothelial ligands for soluble intercellular (sICAM-1) and soluble vascular cell adhesion molecules (sVCAM-1) allows leukocyte transmigration into the damaged tissues [16].

Elevated serum levels of adhesion molecules may therefore reflect low-grade chronic inflammation. Such elevation has been associated with cognitive decline in the elderly [17,18], in stroke patients [19], and in animal study [20]. However, its role in the pathogenesis of TBI is unknown.

2. Patients and methods

2.1. Patients

This prospective study on the time course of serum adhesion molecule levels included 68 adult patients (age ≥20 years) admitted within 24 h after the onset of acute TBI to Kaohsiung Chang Gung Memorial Hospital.

2.2. Study population

The diagnosis of acute TBI was confirmed by history and brain computed tomography (CT) scans. Patients were excluded if they: 1) were taking anti-platelet or anti-coagulant drugs before the acute TBI; 2) had evidence of alcoholism or any other addictive disorders, or known affective or other psychiatric diseases than those caused by sedatives or neuroleptics; 3) had known neurologic disorders potentially affecting the central nervous system, or severe recent life events that might interfere with neuro-psychological testing; and 4) major systemic diseases like end-stage renal disease, liver cirrhosis, or congestive heart failure.

The Ethics Committee of the hospital's Institutional Review Board approved the study. All of the patients or their representatives provided written informed consent. For comparison, 57 age- and sex-matched healthy volunteers who received annual physical check-up became the control group for blood and neuro-psychological testing.

2.3. Clinical assessment

The patients were under continuous observation and monitored regularly for Glasgow Coma Scale (GCS) Score, electrocardiogram, blood pressure, pulse rate, temperature, fluid balance, and laboratory parameters. They were also divided into 3 groups according their initial GCS score: mild (GCS score 13–15), moderate (GCS score 9–12) and severe TBI (GCS score 3–8). Outcome was assessed upon discharge using the Glasgow Outcome Scale (GOS), with good outcome as GOS ≥4 and poor outcome as GOS ≤3. The Abbreviated Injury Score for individual body regions was determined and the total extent of the injury was calculated at the time of admission using the objective Injury Severity Score (ISS) [21].

2.4. Radiologic assessment

All of the patients underwent brain CT scan shortly after arriving at the emergency room. Repeat brain CT scan or/and magnetic resonance imaging (MRI) were performed for any clinical deterioration

Table 1
Demographic data of patients and controls on admission.

Parameter	Patients (n = 68)	Volunteer subjects (n = 57)	*p* value	OR	95% CI (lower, upper)
Age (y), Median (IQR)	37.5 (22.3, 55)	36 (32.5, 53)	NS		
Male	40 (58.8%)	34 (59.6%)	NS	1.04	0.51, 2.12
Underlying diseases					
Hypertension	5 (7.4%)	10 (17.5%)	NS	2.06	0.7, 6.07
Diabetes mellitus	2 (2.9%)	1 (1.8%)	NS	0.55	0.05, 6.27
Alcoholism	7 (10.3%)	0			
Smoking	5 (7.4%)	6 (10.5%)	NS	1.39	0.4, 4.82
Clinical features at presentation					
Posttraumatic amnesia	14 (20.6%)	NA			
Brief unconsciousness	36 (52.9%)	NA			
Motor deficits	13 (19.1%)	NA			
GCS at presentation	15 (13, 15)	NA			
Severity of traumatic brain injury					
Mild	52 (76.5%)	NA			
Moderate	7 (10.3%)	NA			
Severe	9 (13.2%)	NA			
Injury Severity Score at presentation	16 (11, 20)	NA			
Laboratory data at presentation, Median (IQR)					
WBC ($x10^3$/ml)	12.7 (10.3, 16.0)	5.6 (4.9, 7.8)	≤0.001		
Platelet counts ($x10^3$/ml)	208.5 (107, 279)	245 (202, 306.5)	0.033		
Brain Imaging Findings at presentation					
Depressed skull fracture	2 (2.9%)	NA			
Pneumocranium	8 (11.8%)	NA			
Traumatic SAH	33 (48.5%)	NA			
Subdural hemorrhage	25 (36.8%)	NA			
Epidural hemorrhage	13 (19.1%)	NA			
Parenchymal contusion hemorrhage	15 (22.1%)	NA			
Neurosurgical intervention	13 (19.1%)	NA			
Soluble intercellular adhesion molecule at presentation, Median (IQR)					
sL-selectin (ng/ml)	842.5(763.4, 935.0)	970.5(844.8, 1045.1)	0.009		
sP-selectin (ng/ml)	87.5 (78.5, 102.8)	85.1 (78.4, 92.5)	NA		
sE-selectin (ng/ml)	24.0 (17.2, 40.9)	39.4 (31.9, 44.6)	≤0.001		
sICAM-1 (ng/ml)	203.5(177.6, 240.2)	183.7(155.0, 202.2)	0.002		
sVCAM-1 (ng/ml)	703.8(562.9, 860.2)	613.5(527.4, 674.4)	0.021		

Abbreviations: GCS, Glasgow outcome scale; IQR, inter-quartile range.
Data are presented either as absolute numbers or as medians (inter-quartile range) Statistical significance was set at $p = 0.05$. Statistical variance between groups was assessed by the Fisher's exact test for discrete variables and by the Mann–Whitney U test for continuous variables.