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Temporal profile and clinical significance of serum neuron-specific enolase and S100 in ischemic and hemorrhagic stroke

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Abstract

Background: Neuron-specific enolase (NSE) and S100 protein are implicated in several brain injuries, including stroke. Our objective was to analyze the temporal profile and the clinical significance of NSE and S-100 in acute ischemic (IS) and intracerebral hemorrhage (ICH).

Methods: We studied 224 patients with IS and 44 patients with ICH. Computerized tomography (CT) scans were performed to assess infarct volume. Stroke severity was evaluated using the National Institute of Health Stroke Scale (NIHSS), and functional outcome at 3 months with the modified Rankin Scale (mRS). Serum NSE and S100 protein were measured using an electrochemiluminescence-immunoassay.

Results: Peak values were found at 72 h for NSE and at 24 h for S100 in IS. For ICH, peak values were found at 24 h for both NSE and S100. At these time intervals S100 and NSE correlated with the NIHSS score and were independently associated with poor outcome.

Conclusions: High serum NSE and S100 are associated with poor outcome in IS, and high serum NSE is associated with poor outcome in ICH. These findings suggest the potential utility of NSE and S100 as prognostic markers for acute stroke.

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Keywords: acute stroke; neuron-specific enolase; outcome; S100 protein.

Introduction

In recent years, biochemical markers of brain damage have gained particular attention. The study of molecular markers associated with stroke has proven to be useful for both diagnostic and prognostic purposes. Molecular markers of neurotoxicity (1) and inflammation (2, 3) have been associated with early neurological deterioration (4), infarct volume, hemorrhagic transformation (5, 6) and other clinical variables.

Protein S100 is a dimeric acidic calcium binding protein whose isoforms S100 and S100A1β are found predominantly in glial cells and Schwann cells (7–9). This protein performs intracellular functions, such as modulation of cytoskeleton proteins, regulation of cellular cycles, and extracellular functions, all of which are concentration dependent. Neuron-specific enolase (NSE) is the neuronal form of the intracytoplasmic glycolitic enzyme enolase. The γγ isoform is found in neurons, as well as in cells with neuroendocrine differentiation. This dimeric enzyme has a molecular weight of 78 kDa and catalyzes the interconversion of 2-phosphoglycerate and phosphoenolpyruvate (10). Since NSE is not secreted physiologically, an increase in serum and cerebrospinal fluid (CSF) concentrations is considered to be a marker for neuronal cell damage. Several studies have been performed to investigate its potential role as a peripheral biochemical marker for neuronal injury involving reactive gliosis, astrocytic death and/or blood-brain-barrier dysfunction (11).

Some studies have found correlation between NSE and S100 serum values and brain damage following stroke. However, the temporal profile of these biomarkers in serum is not clear because different peak values are found in the literature (12). In addition, there is some controversy regarding the best time-point for measuring NSE and S100 in serum. Different investigators describe the correlation between these biomarkers and clinical variables using various times (13–19).

We investigated the relationship between the temporal profile of proteins S100 and NSE and their correlation with clinical variables and functional outcome in a large series of patients with ischemic stroke (IS) and intracerebral hemorrhage (ICH).

Materials and methods

Study population and patients characteristics

Between May 2004 and September 2005, 355 patients with a first time stroke in the anterior territory of <12 h duration, and previously independent with respect to their daily living activities, were prospectively evaluated for inclusion. Patients with chronic inflammatory diseases ($n=7$), severe hepatic ($n=4$) or renal ($n=3$) diseases, hematological diseases ($n=3$), cancer ($n=5$), or infectious disease within

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15 days prior to admission (n = 11) and patients included in other clinical trials (n = 41) were excluded. Five patients did not agree to participate in the study and eight patients were lost to follow-up. Thus, a total of 224 patients (mean age 70.2 years, mean time from onset 7.2 h) with IS, and 44 patients (mean age 61.5 years, mean time from onset 4.7 h) with ICH were included.

This study was approved by the Ethics Committee of our hospital and was in accordance with the Helsinki Declaration of 1975, as revised in 1983. Informed consent was obtained from patients or their relatives.

Clinical variables

All patients were admitted in the Acute Stroke Unit and treated by the same unit staff according to the Guidelines of the Cerebrovascular Diseases Study Group of the Spanish Society of Neurology (20). Medical history, potential vascular risk factors, blood and coagulation testing, 12-lead ECG, chest radiography, and carotid ultrasonography were performed at admission.

Stroke severity was assessed by a certified neurologist using the National Institute of Health Stroke Scale (NIHSS) at admission, 1, 3, 7 ± 1 and 90 ± 7 days from onset of symptoms (21, 22). Functional outcome was evaluated at 90 days from onset of symptoms using the modified Rankin Scale (mRS) (22).

Neuroimaging studies

Computerized tomography (CT) scans were performed at admission and between days 4 and 7 of hospitalization. Early CT signs of infarction were evaluated upon admission, and infarct and ICH volume were assessed using the second CT-scan. Infarct and ICH volume were calculated using the radiographic plate with the formula $0.5 \times a \times b \times c$ (where a is the maximal longitudinal diameter, b is the maximal transverse diameter perpendicular to a, and c is the number of 10 mm slices from the site of infarct or hemorrhage).

All CT scans were evaluated by neuroradiologists blinded to the clinical and biochemical data.

Outcome variables

The primary endpoint was poor functional outcome defined as mRS >2 at 90 days from onset of symptoms.

Laboratory tests

Blood samples, drawn from all patients at admission, 24 and 72 h, were collected in test tubes, centrifuged at 3000 *g* for 10 min, and immediately frozen and stored at –80°C. Serum NSE and S100 (Isoforms S100 and S100A1β) concentrations were measured with an electrochemiluminescence immunoassay using the ELECSYS 2010 (Roche Diagnostics, Penzberg, Germany). This technique is based on a double sandwich assay using antibodies bound with ruthenium (luminescent label). Sensitivity of the method is 0.05 ng/mL for NSE and 0.005 μg/L for S100. The inter-assay variability was 4.2% for NSE and 2.4% for S100 determinations.

Determinations were performed in an independent laboratory blinded to clinical and neuroimaging data.

Statistical analysis

Results are expressed as percentages for categorical variables and as means (SD) or medians [quartiles] for continuous variables. Proportions were compared using the χ^2-test. Student's t-test or the Mann-Whitney test were used to compare continuous variables between groups. Spearman analysis was used for bivariate correlations.

The influence of the molecular profile of NSE and S100 protein on functional outcome was assessed using logistic regression analysis after adjusting for main baseline variables related to outcome in the univariate analyses (enter approach and probability of entry $p < 0.05$). Results were expressed as adjusted odds ratios (OR) with the corresponding 95% confidence intervals (95% CI).

Results

Baseline clinical characteristics, vascular risk factors, stroke subtype, biochemical parameters, neuroimaging findings and molecular markers in patients with IS or ICH are shown in Table 1. Poor outcomes (mRS >2) were found in 39.3% of patients with IS and in 59.1% of patients with ICH. For patients with IS, peak values were seen at 72 h for NSE (10.4 ng/mL) and at 24 h for S100 (0.15 μg/L). However, for subjects with ICH, peak values were seen at 24 h for both NSE (13.5 ng/mL) and S100 (0.13 μg/L) (Figure 1). At these time intervals, S100 and NSE concentrations correlated with greater NIHSS scores at the same time. In fact, NSE serum concentrations correlated with NIHSS for IS at 72 h ($r = 0.319$, $p < 0.0001$) and at 24 h for ICH ($r = 0.407$, $p < 0.0001$). Serum concentrations of S100 were associated with NIHSS for IS ($r = 0.558$) and ICH ($r = 0.607$) at 24 h (all $p < 0.0001$). In addition, concentrations correlated with infarct volumes determined between the 4th and 7th days (NSE serum concentrations at 72 h: Spearman coefficient 0.456, $p = 0.002$; S100 serum concentrations at 24 h: Spearmen coefficient 0.714, $p < 0.0001$).

Table 2 shows the temporary profile of molecular markers in patients with poor or good functional outcome in IS or ICH. Patients with IS who had a poor outcome showed greater serum concentrations of NSE at 72 h and S100 at 24 h (13.7 [8.2, 15.9] vs. 8.9 [5.3, 11.6] ng/mL; $p < 0.0001$) and (0.28 [0.12, 0.46] vs. 0.11 [0.07, 0.28] μg/L; $p < 0.0001$), respectively. Also, serum concentrations of NSE at 24 h were significantly greater for ICH patients with poor outcome compared to those with good outcome (17.8 [13.4, 21.5] vs. 11.6 [8.1, 14.2] ng/mL; $p < 0.0001$).

After adjustment for variables that were significant in the univariate analysis, NSE at 72 h (OR, 2.9; 95% CI, 1.3–8.5; $p = 0.032$) and S100 at 24 h in patients with IS were independent markers for poor outcome (OR, 4.7; 95% CI, 2.5–7.6; $p < 0.0001$). Also, after adjustment for variables that were significant in the univariate analysis, NSE at 24 h in ICH was independently associated with poor outcome (OR, 2.6; 95% CI, 1.9–15.6; $p = 0.038$).

Discussion

Peripheral markers of injury to the central nervous system may help in the diagnosis and management of IS (23). This prospective study evaluates the rela-

Table 1 Baseline clinical characteristics, vascular risk factors, stroke subtype, biochemical parameters, neuroimaging findings and molecular markers in patients with acute ischemic or hemorrhagic stroke.

	Acute stroke	
	Ischemic n = 224	Hemorrhagic n = 44
Epidemiological variables		
Age, years	70.2 (5.6)	61.5 (12.7)
Male, %	69.6	59.1
Time from stroke onset, h	7.2 (4.5)	4.7 (2.9)
History of hypertension, %	52.2	60.0
History of diabetes, %	17.3	14.8
History of dyslipemia, %	23.3	20.4
Smoking habit, %	15.4	15.0
Clinical characteristics		
NIHSS at admission	9 [5, 15]	12 [6, 16]
NIHSS at 1 day	6 [2, 12]	8 [3, 13]
NIHSS at 3 days	4 [1, 11]	7 [1, 15]
Early neurological deterioration, %	18.7	29.5
Stroke subtype (TOAST)		
Atherothrombotic, %	13.3	–
Cardioembolic, %	37.8	–
Lacunar, %	11.0	–
Undetermined, %	34.4	–
Others, %	3.3	–
Dead patients in the first 3 months, %	2.1	11.0
mRS >2 at 3 months, %	39.3	59.1
Neuroimaging findings		
Infarct or ICH volume, cm^3	18 [0–54]	19 [10–30]
Biochemistry and vital signs		
Mean systolic blood pressure, mm Hg	149.0 (22.1)	180.1 (30.2)
Mean diastolic blood pressure, mm Hg	79.2 (14.6)	98.1 (20.3)
Glucose concentration, mmol/L	67.72 [56.06–81.04]	67.16 [61.61–89.37]
Temporal profile of molecular markers		
NSE serum concentration at admission, ng/mL	8.6 [5.7, 10.9]	8.9 [7.4, 12.2]
NSE serum concentration at 24 h, ng/mL	9.1 [6.9, 10.9]	13.5 [9.7, 15.1]
NSE serum concentration at 72 h, ng/mL	10.4 [7.3, 13.6]	10.5 [6.7, 15.1]
S100 serum concentration at admission, μg/L	0.07 [0.05–0.11]	0.08 [0.07–0.15]
S100 serum concentration at 24 h, μg/L	0.15 [0.07, 0.32]	0.13 [0.06, 0.27]
S100 serum concentration at 72 h, μg/L	0.06 [0.04–0.16]	0.12 [0.09–0.23]

Data are given as percentages for categorical variables and as means (SD) or medians [quartiles] for continuous variables.

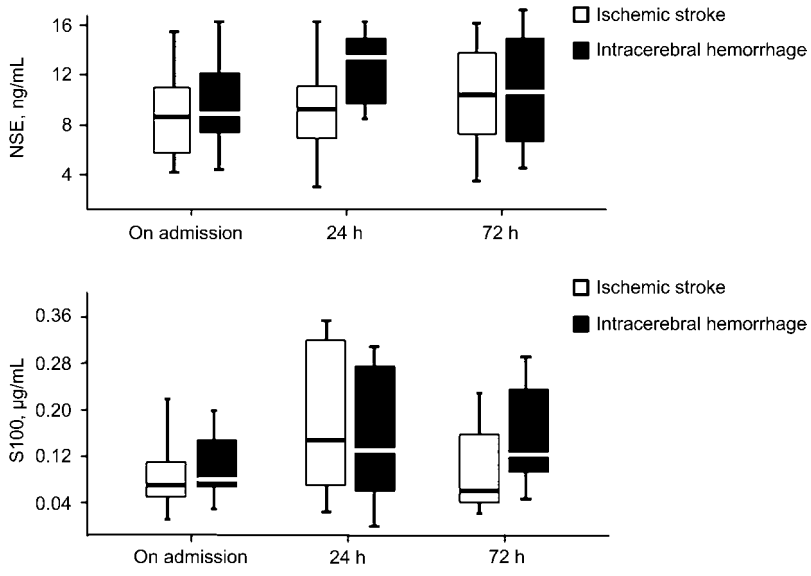

Figure 1 Temporal profile (admission, 24 h and 72 h) of serum concentrations of NSE and S100 protein in acute ischemic and hemorrhagic stroke.
Boxplots show median values (horizontal lines inside the box), quartiles (box boundaries), and the largest and smallest observed values (lines drawn from the end of the box).

Table 2 Temporal profile of molecular markers in patients with poor or good outcome classified in ischemic or hemorrhagic stroke.

	Good outcome (mRS ≤ 2)	Poor outcome (mRS > 2)	p-Value
Ischemic stroke	n = 136	n = 88	
NSE serum concentration at admission	8.5 [5.2, 11.9]	9.2 [5.3, 12.1]	0.067
NSE serum concentration at 24 h	8.5 [5.1, 11.6]	10.8 [5.2, 13.4]	0.057
NSE serum concentration at 72 h	8.9 [5.3, 11.6]	13.7 [8.2, 15.9]	<0.0001
S100 serum concentration at admission	0.06 [0.05, 0.12]	0.08 [0.05, 0.15]	0.064
S100 serum concentration at 24 h	0.11 [0.07, 0.28]	0.28 [0.12, 0.46]	<0.0001
S100 serum concentration at 72 h	0.06 [0.03, 0.17]	0.06 [0.05, 0.14]	0.832
Hemorrhagic stroke	n = 18	n = 26	
NSE serum concentration at admission	7.4 [6.5, 10.8]	9.3 [7.2, 13.6]	0.052
NSE serum concentration at 24 h	11.6 [8.1, 14.2]	17.8 [13.4, 21.5]	<0.0001
NSE serum concentration at 72 h	8.2 [5.5, 14.0]	12.2 [5.9, 18.6]	0.061
S100 serum concentration at admission	0.08 [0.06, 0.14]	0.08 [0.05, 0.15]	0.369
S100 serum concentration at 24 h	0.12 [0.05, 0.23]	0.14 [0.09, 0.31]	0.174
S100 serum concentration at 72 h	0.06 [0.02, 0.21]	0.07 [0.02, 0.30]	0.805

Data are given as medians [quartiles].

tionship between serum concentrations of NSE and S100 (Isoforms S100 and S100A1β) and functional outcomes in patients with IS or ICH. High serum concentrations of NSE at 72 h and S100 at 24 h following onset of stroke were associated with poor functional outcome in patients with IS. High serum concentrations of NSE 24 h following onset of stroke were associated with poor functional outcome in patients with ICH. In addition, at these time intervals we found correlation with molecular markers and infarct or hemorrhage volume.

We found that NSE at 72 h and S100 at 24 h for IS and NSE at 24 h for ICH are associated with functional outcome. Concentrations of these biomarkers at other time intervals did not show prognostic value. This demonstrates the importance of serial determinations of these biomarkers. Prognostic information is particularly relevant for estimating the risk of severe complications, and how intensive the rehabilitation program needs to be for individual patients. Several clinical scores are known to be predictive of outcome, but blood markers might also contain additional prognostic information. Because development of ischemia is a dynamic process, changes in NSE and S100 during the first 72 h following onset of stroke are relevant to outcome. We have demonstrated that NSE at 72 h and S100 at 24 h in patients with IS, and NSE at 24 h for patients with ICH are associated with poor functional outcome at 3 months. Thus, these biomarkers could provide additional information about the outcome of stroke patients.

The mean values of NSE in our laboratory were relatively low when compared to published cut-offs for normal values (12.5 ng/mL). It is known that measurement of NSE with the ELECSYS results in lower systematically concentrations (~9%). However, this method presents some advantages with respect to other ELISA methods. The ELECSYS has a low intra- and interassay coefficient of variation (0.7%–5.3%), reportable range between 0.0 and 320 ng/mL and a short incubation time of 18 min (24). In addition, in the study by Wunderlich et al. (19), the concentrations of NSE assessed with the LIAISON kit (DiaSorin, Diagnostica, Dietenzbach, Germany) exceeded the cut-off value of 12.5 ng/mL in 13% of stroke patients only, during the first 24 h.

Comparing the association of these molecular markers with functional outcome, we found that similar studies conducted by Jauch et al. (25) on patients with acute IS showed that the strongest correlation between NSE and S100 concentrations and outcome was seen in samples drawn within 24 h from onset of stroke. Likewise, our results are in agreement with those reported by Martens et al. (26) who used serum concentrations of S100 protein at 24 h as a marker for cerebral damage in patients affected with global cerebral ischemia. However, our finding contrasts with the study of Cunningham et al. (27) who reported correlation between NSE concentrations and infarct volume, but not with outcome. This study evaluated a total of 24 patients only, which might explain the lack of an association with outcome. Other studies have found a correlation between S100 concentrations and outcome in patients with subarachnoid hemorrhage (28, 29).

The analysis of the expression profile of these proteins revealed that the highest concentrations for NSE and for S100 were seen at 24 h in patients with ICH, whereas, patients with IS showed highest concentrations of NSE and S100 at 72 h and 24 h, respectively. These results are in agreement with previous studies that show a peak value at 24 h for NSE concentrations in patients with IS, as well as those treated with tissue plasminogen activator (tPA) (30). However, other investigators report peak concentrations 2–3 or more days following onset (17, 30, 31).

In this prospective study, we analyzed the relationship between serum concentrations of NSE and S100 proteins with neurological and functional outcomes in more than 200 patients with IS and more than 40 patients with ICH. Other studies have been carried out using different evaluation scales for functional outcome, such as the Glasgow Outcome Score, studying shorter evolution times, differentiating the infarcts by territories and using smaller number of patients. These variables may explain why many of the results

reported previously could be different with those reported in our study (32).

In summary, high serum concentrations of NSE at 72 h and S100 at 24 h following stroke are associated with poor outcome in patients with IS. High serum concentrations of NSE at 24 h following stroke are associated with poor outcome in patients with ICH. These findings suggest the potential prognostic utility of these markers for acute stroke.

Conflict of interest statement

The authors state that they have not accepted any funding or support from an organization that may in any way gain or lose financially from the results of our study. We have not been employed by an organization that may in any way gain or lose financially from the results of our study and we do not have any other conflicting interests.

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