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ELEVATED SERUM PROTEIN S100B AND NEURON SPECIFIC ENOLASE VALUES AS PREDICTORS OF EARLY NEUROLOGICAL OUTCOME AFTER TRAUMATIC BRAIN INJURY

POVIŠENE SERUMSKE VREDNOSTI PROTEINA S100B I NEURON-SPECIFIČNE ENOLAZE KAO PREDIKTORI RANOG NEUROLOŠKOG ISHODA NAKON TRAUMATSKE LEZIJE MOZGA

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Summary

Background: The objective of our study was to determine the serum concentrations of protein S100B and neuron specific enolase (NSE) as well as their ability and accuracy in the prediction of early neurological outcome after a traumatic brain injury.
Methods: A total of 130 polytraumatized patients with the associated traumatic brain injuries were included in this prospective cohort study. Serum protein S100B and NSE levels were measured at 6, 24, 48 and 72 hours after the injury. Early neurological outcome was scored by Glasgow Outcome Scale (GOS) on day 14 after the brain injury.
Results: The protein S100B concentrations were maximal at 6 hours after the injury, which was followed by an abrupt fall, and subsequently slower release in the following two days with continual and significantly increased values ($p<0.0001$) in patients with poor outcome. Secondary increase in protein S100B at 72 hours was recorded in patients with lethal outcome (GOS 1). Dynamics of NSE changes was characterized by a secondary increase in concentrations at 72 hours after the injury in patients with poor outcome.

Kratak sadržaj

Uvod: Cilj studije je bio da se odrede serumske koncentracije proteina S100B i neuron-specifične enolaze (NSE) i njihova sposobnost i preciznost u predikciji ranog neurološkog ishoda nakon traumatske lezije mozga.
Metode: Sto trideset politraumatizovanih pacijenata sa udruženom traumatskom lezijom mozga je uključeno u ovu prospektivnu kohortnu studiju. Serumski nivoi proteina S100B i NSE su mereni u 6, 24, 48. i 72. satu nakon povređivanja. Rani neurološki ishod je procenjivan Glasgow Outcome Scale (GOS) skorom četrnaestog dana nakon povrede mozga.
Rezultati: Koncentracije proteina S100B su bile maksimalne u 6. satu nakon povređivanja i praćene su naglim padom, a zatim sporijim oslobađanjem u naredna dva dana uz konstantno i signifikantno povišene vrednosti ($p<0,0001$) kod pacijenata sa lošim ishodom. Sekundarni porast proteina S100B u 72. satu zabeležen je kod pacijenata koji su preminuli (GOS 1). Dinamiku promena za NSE karakteriše sekundarni porast koncentracija u 72. satu nakon povređivanja kod pacijenata sa lošim ishodom.

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List of abbreviations: ISS, Injury Severity Score; GCS, Glasgow Coma Scale Score; GOS, Glasgow Outcome Scale Score; TBI, Traumatic Brain Injury; NSE, Neuron Specific Enolase.

Conclusions: Both markers have good predictive ability for poor neurological outcome, although NSE provides better discriminative potential at 72 hours after the brain injury, while protein S100B has better discriminative potential for mortality prediction.

Keywords: traumatic brain injury, protein S100B, neuron specific enolase, outcome

Zaključak: Oba markera imaju dobru prediktivnu sposobnost za loši neurološki ishod, mada NSE obezbeđuje bolji diskriminativni potencijal u 72. satu nakon povrede mozga, dok protein S100B ima bolji diskriminativni potencijal u predikciji mortaliteta.

Ključne reči: povreda mozga, protein S100B, neuron-specifična enolaza, ishod

Introduction

Traumatic brain injury is a global public, medical and socioeconomic problem, and a leading cause of mortality and life-time disabilities worldwide, regardless of the geographical region (1, 2). Traumatic brain injury occurs when an external force causes harm to the skull and the content of the skull cavity, causing transient or permanent damage, functional disorder or psychosocial and behavioral maladaptivity (3, 4). The most common causes are as follows: traffic traumatism, industrial traumatism, falls from height and violence. In spite of modern diagnostic procedures and advanced multidisciplinary intensive treatment of these patients, the percentage of mortality and morbidity remains high.

The past few decades were marked by growing interest in the biochemical markers of cerebral lesions in both experimental (5) and clinical neuro-traumatology (6). Based on numerous clinical studies, protein S100B and neuron specific enolase are promising predictive markers of both early and long-term outcome after traumatic brain injury. Protein S100B is a small cytosolic dimer protein, of the calcium-binding protein type, with a molecular mass of 21 kDa on average, and a biological half-life of 30 minutes to 2 hours (7). It is primarily located in the cytoplasm of Schwann and astroglial cells, but it may also be found in the cells beyond the nervous system: adipocytes, chondrocytes and melanoma cells. In distinction from other markers, it is actively excreted in the extracellular space, but is also passively released after cellular destruction (8). Clinical protein S100B is a safe and reliable marker of brain damage and a good indicator of outcome after traumatic brain injury (9). Protein S100B is also a very precise predictor of mortality after 24, 48 and 72 hours of trauma. Sensitivity and specificity for mortality prediction after traumatic brain injury are more accurate after isolated brain trauma in relation to multiple traumas associated with traumatic brain injury.

Neuron specific enolase is an isoenzyme of the glycolytic enzyme enolase, with a molecular mass of 78 kDa and biological half-life of 48 hours (10). It is predominantly located in the cytoplasm of neurons, and, therefore, it is the only marker which directly estimates functional neuronal damage. Clinically, NSE is a marker of neuronal damage, and its elevated serum concentrations may be detected after traumatic brain injury. It is an evidence-based claim that increased serum NSE concentrations correlate with poor outcome and clinical complications in intensive therapy units after brain trauma as well as multiple traumas (11, 12).

Patients and Methods

Study design

This was a prospective, cohort study completed in the period from January 2015 to January 2016. The study included 130 polytraumatized patients with the associated traumatic brain injury (TBI), hospitalized in the Central Intensive Therapy Unit of the Clinic for Emergency Surgery, Clinical Center of Serbia in conjunction with the Department of emergency laboratory diagnostics of the Center for Medical Biochemistry, Clinical Center of Serbia, Belgrade.

Patients

Key mechanisms of injury were traffic traumatism and fall from height over 3 m. The inclusion criteria were: age ranging from 18–65 years, polytraumatized patients with the associated TBI of varying severity. Exclusion criteria were: patients with a history of neurological and psychiatric diseases and disorders, and patients addicted to drugs, opioids and alcoholic beverages.

Initially, the level of injury severity was estimated by the Injury Severity Score (ISS), and the level of craniocerebral injury severity was assessed by the Glasgow Coma Score (GCS). ISS was estimated in the Emergency department, immediately upon a patient's admission, while GCS was determined during the first contact with a patient, before intubation, sedation and/or muscular relaxation, according to the ATLS Protocols for management of polytraumatized and Brain Trauma Foundation Guidelines for TBI patients. Functional neurological outcome on day 14 after the trauma was estimated by the Glasgow Outcome Scale (GOS) score. According to the GOS score, our patients were divided into two groups: 1) patients with unfavorable outcome GOS $\leq$ 3 and 2) patients with favorable outcome GOS 4–5.

Neuroradiological examination

Neuroradiological examinations were based on cranial CT scans. The initial cranial CT scans were assessed according to the Marshall CT classification and Rotterdam CT scores. For easier presentation of the results of initial CT diagnostics, the study used the following CT presentations: subdural hematoma (SDH), epidural hematoma (EDH), traumatic subarachnoid hemorrhage (tSAH), cerebral contusion and diffuse axonal injury.

Neurobiochemical examination

This examination includes measurements of serum protein S100B and NSE. Venous blood samples were collected for protein S100B and NSE first at 6 h after the injury, and thereupon at 24 h, 48 h and 72 h after the injury. The period of 72 hours was assumed as an early period after brain injury in polytraumatized patients, according to clinical and radiological findings. As such, both daily biomarkers' levels were taken till the period of 72 hours.

These samples were centrifuged at 4000 rpm for 10 minutes and the serum samples were used for determination of NSE and protein S100B levels. Measurement of the serum protein S100B and NSE was done by an electro-chemiluminescence immunoassay on a Roche Cobas 6000/e601 automated analyzer (Roche Diagnostics, Mannheim, Germany). According to the manufacturer's package insert, Roche Cobas S100 (S100A1 and S100b) reagent kit (Roche Diagnostics GmbH, Germany) had a measurement range of 0.005 to 39 μg/L with a limit of detection of 0.005 μg/L. The Roche S100B assay revealed intra- and inter-assay coefficients of variation between 0.7% and 3.1%. According to the manufacturer's package insert, Roche Cobas NSE reagent kit (Roche Diagnostics GmbH, Germany) had a measurement range of 0.050–370 μg/L with a limit of detection of 0.05 μg/L. The NSE reference value in our laboratory was < 16.3 μg/L. The Roche NSE assay revealed intra- and inter-assay coefficients of variation between 0.6% and 3.8%.

Statistical analysis

The Kolmogorov-Smirnov test was performed to assess the assumption of normality of continuous variables. Normally distributed continuous data were presented as mean ± SD and skewed data were presented as median (IQR, inter-quartile range). Categorical data were presented as frequency (percentage). Comparison of neuro-biomarker concentrations between two groups of GOS was done using Mann-Whitney U test. Receiver operation characteristic analysis was done and c-statistic was calculated for both neuro-biomarkers in order to examine their discriminative ability to predict unfavorable outcome and mortality after 14 days. The comparisons of areas under the curves of protein S100B and NSE at different time points were done by De Long method. Optimal diagnostic cut-off values were calculated using Youden Index. The sensitivity, specificity, likelihood ratios and predictive values were calculated for previously calculated cut-off values. All tests were two-sided and p-values ≤ 0.05 were considered as statistically significant. Statistical analysis was done using SPSS 20.0 software (IBM Corp., Armonk, NY, USA) and Med Calc Version 12.5.0.0 for Windows (Med Calc Software bvba, Ostend, Belgium).

Results

A total of 130 patients (100 males and 30 females) with traumatic brain injuries were included in the study. The mean age ± SD of patients was 40.2±13.8. The major mechanism of trauma was motor vehicle crush (113 patients, 86.9%) followed by fall from height (17 patients, 13.1%). The majority of patients sustained moderate head injuries (median GCS of 9) and were critically injured according to mean ISS ± SD, 34.2±15.9. Unfavorable outcome after 14 days of follow-up occurred in 44 (33.8%) patients, while 15 patients (11.5%) died. Considering the initial CT findings, assessed by the Marshall CT classification and Rotterdam CT score, 24.6% patients underwent neurosurgical operation (evacuated mass lesions) while 6.2% had unsurvivable lesions (*Table I*).

The concentrations of protein S100B and NSE, and the comparisons of these concentrations between the patients with good outcome and those with bad outcome on day 14 after TBI were shown in *Table II*. Median concentrations of protein S100B and NSE at 6 h, 24 h, 48 h and 72 h from TBI were 0.67 μg/L, 0.24 μg/L, 0.12 μg/L and 0.09 μg/L, and 38.2 μg/L, 24.4 μg/L, 16.0 μg/L and 15.4 μg/L, respectively. Notably, levels of both neuro-biomarkers were, at every measurement point, significantly higher in the group of patients who experienced bad outcome than those with good outcome.

Areas under the ROC curves and c-statistics analysis of protein S100B and NSE (at four different time points) for prediction of unfavorable outcome were presented in *Table III*, while ROC curves were plotted in *Figures 1* and *2*, respectively. While protein S100B evinced moderate discriminative ability to predict unfavorable outcome in patients with TBI at all four time points (AUCs 0.7–0.8), NSE showed the best discriminative ability for unfavorable outcome at 72 h after TBI according to an AUC of 0.856 (95% CI, 0.788–0.923, p<0.0001). Optimal cut-off value for this biomarker at 72 h was 15.5 μg/L, with 94.9% sensitivity, 72.1% specificity and positive likelihood ratio 3.4. Optimal cut-off values for all time points of protein S100B and NSE were presented in *Table IV*.

Table I Demographic and clinical characteristics of patients (n=130).

Age (years), mean ± SD	40.2±13.8
18–25	25 (19.2)
26–64	101 (77.7)
65	4 (3.1)
Gender (males), n (%)	100 (76.9)
GCS, median (IQR)	9 (4)
Mild (13–15)	10 (7.7)
Moderate (9–13)	70 (53.8)
Severe (≤8)	50 (38.5)
Marshall score	
I	9 (6.9)
II	36 (27.7)
III	30 (23.1)
IV	15 (11.5)
V	32 (24.6)
VI	8 (6.2)
Rotterdam score	
I	7 (5.4)
II	39 (30.0)
III	23 (17.7)
IV	21 (16.2)
V	32 (24.6)
VI	8 (6.2)
ISS, mean ± SD	34.2±15.9
Mild (<9)	0
Moderate (9–15)	2 (1.5)
Severe (16–24)	33 (25.4)
Critical (≥25)	95 (73.1)
Outcome after 14 days (GOS score)	
Death (1)	15 (11.5)
Severe disability (2)	6 (4.6)
Mild disability (3)	23 (17.7)
Partial recovery (4)	52 (40.0)
Full recovery (5)	34 (26.2)

Values are numbers (%) if not stated otherwise.
GCS, Glasgow coma score; GOS, Glasgow coma scale; ISS, injury severity score.

Table II Comparison of protein S100B and NSE concentrations between good and bad outcome.

Time point	Protein S100B				NSE			
	Total, μg/L	Good outcome μg/L	Bad outcome μg/L	*P*[a]	Total, μg/L	Good outcome μg/L	Bad outcome μg/L	*P*[a]
6h	0.67 (0.63)	0.48 (0.41)	0.96 (0.53)	<0.0001	38.2 (35.6)	32.53 (23.80)	56.50 (26.48)	<0.0001
24h	0.24 (0.3)	0.20 (0.23)	0.39 (0.46)	<0.0001	24.4 (15.4)	20.20 (11.38)	32.35 (15.30)	<0.0001
48h	0.12 (0.12)	0.11 (0.10)	0.22 (0.19)	<0.0001	16.0 (7.8)	15.45 (7.78)	18.90 (7.50)	0.001
72h	0.09 (0.08)	0.08 (0.05)	0.18 (0.23)	<0.0001	15.4 (8.7)	11.95 (8.35)	19.20 (6.10)	<0.0001

[a]Mann-Whitney U test.
Values are median (IQR).

Table III Area under the Receiver Operating Characteristic Curve (AUC) for protein S100B in the prediction of unfavorable outcome after traumatic brain injury.

Variable	AUC	SE	95% CI	*p*
S100B 6h	0.768	0.044	0.681–0.854	<0.0001
S100B 24h	0.788	0.043	0.704–0.873	<0.0001
S100B 48h	0.747	0.047	0.654–0.839	<0.0001
S100B 72h	0.786	0.047	0.693–0.879	<0.0001
NSE 6h	0.746	0.044	0.659–0.833	<0.0001
NSE 24h	0.739	0.047	0646–0.831	<0.0001
NSE 48h	0.694	0.047	0.601–0.786	<0.0001
NSE 72h	0.856	0.034	0.788–0.923	<0.0001

SE, standard error; CI, confidence interval.

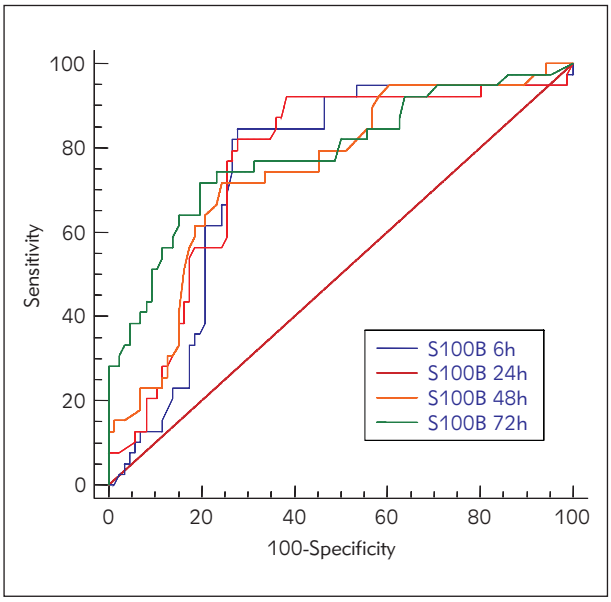

Figure 1 Receiver operating curves (ROC) of protein S100B 6 h, 24 h, 48 h and 72 h after TBI in the diagnosis of unfavorable outcome.

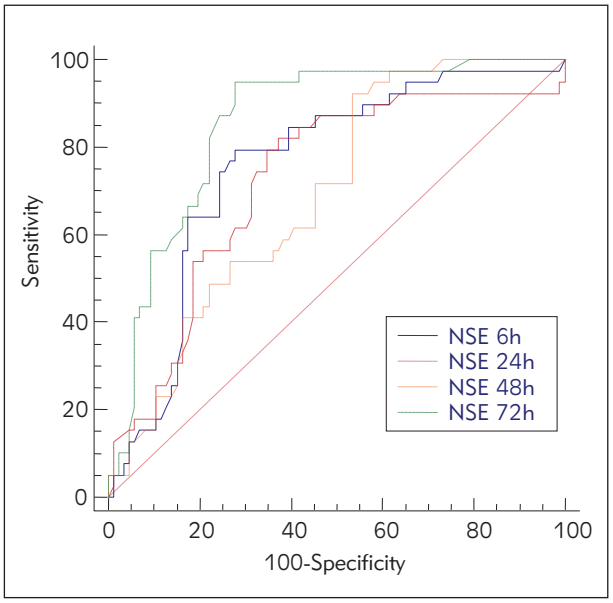

Figure 2 Receiver operating curves (ROC) of neuron specific enolase 6 h, 24 h, 48 h and 72 h after TBI in the diagnosis of unfavorable outcome.

Areas under the ROC curves and c-statistics analysis of protein S100B and neuron specific enolase (at four different time points) for prediction of mortality were presented in *Table V*. Protein S100B showed good predictive ability for prediction of mortality after 14 days from TBI (AUCs 0.8–0.9, $p<0.0001$). However, NSE showed good predictive ability only when measured at 72 hours from TBI (AUC 0.874, $p<0.0001$), similarly to prediction of unfavorable outcome. Optimal cut-off value of NSE at 72 h appeared to be > 16.2 µg/L with 100% sensitivity, 60.9% specificity and positive likelihood ratio 2.6.

Areas under the curves were compared between protein S100B and NSE in order to estimate which has better prognostic ability for prediction of unfavorable outcome 14 days after TBI (data not shown). Although both markers appeared to be useful in the prediction of unfavorable outcome, especially when measured at 72 h, protein S100B had higher areas under the curve than NSE for all time point measurements except at 72 h whereas NSE showed higher accuracy than S100B (AUCs, 0.856 *vs*. 0.786) (with borderline significance, $p=0.053$). Similarly, protein S100B had higher diagnostic potential to predict mortality 14 days after TBI than NSE at every time point of measurement. However, the observed difference had not reached a statistically significant level.

Discussion

An assessment of brain injury severity as well as early determination of outcome after TBI, especially moderate and severe, are the priorities of a multidis-

Table IV Predictive performance of protein S100B and neuron specific enolase in the diagnosis of unfavorable outcome after traumatic brain injury.

Marker	Cut-off value µg/L	Sensitivity (%)	Specificity (%)	LR+	LR-	PPV (%)	NPV (%)
S100B 6h	> 0.695	86.4	72.1	3.1	0.2	61.3	91.2
S100B 24h	> 0.258	84.1	72.1	3.0	0.2	60.7	89.9
S100B 48h	> 0.162	71.8	75.6	2.9	0.4	57.1	85.5
S100B 72h	> 0.113	71.7	80.2	3.6	0.4	62.2	86.3
NSE 6h	> 42.4	72.7	72.1	2.6	0.4	57.1	83.8
NSE 24h	> 24.3	81.8	65.1	2.4	0.3	54.6	87.5
NSE 48h	> 14.2	92.3	46.5	1.7	0.2	43.9	93.0
NSE 72h	> 15.6	94.9	72.1	3.4	0.1	60.7	96.9

LR, likelihood ratio; PPV, positive predictive value; NPV, negative predictive value.

Table V Area under the Receiver Operating Characteristic Curve (AUC) for protein S100B in the prediction of mortality after traumatic brain injury.

Variable	AUC	SE	95% CI	p
S100B 6h	0.810	0.07	0.732–0.874	<0.0001
S100B 24h	0.856	0.06	0.787–0.913	<0.0001
S100B 48h	0.860	0.06	0.787–0.916	<0.0001
S100B 72h	0.868	0.07	0.797–0.922	<0.0001
NSE 6h	0.675	0.07	0.587–0.754	0.011
NSE 24h	0.776	0.07	0.695–0.844	0.0001
NSE 48h	0.717	0.10	0.629–0.794	0.033
NSE 72h	0.847	0.05	0.771–0.905	<0.0001

SE, standard error; CI, confidence interval.

Table VI Diagnostic performance of protein S100B and neuron specific enolase in the prediction of mortality after traumatic brain injury.

Marker	Cut-off value µg/L	Sensitivity (%)	Specificity (%)	LR+	LR-
S100B 6h	> 0.876	86.7	74.8	3.4	0.2
S100B 24h	> 0.548	73.3	87.8	6.0	0.3
S100B 48h	> 0.204	90.0	75.7	3.7	0.1
S100B 72h	> 0.327	70.0	98.3	2.7	0.3
NSE 6h	> 35	93.3	46.1	1.7	0.1
NSE 24h	> 34.2	73.3	82.6	4.2	0.3
NSE 48h	> 32.5	50.0	96.5	3.6	0.5
NSE 72h	> 16.2	100.0	60.9	2.6	0.0

LR, likelihood ratio; PPV, positive predictive value; NPV, negative predictive value.

ciplinary medical team engaged in the complex intensive treatment of these patients.

Neuron specific enolase and protein S100B are the most commonly studied markers. Measurement of their serum and CSF concentrations after brain injury makes them trustworthy indicators of the brain injury level and enables prediction of the outcome (12–14).

Based on a study by Pleines et al. (15), both markers have diagnostic and prognostic significance. Protein S100B provides information on the extensiveness of the injury and post-injury outcome, while NSE is a better indicator of neuroinflammation in patients with very severe brain injury. Our intent was to analyze the prognostic values of serum NSE and protein S100B levels in polytraumatized patients with the associated TBI, with special focus on their role in the prediction of an early neurological outcome on day 14 following the brain injury. Critical injuries were found in 95 patients (73.1%) whose mean Injury Severity Score was 34.2 ± 15.9, and who experienced moderate brain injury and mean GCS 9. According to the early functional neurological outcome measured by the Glasgow outcome scoring system on day 14 after the brain injury, our patients were divided into two groups: 1) patients with poor outcome (GOS 1–3), and 2) patients with good outcome (GOS 4,5). There were 44 (33.8%) patients with poor outcome (GOS 1–3) after day 14, out of which 15 (11.5%) died (GOS1), while 86 (66.2%) patients had good functional outcome (GOS 4,5). The study demonstrated significant dynamic changes in the concentrations of both markers through all time intervals.

Maximal protein S100B concentration was reported at 6 h after the injury, with additional slow release in the following two days and continuously elevated values in patients with poor outcome. In comparison to patients with good outcome, these values were significantly higher ($p<0.0001$) at all 4 time intervals. Secondary increase in protein S100B concentration at 72 h of the injury was recorded in patients who died (GOS 1). Similar dynamics of changes in protein S100B concentrations were shown by Thelin et al. (16, 17) and Raabe et al. (18) in their studies. These authors reported higher serum protein S100B concentrations or secondary peaks which correlated with computerized tomography findings and with poor long-term neurological outcome in patients with moderate and severe TBI. Similar results are found also in the meta-analysis of Mercier et al. (19). Elevated serum concentrations or secondary peaks might suggest development of secondary cerebral lesions in neurotraumatized patients. Increased serum protein S100B concentrations in peripheral circulation, without any apparent pathology verified by computerized tomography, could be valuable indicators of mild brain injury. The presence of protein S100B in peripheral circulation indicates to hematoencephalic barrier malfunction, and therefore it may be a marker of hematoencephalic barrier dysfunction or its higher permeability (20, 21).

Our study showed that maximal NSE concentrations were also found at 6 h after the injury. These initially high concentrations were significantly higher in patients with poor outcome. After a 6 h interval, a somewhat slower fall of NSE concentration was noted, with still significantly higher concentrations in patients with GOS 1–3, and with a secondary rise in concentrations on day 3, i.e. 72 hours after the brain injury in patients with poor outcome (GOS 1–3). Long-term increased NSE concentrations were monitored in patients with poor outcome with a secondary NSE peak. Such dynamics of changes was not recorded in the group of patients with good outcome (GOS 4,5). Secondary increase of NSE, on day 3 after the brain injury, may suggest the development of a secondary cerebral lesion or lethal outcome, which was confirmed by Raabe and Thelin (17, 18), as well as by Cheng et al. (12) in their meta-analysis.

According to the latest report made by Thelin et al. (22), the effects of multiple traumas on protein S100B levels were limited to the initial 12 hours after the injury, while the effect on NSE was much more intensive and significantly longer (up to 30 hours). Thelin et al. (23) mention that serum protein S100B levels are a very useful marker of the brain tissue 'future condition' in TBI.

It is intriguing that the levels of neuro-biomarkers were, at every time point, significantly higher in the group of patients who experienced poor outcome (GOS 1–3) than in those with good outcome (GOS 4,5) on day 14 after TBI. ROC curve defined NSE as a sensitive predictive marker of poor outcome and protein S100B as a specific predictive marker of mortality.

Conclusion

Both markers have good predictive ability. While NSE provides better discriminative potential for predicting poor outcome (poor vs. good outcome), protein S100B is a specific mortality predictor.

Conflict of interest statement

The authors stated that they have no conflicts of interest regarding the publication of this article.

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