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Comparison of predictive powers of S100B and cell-free plasma DNA values in intensive care unit patients with intracranial hemorrhage☆,☆☆,★

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Abstract
Purpose: To investigate predictive powers of S100B and cell-free DNA (cfDNA) levels in patients in the intensive care unit (ICU) who have with intracranial hemorrhage (ICH) for prognosis.
Methods: Ninety-nine patients diagnosed with ICH were included in the study. The blood samples were drawn on the day of admittance to ICU and again on the third day. Duration of stay in the ICU and mortality were recorded.
Results: A positive correlation was determined between the values of S100B and cfDNA from both the analysis and the Acute Physiology and Chronic Health Evaluation II scores. For all patients, there was a positive correlation between the duration of stay in the ICU and the values of S100B and cfDNA on the third day. The levels of both S100B and cfDNA in patients who died in the ICU were significantly higher than of those who survived on the day of admittance.
Conclusions: Both S100B and cfDNA values can be used as markers to predict the prognosis of ICU patients with ICH. However, S100B is more powerful for predicting the prognosis.

1. Introduction

A correct prediction of prognosis in the intensive care unit (ICU) patients with intracranial hemorrhage (ICH) is very important for the patient's clinical future. The Acute Physiology and Chronic Health Evaluation (APACHE) II [1] and the Sequential Organ Failure Assessment (SOFA) scores [2] are often used to predict the risk of mortality and

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morbidity in the ICUs. However, the main standard methods used to measure the severity of brain damage in patients with ICH include neurological examinations, neurological imagining methods, intracranial pressure monitoring, electro diagnostic tests, and transcranial Doppler studies [3]. The markers for presenting the severity and progression rate of damage are essential because none of these methods are able to completely show the severity of damage to the central nervous system.

The biomarkers such as glial fibrillary acidic protein, S100B, neuron specific enolase [4], heart type fatty acid binding protein, brain type fatty acid binding protein [5], and interleukin-11 [6] were used to diagnosis different neurological diseases, the treatment follow-up period, and the monitoring of prognosis.

S100B is a protein contained in the central nervous system, and it is mainly found in glial cells [7,8]. It is metabolized by the kidneys and its half-life is short (approx. 30 min) [9]. S100B is found at very low levels in the blood in healthy persons [10]. When Schwann cells and microglia cells are damaged, S100B is initially secreted into cerebrospinal fluid then mixed with the blood. This is the result of blood brain barrier damage [11].

S100B is elevated in ischemic stroke, anoxic encephalopathy [12], traumatic brain damage [8], subarachnoid hemorrhage [13,14], vasospasm [15], and infections of the central nervous system [16]. The level of S100B in the infections of the central nervous system can also be used to monitor the patient's response to treatment [16]. Furthermore, a late increase in S100B, starting 48 to 72 hours after the onset of stroke, is one of the optimum markers for determining a long-term clinical course [17].

Recently, there has been increased interest in using cell-free DNA (cfDNA) as a prognostic marker [18]. A cfDNA is known to be a DNA fragment and is detected in extracellular fluid. DNA detected in the plasma is either the DNA that is transmitted from apoptotic cells to plasma, or it is the DNA that is found in the cells such as lymphocytes [19]. It is found in very low levels in the plasma of healthy persons [20]. Increased levels of cfDNA have an association with cancer [20], stroke [18], myocardial infarction [21], trauma [22], and sepsis [23].

Our aim in this study is to investigate the predictive powers of S100B and cfDNA levels in ICU patients with ICH as a prognostic factor.

2. Methods

2.1. Patients

The study was carried out at twelve-bed surgical ICU in the tertiary care Ondokuz Mayis University School of Medicine. The study began with the approval of the Medical Research Ethics Committee of Ondokuz Mayis University. To include the patients in the study, permission was obtained from conscious patients who could cooperate and from the first-degree relatives of the other patients. Diagnosis of patients who presented at the emergency room was made with the required imagining methods after evaluation by related departments. Patients aged 18 and over who were diagnosed with ICH were put in the ICU after necessary surgical interventions and then included in the study. The patients, who had no final diagnosis by imagining methods, had a known neurological disease history and chronic renal failure, have been excluded from the study.

The final diagnosis of the patients who were suspected of cerebral death during clinical follow up was made by the "*committee for determination of brain death*" which consisted of four specialists (neurologist, neurosurgeon, anesthesiologist, and cardiologist). The relationship between brain death and S100B and cfDNA was analyzed.

2.2. Scores

Glasgow Coma Scale (GCS) [24] was used for patient's neurological examinations. The SOFA values and APACHE II scores of the patients in the ICU on the first day were calculated and recorded. The relationship between the GCS, APACHE II, and SOFA scores as well as the cfDNA and S100B levels were analyzed. The patients were divided in two groups by APACHE II values: Group I (1-19) and Group II (≥ 20). The patients were divided in three groups by GCS scores: Group I (3-7), Group II (8-11), and Group III (12-15).

2.3. Biochemical parameters

Blood was drawn from the patients twice on day of admittance in the ICU and again on the third day. The first sample was taken within 12 hours of the patient being admitted to the ICU.

Blood was collected in a tube containing no anticoagulants and centrifuged at 3000xg for 10 minutes to obtain the serum. The serum samples were kept at −80°C until they were analyzed. The level of S100B was analyzed in serum samples using the ELISA method in accordance with the instructions of manufacturer (BioVendor, Cat. No.: RD192090100R, Czech Republic). The results are presented in pg/mL.

The cfDNA was determined using plasma samples. The protocol of Chiu et al. [25] was used. The blood was collected in a tube containing potassium EDTA as anticoagulant and centrifuged at 1600*g* for 10 minutes. The plasma obtained was transferred into an Eppendorf tube and centrifuged at 16 000*g* for another 10 minutes. The plasma samples were kept at −80°C until they were analyzed. The DNA was isolated from the plasma samples using High Pure Viral Nucleic Acid Kit (Roche Diagnostics GmbH, Penzberg, Germany). Real-time polymerase chain