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Role of S100B protein in urine and serum as an early predictor of mortality after severe traumatic brain injury in adults

Ana Rodríguez-Rodríguez [a], Juan José Egea-Guerrero [b], Antonio León-Justel [a], Elena Gordillo-Escobar [b], Jaume Revuelto-Rey [b], Ángel Vilches-Arenas [c], Antonio Carrillo-Vico [b], José María Domínguez-Roldán [b], Francisco Murillo-Cabezas [b], Juan Miguel Guerrero [a,*]

[a] Department of Clinical Biochemistry, Virgen del Rocio University Hospital, IBIS/CSIC/University of Seville, Spain
[b] NeuroCritical Care Unit, Virgen del Rocío University Hospital, IBIS/CSIC/University of Seville, Seville, Spain
[c] Department Preventive Medicine and Public Health, University of Seville, Spain

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ABSTRACT

S100B is a calcium-binding protein released into the blood from astroglial cells due to brain injury. Some authors have described a correlation between S100B serum concentration and severity of brain damage. There is not much information about the accuracy of urinary S100B for predicting outcome after severe traumatic brain injury (TBI). 55 patients with severe TBI were included in the study. Blood and urine samples were drawn to determine S100B levels on admission and on the subsequent 24, 48, 72 and 96 h. S100B concentrations (serum and urine) were significantly higher in patients who were dead a month after the accident compared to survivors. ROC-analysis showed that S100B at 24 h post-severe TBI is a useful tool for predicting mortality (serum: AUC 0.958, urine: AUC 0.778). The best cut-offs for S100B were 0.461 μg/L and 0.025 μg/L (serum and urine respectively), with a sensitivity of 90% for both measurements and a specificity of 88.4% (serum) and 62.8% (urine). We can state that the determination of S100B levels both in urine and serum acts as a sensitive and an effective biomarker for the early prediction of mortality after severe TBI.

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1. Introduction

The use of biochemical markers in daily clinical practice to diagnose and monitor diverse diseases or pathologic situations has increased in the last decades [1–3]. Nevertheless, no biomarkers are currently used in clinical practice as markers for brain damage. Some authors have described a series of biomarkers, including neuron-specific enolase, TAU protein, glial fibrillary astrocytic protein, cell-free DNA and S100B protein as damage markers of the central nervous system [4–7].

S100B protein is a calcium-binding protein released into the blood from the cytosol of astroglial and Schwann cells due to a lesion to the cephalous [8–11]. S100B acts in a bimodal manner [12,13]. Nanomolar concentrations stimulate neurite growth and promote neuron survival. However, micromolar concentrations have the opposite effect and can even induce neuronal apoptosis, leading to the induction of pro-inflammatory cytokines and inflammatory stress-related enzymes [14–16]. The short biological half-life of S100B (between 30 and 60 min) and its renal clearance (2 h) imply that any persistent elevation of S100B concentration in the blood reflects a continuous active secretion or passive release from damaged tissues [17].

Over the last decade, several research groups have published their results correlating S100B levels in serum to the severity of traumatic brain damage and patient outcome [18–20]. Bloomfield et al. affirmed that a normal S100B level reliably predicts the absence of significant central nervous system injury, whereas elevations of S100B above certain threshold levels might be able to accurately predict brain death or mortality [19]. In reference to urine there is not much information about the utility of urinary S100B levels. Few research groups have studied urinary S100B as a marker of brain damage and most of them have only focused in pediatric population. Thus, several authors confirm a rise in urinary S100B levels in patients who suffered a TBI compared to controls or patients who did not suffer a TBI [18,21–23].

The present study was designed to study the role of serum and urine S100B levels as an early predictor of mortality after severe TBI in adults.

Abbreviations: TBI, Traumatic Brain Injury; GCS, Glasgow Coma Scale; CT, Computed Tomography; ISS, Injury Severity Score; ROC, Receiver Operator Characteristics; NCCU, NeuroCritical Care Unit; AIS, Abbreviated Injury Score; AUC, Area Under the Curve; TCDB, Trauma Coma Data Bank.

* Corresponding author at: Department of Clinical Biochemistry, Virgen del Rocio University Hospital, IBIS/CSIC/University of Seville, Avda. Manuel Siurot s/n, 41013 Seville, Spain. Tel.: +34 955 013237, +34 651653642; fax: +34 955013154.
E-mail address: guerrero@us.es (J.M. Guerrero).

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2. Materials and methods

2.1. Patients and samples

During eighteen months, fifty-five severe head injury patients admitted to the NeuroCritical Care Unit (NCCU) were prospectively selected for this study. The protocol, carried out in accordance with the Declaration of Helsinki, was approved by the Virgen del Rocío University Hospital Institutional Review Board. TBI patients were eligible based on the following inclusion criteria: aged 14 or over, Glasgow Coma Scale score (GCS) ≤8 after hemodynamic and metabolic resuscitation, first serum sample extracted on admission (within 6 h post-trauma) and mean arterial pressure above 75 mm Hg. Written consent to conduct biological sample analyses not typically included in standard clinical procedures was obtained from the patient relatives. Exclusion criteria were: under 14 years of age, pregnancy or possibility of pregnancy, previous history of drug/alcohol abuse, renal failure, cardiorespiratory arrest after TBI, multiple trauma with an Abbreviated Injury Score above 5 in different organs from the brain [24] and previous history related to the presence of histological injury compatible with melanoma and other previous concurrent nervous system disorders.

Clinical and demographic variables, collected prospectively, included gender, age, reference GCS score after resuscitation, Injury Severity Score (ISS), CT findings based on Trauma Coma Data Bank (TCDB), presence of other associated injuries, S100B levels in serum and urine, as well as mortality or survival at one month of the trauma. According to survival outcome, we classified patients in two groups: survival group (45 patients) and death group (10 patients).

2.2. Measurement of S100B levels

Venous blood and urine samples were collected on admission and every 24 h for up to 4 days. Once collected, the samples were immediately transported to the laboratory. Blood samples were centrifuged at 900 ×*g* for 10 min at room temperature. The separated sera were then frozen in aliquots at −80 °C until analyzed. Urine samples were centrifuged at 450 ×*g* for 10 min in room temperature. The supernatants were frozen and stored at −80 °C until batch evaluation.

Serum S100B protein levels were measured by electrochemiluminescence using the commercially available test (ECLIA) produced by Elecsys 2010 immunoassay system (Roche Diagnostics, Germany) following the manufacturer's indications. This test measures both S100A1B and S100BB dimers. The test takes 18 min and requires a probe volume of at least 20 μL of serum. The results are given in micrograms per liter (μg/L). Detection begins at 0.005 μg/L and any concentration over 39 μg/L can be quantified without dilution.

Urinary S100B protein was assayed by the method previously described. Although the manufacturer has not validated the S100B method for urine, other researchers [25] have carried out local validation series concluding that the serum protocol is suitable for the urine assessment. Creatinine was also analyzed in the urine samples to evaluate possible dilution effects [26]. Creatinine was measured by Jaffé enzymatic reaction.

Data on precision was provided by the manufacturer. It was determined using Elecsys reagents, pooled human sera and controls, measuring six times daily for ten days (n = 60) (Table 1).

The biochemist performing the assay was blind to the clinical and radiological findings.

Table 1
Precision on the Elecsys S100 assay. SD: standard deviation. CV: coefficient of variation.

Sample	Repeatability			Intermediate precision		
	Mean μg/L	SD μg/L	CV %	Mean μg/L	SD μg/L	CV %
Human serum 1	0.09	0.001	1.0	0.09	0.003	3.1
Human serum 2	0.26	0.005	1.8	0.26	0.006	2.5
Human serum 3	2.25	0.015	0.7	2.24	0.064	2.9
PreciControl S100_1	0.27	0.004	1.3	0.28	0.007	2.7
PreciControl S100_2	3.39	0.031	0.9	3.38	0.092	2.7

2.3. Statistical analysis

A descriptive analysis was carried out using qualitative variables, represented in the tables as absolute frequencies and percentages. Quantitative variables were expressed using median and Standard Deviation (SD) or mean interquartile range (P25–P75), depending on whether or not they followed a normal distribution. Comparisons of means of quantitative variables between subgroups were made applying Student's t test for independent samples or the nonparametric Mann–Whitney U test if variables presented a non-normal distribution. For comparing more than two groups, Kruskal–Wallis test was applied. If significant differences were obtained confidence intervals (CI) were calculated at 95%. Analysis of relationships between variables was made by contingency tables using the Chi-Square test or the Fisher's exact test. The interpretation of the tables was made using the typified corrected residuals. Inferential univariate and multivariate analyses were performed using a Cox proportional-hazards regression. We applied this method to investigate the effect of several variables (hypothetical predictive factors) upon the time a specified event (death) takes to happen. This method selects the best set of predictive variables for death among those reaching a significance level <0.15 in the univariate analysis. Hazard Ratio (HR) with 95% CI was calculated for all the variables entered into the model. Receiver Operator Characteristic (ROC) curve analysis on S100B serum values was used to allocate patients in the mortality or survival groups. This analysis, which provides the area under the ROC curve (AUC) measurements, was used to establish a cut-off point for patient classification. All statistical analyses were conducted using software from the Statistical Package for the Social Sciences (SPSS) (Version 18.0, Chicago, IL, USA).

3. Results

3.1. Demographics and clinical characteristics

Fifty-six severe TBI patients were admitted in our NCCU. One family declined participation on the part of their injured relative. A total of 55 patients met the inclusion criteria for the study. Fifty patients were male (91.38%) and five female (8.62%). Mean age was 37.6 (SD ± 16.3). No patient was under 16 years of age. All patients presented with intracranial lesions on an admission head CT scan (TCDB I, n = 0). Ten patients were dead one month after TBI (18.2%). The clinical characteristic and demographic data of the 55 patients are shown in Table 2. A total of 395 samples were analyzed: 195 serum and 200 urine samples. S100B was detectable in all serum and urine samples.

3.2. Relationship of mortality, GCS and ISS with serum and urinary S100B concentrations

As regards the relationship of S100B levels with mortality, patients who died had significantly higher serum (Fig. 1A) and urinary (Fig. 1B) S100B concentrations than survivors. After studying the correlation between S100B levels and different severity scales, we found that both serum and urinary S100B levels showed an inverse correlation with GCS (r = −0.458 for serum, r = −0.487 for urine; P<0.01) and a positive correlation with the ISS (r = 0.493 for serum, r = 0.466 for urine; P<0.01) (Fig. 2). In order to study a possible

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