S-100 Protein and Neuron-Specific Enolase in Cerebrospinal Fluid and Serum: Markers of Cell Damage in Human Central Nervous System

Lennart Persson, MD, PhD, Hans-Göran Härdemark, MD, Jörgen Gustafsson, BSc, Gerd Rundström, BSc, Ib Mendel-Hartvig, PhD, Thomas Esscher, MD, PhD, and Sven Pahlman, PhD

The development of a radioimmunoassay for S-100 protein is described. This method was used in combination with a recently developed radioimmunoassay for neuron-specific enolase in cerebrospinal fluid and serum from 47 patients with cerebral infarction, transient ischemic attack, intracerebral hemorrhage, subarachnoid hemorrhage, and head injury. In cerebrospinal fluid, increased concentrations of both S-100 and neuron-specific enolase were found after large infarcts, whereas after small infarcts and transient ischemic attacks, only neuron-specific enolase increased. The increased concentrations of S-100 and/or neuron-specific enolase were noted 18 hours to 4 days after cerebral infarction and transient ischemic attacks. Cerebrospinal fluid concentrations of these proteins also reflected the severity of the disease in patients with intracerebral hematoma, subarachnoid hemorrhage, or head injury. Temporal changes in serum S-100 and neuron-specific enolase concentrations reflected the clinical course in 4 patients. In stroke patients, the S-100 and neuron-specific enolase concentrations may reflect the extent of brain damage and could be useful in selecting patients with major stroke for more aggressive treatment during the acute phase. (Stroke 1987;18:911-918)

S-100 is an acidic calcium-binding protein found in the brain as homodimers or heterodimers of 2 isomeric subunits, α and β, that have apparent molecular weights of 10.4 and 10.5 kD, respectively. S-100b (ββ-S-100) is present in high concentrations in glial cells and Schwann cells, S-100a (αβ-S-100) is present in glial cells but not in Schwann cells, and S-100αa (αα-S-100) is found exclusively in neurons. There are reports of S-100 in nonnervous tissues and cells such as adipose tissue, melanocytes, and T-lymphocytes. S-100 has been demonstrated in certain tumors such as glioma, melanoma, schwannoma, and highly differentiated neuroblastomas (ganglieneuroblastoma and ganglioneuroma).

Neuron-specific enolase (NSE, defined as γ-subunit of enolase) is predominantly present in neurons, neuroendocrine cells, and neuroendocrine tumors, although nonneuroendocrine cells, both malignant and nonmalignant, contain the γ-subunit at low concentrations. NSE has been demonstrated by enzymatic assay and immunoassay in tumor tissue and serum from patients with neuroblastoma and small-cell carcinoma of the lung and can therefore be used as a marker for these tumors.

Studies on cerebrospinal fluid (CSF) concentrations of S-100 and NSE in patients with neurologic lesions indicate a quantitative relation between the degree of cell damage in the central nervous system (CNS) and the concentration of these proteins in CSF. Thus, S-100 and NSE could be of potential use as markers for destructive processes in the CNS. Such markers would be useful not only for prognostic purposes but also to monitor the course of states such as ischemic stroke, subarachnoid hemorrhage (SAH), or severe head injury. Cell damage markers could also be of clinical value in evaluating the effect of measures to reduce cerebral cell damage such as vascular reconstruction, hemodilution, hyperventilation, and treatment with barbiturates, calcium blockers, or mannitol.

This study uses our radioimmunoassay (RIA) for NSE and the newly developed RIA for S-100 and examines the concentrations of these proteins in CSF and serum from patients with neurologic disorders involving cell damage.

Subjects and Methods

Patients

CSF and serum were collected from patients at the Departments of Neurosurgery and Neurology, Södersjukhuset, Stockholm. CSF was aspirated by lumbar puncture or via an intraventricular catheter. Serum was obtained from venous blood. The samples were frozen and kept at -20°C until analyzed.

We examined CSF from 43 patients and serum from 4 patients. In some cases, CSF and serum were consecutively sampled. As controls, we used lumbar CSF.
from 16 subjects investigated for symptoms such as headache or dizziness but in whom no organic disease could be found or who underwent myelography for suspected lumbar disk disease.

All CSF was taken from patients or control subjects in whom lumbar puncture or ventricular drainage were done for other reasons. The study was approved by the ethics committee of Karolinska Institutet, Stockholm.

Twenty-eight patients had cerebral infarction (CI) or transient ischemic attack (TIA); 27 of these patients were examined by computed tomography (CT, EMI scanner CT 1010) and/or 99mTc brain scintigraphy 2–6 days after the onset of symptoms. The CT scans were classified as normal (no signs of cerebral disease), small (hypodense area without mass effect), moderate (hypodense area with slight mass effect), or large cerebral infarct (hypodense area with a clear mass effect). The brain scintigraphy findings were classified as normal (no pathologic uptake), small (2–4 cm diam. uptake), moderate (5–6 cm diam. uptake), or large cerebral infarct (>6 cm diam. uptake). The CT scans of patients with intracerebral hemorrhage (ICH) were divided into 3 groups: small (hypodense area <5 ml), moderate (hypodense area 5–25 ml), or large intracerebral hemorrhage (hypodense area >25 ml). The clinical outcome of the patients was evaluated on discharge from the hospital using an outcome scale, with minor modifications suggested by Jennett and Bond: 0, good recovery (no residual symptoms); 1, minor disability (resumption of normal life); 2, moderate disability (independent in daily life); 3, severe disability (dependent for daily support); 4, vegetative state; or 5, death. The Mann-Whitney U test was used for statistical comparison of S-100 and NSE levels in ischemic stroke patients with lesions visible on CT and/or brain scintigraphy (see below).

**Purification of S-100 From Bovine and Human Brain**

During purification, S-100 was assayed by rocket immunoelectrophoresis using antiserum prepared against bovine α and β subunits of S-100 (Dakopatts a/s, Glostrup, Denmark). S-100 from bovine brain was prepared essentially as described by Moore and by Dannie and Levine. All purification steps were performed at 4°C. Bovine brain was homogenized in 10 mM Tris-HCl buffer (pH 7.4) containing 5 mM MgCl₂, 0.6 mM phenylmethylsulfonylfluoride, and 0.6 mM iodoacetic acid. After centrifugation at 100,000g for 45 minutes, the supernatant was taken for repeated ammonium sulfate precipitations at 50, 65, and 80% saturation, and the 80% supernatant was concentrated and dialyzed against Buffer A (10 mM Tris-HCl [pH 7.5], 1 mM of ethylene diamino tetraacetic acid [EDTA], and 1 mM 2-mercaptoethanol). This material was adsorbed on a DEAE-Sepharose CL-6B column (Pharmacia AB, Uppsala, Sweden), and S-100 immunoactivity was eluted by a linear gradient of NaCl in Buffer A running from 0 to 0.7 M NaCl.

S-100 from human brain was purified as described by Isobe et al.

**Sodium Dodecyl Sulfate-Polyacrylamide Gradient Gel Electrophoresis and Immunoblotting**

The S-100 preparation was analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) (gradient 12–20%) under reducing conditions as described by Laemmli. The proteins were stained with 0.05% Coomassie BB G-250. The molecular weight markers used were phosphorylase b (94 kD), bovine serum albumin (BSA) (67 kD), ovalbumin (43 kD), carbonic anhydrase (30 kD), trypsin inhibitor (20.1 kD), and α-lactalbumin (14.4 kD).

Immunoblotting was performed essentially as described by Towbin et al. Purified S-100 protein was run on SDS-PAGE (15–30% gradient), and the separated polypeptides were blotted onto a nitrocellulose filter. After blocking with 5% BSA and 0.25% hemoglobin, anti-S-100 antiserum (diluted 1:100, Dakopatts) was added. After washing, 125I-protein A (1 μg/ml, Pharmacia) was used to visualize the S-100 subunits by autoradiography.

**Radioimmunoassay for S-100**

The purified S-100 was labelled with 125I, using the chloramin T method. In the standard protocol for determination of S-100 in body fluids, 0.1 ml of the tracer (0.1 ng S-100, approximately 20,000 cpm), 0.1 ml of S-100 antiserum (1:3,600 dilution, Dakopatts), and 0.1 ml of the sample were incubated at room temperature overnight. Purified bovine S-100 was used as a standard. Bound S-100 tracer was separated from free tracer by precipitation of the immunocomplexes with sheep anti-rabbit IgG antibodies bound to Sepharose. All samples were determined in duplicate, and S-100 values were expressed as ng/ml body fluid.

**Determination of Neuron-Specific Enolase**

NSE was determined by a Pharmacia RIA as described by Pålman et al, using human NSE as a standard and an antiserum raised against human NSE.

**Results**

**Purification of Bovine S-100**

SDS-PAGE analysis of the purified S-100 immuno-reactive material showed 1 protein band with an apparent molecular weight of approximately 10 kDa (Figure 1A). The molecular weight and the immunologic identification of the 10-kDa protein during purification strongly suggested that the purified protein was S-100. The broad S-100 band indicated that the preparation contained both the α and the β subunits. This possibility was tested by immunoblotting. Two bands corresponding to the molecular weights of the α and β subunits were then identified by the S-100 antiserum (Figure 1C).

**S-100 Radioimmunoassay**

Autoradiographic analysis of 125I-labelled S-100 protein (Figure 1B) separated by SDS-PAGE showed, in addition to the 2 S-100 subunits, a minor impurity not detectable by Coomassie staining (Figure 1A) or
FIGURE 1. Sodium dodecylsulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and immunoblotting of purified, bovine S-100. A: Lane 1, Molecular weight markers (see “Subjects and Methods”). Lane 2, Bovine S-100 separated on polyacrylamide gradient gel (12–20%) and stained with Coomassie BB. B: Autoradiogram of 125I-labelled S-100 separated by SDS-PAGE as in A. C: S-100 protein separated on 15–30% polyacrylamide gel and immunoblotted as in “Subjects and Methods.” Arrow indicates S-100 protein.

immunoblotting (Figure 1C). Under the given conditions, RIA detected the equivalent of 1 ng S-100/ml. Cross-reactivity of the RIA with human S-100 was confirmed by competition experiments in which purified human S-100 protein fully competed with binding of the bovine S-100 standard. Thus, S-100 immunoreactivity measured in this RIA, in patient CSF, and in serum reflected the concentration of human S-100.

Cerebrospinal Fluid and Serum Concentrations of S-100 and Neuron-Specific Enolase Immunoreactivity in Controls

CSF S-100 values in control subjects ranged from < 1 to 6.8 ng/ml. CSF NSE values were <2 ng/ml in all but 1 case (2.4 ng/ml). Mean serum concentration of NSE in healthy controls was 7 ng/ml (SD 1.6 ng/ml, range <2–13 ng/ml) in 152 cases,7 and the mean serum concentration of S-100 was 5.3 ng/ml (SD 2.4 ng/ml, range 2.8–11.5 ng/ml) in 16 cases.

Cerebral Infarction and Transient Ischemic Attacks

CSF S-100 and NSE concentrations in 24 patients with CI (12 men, 5 women; mean age 59 years) or TIA (4 men, 3 women; mean age 58 years) are given in Table 1. Wide variations in S-100 and NSE concentrations were noted. However, a relation emerged be-

tween the concentrations of S-100 and NSE in CSF and the time between onset of stroke and lumbar puncture (Figure 2). Normal S-100 and NSE concentrations were noted 8 hours after the onset of stroke; CSF aspirated between 18 hours and 4 days after the onset of symptoms showed increased concentrations of S-100 and/or NSE in 17 of 20 patients; later, lower concentrations were found. The highest concentrations of the markers were found in patients with severe stroke, whereas lower concentrations were obtained in patients with less severe stroke or TIA (Table 1). No CT or brain scintigraphy changes were found in the 3 patients in whom the CSF markers were not increased during the 18 hours-to-4 days period; these 3 patients had minor disability. In CSF from the 7 patients with TIA, NSE was increased in 6 and S-100 was increased in 3; in 2, both NSE and S-100 were increased. Furthermore, the NSE concentrations were generally higher than the S-100 concentrations in patients with TIA, while the opposite was true for most patients with CI (Table 1).

In Figure 3, 19 patients in whom CSF was taken 18 hours to 4 days after ictus are grouped according to CT and/or brain scintigraphy findings and divided into groups with visible and nonvisible lesions. Compared with controls, NSE concentration was increased in the CSF of both the visible (p<0.001) and nonvisible groups (p<0.01), although higher values were obtained in patients with visible lesions (p<0.05). Increased levels of S-100 were predominantly found in the CSF of patients with visible lesions (p<0.01), whereas most patients with nonvisible lesions had lower levels of S-100 (p<0.05).

In 4 patients with ischemic stroke (2 men, 2 women; mean age 64 years), consecutive serum samples taken at various times after ictus were analyzed. In 2 patients, 1 with a small CI and 1 with TIA, serum S-100 and NSE were within the normal range (4–8 ng/ml for both markers). In the 2 other patients (1 moderate and 1 large CI), S-100 and NSE were increased and varied concomitantly, and the concentrations of the markers reflected fairly well the severity of the ischemic lesion, as exemplified in Figure 4.

Subarachnoid Hemorrhage Resulting From Aneurysm Rupture

CSF from 10 patients with SAH was studied. In all but 1, CSF was obtained via an intraventricular catheter. In the 1 patient in whom CSF was sampled 8 hours after SAH, the S-100 and NSE concentrations were normal. In CSF taken at >24 hours, the concentrations of the markers reflected the severity of the disease (Table 1). CSF was sampled consecutively in 3 of the 10 SAH patients.

Case 1. This patient was deeply unconscious on admission owing to rupture of an aneurysm and to a large intracerebral hematoma. After 2 operations (evacuation of hematoma and clipping) and a period in barbiturate coma, he died of brain herniation. The final deterioration was paralleled by a dramatic increase in CSF S-100 and NSE concentrations (Figure 5 Top).
Table 1. Clinical Diagnoses, Number of Patients, and Individual S-100 and NSE Concentrations in CSF

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>S-100 ng/ml</th>
<th>NSE ng/ml</th>
<th>Days from onset to first CSF sample</th>
<th>CT/BS</th>
<th>Outcome</th>
</tr>
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<tr>
<td>Cerebral infarction n = 17</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>8.2</td>
<td>4.2</td>
<td>0.75</td>
<td>nv/nv</td>
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<td>0.83</td>
<td>nv/nv</td>
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<tr>
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<td>&lt;2</td>
<td>1</td>
<td>nv/nv</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4.4</td>
<td>1.17</td>
<td>nv/nv</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>9</td>
<td>2</td>
<td>nv/nv</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4.9</td>
<td>3</td>
<td>nv/nv</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>3.2</td>
<td>&lt;2</td>
<td>4</td>
<td>nv/nv</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2.2</td>
<td>&lt;2</td>
<td>6</td>
<td>nv/nv</td>
<td>1</td>
<td></td>
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<tr>
<td>1.4</td>
<td>4.9</td>
<td>0.75</td>
<td>nv/nv</td>
<td>2</td>
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</tr>
<tr>
<td>1.4</td>
<td>2</td>
<td>0.33</td>
<td>small/small</td>
<td>1</td>
<td></td>
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<tr>
<td>40.0</td>
<td>10.5</td>
<td>2</td>
<td>small/¬</td>
<td>5*</td>
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<tr>
<td>14.4</td>
<td>7.5</td>
<td>2</td>
<td>small/small</td>
<td>3†</td>
<td></td>
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<tr>
<td>1.6</td>
<td>&lt;2</td>
<td>29</td>
<td>¬/¬</td>
<td>3†</td>
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<td>5.7</td>
<td>3</td>
<td>small/nv</td>
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<td>700</td>
<td>25</td>
<td>4</td>
<td>nv/small</td>
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<tr>
<td>3.4</td>
<td>10.5</td>
<td>4</td>
<td>large/small</td>
<td>1</td>
<td></td>
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<tr>
<td>7</td>
<td>&lt;2</td>
<td>4</td>
<td>small/nv</td>
<td>1</td>
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</tr>
<tr>
<td>460</td>
<td>23</td>
<td>2</td>
<td>large/small</td>
<td>3</td>
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<td>Transient ischemic attack n = 7</td>
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<td>2.9</td>
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<td>nv/nv</td>
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<td>11.4</td>
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<td>8.8</td>
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<td>7.6</td>
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<tr>
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<td>¬/¬</td>
<td>0</td>
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</tr>
<tr>
<td>&lt;1</td>
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<td>14</td>
<td>¬/¬</td>
<td>0</td>
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</tr>
<tr>
<td>&lt;1</td>
<td>4.1</td>
<td>14</td>
<td>nv/nv</td>
<td>0</td>
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</table>

NSE, neuron-specific enolase; CSF, cerebrospinal fluid; CT, computed tomography; BS, brain scintigraphy; nv, no visible lesion; —, not performed. For definition of lesion size and outcome, see text.

* Died from intercurrent disease 9 days after the ictus.
† Same patient.

Case 2. This patient developed angiographic vasospasm and ischemic symptoms after 2 SAHs. S-100 and especially NSE increased, and CT scan changes compatible with infarction developed (Figure 5 Middle).

Case 3. The third patient was in good condition on admission. Both the surgery and the postoperative period were uncomplicated, and she was discharged in an excellent state. The levels of S-100 and NSE in CSF were normal throughout this period (data not shown).

Other States

CSF from 5 patients with ICH was investigated (Table 1). A relation emerged between the concentrations of the markers, especially S-100, and clinical outcome. CSF from 4 patients with head injury was also studied (Table 1).

Case 4 had a severe head injury with acute subdural hematoma and intracerebral contusions. The first CSF sample was obtained about 48 hours after the trauma and showed high concentrations of S-100 and moderately increased NSE values, 38 and 8.6 ng/ml, respectively (Figure 5 Bottom). After surgery, the patient was treated with barbiturates, mannitol, and hyperventilation to control the intracranial pressure. Follow-up samples showed falling concentrations of the markers, and the patient recovered and was only slightly disabled after 2 months. Two patients with prolonged coma after head injury were investigated 6 days after trauma. Both showed normal serial CT scans, and the diagnosis of diffuse axonal injury was made. One showed raised concentrations of S-100 and NSE (12 and 6.8 ng/ml); this patient died after 4.5 months. The other had normal concentrations in CSF and was slowly recovering when discharged. The fourth patient with head injury had a postconcussional syndrome; CSF showed normal concentrations of both markers 50 days after trauma.

Discussion

In the present study, we used 2 newly developed RIAs for determining S-100 and NSE. The NSE RIA has been described previously and does not cross-react with α and β subunits of enolase. The S-100 RIA is based on an antiserum that recognizes both α and β subunits of enolase.
Table 1. (Continued)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>S-100 ng/ml</th>
<th>NSE ng/ml</th>
<th>Days from onset to first CSF sample</th>
<th>CT/BS</th>
<th>Outcome</th>
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<td>3</td>
<td>8</td>
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<td>&lt;2</td>
<td>1</td>
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<td></td>
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<td></td>
<td>12</td>
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<td>2.3</td>
<td>&lt;2</td>
<td>30</td>
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<td>1</td>
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subunits of bovine S-100, as evidenced by the immunoblotting experiments. Furthermore, the RIA recognizes human S-100 as shown by the competition studies with purified human S-100 protein. CSF concentrations of NSE and S-100 in controls, determined with these RIAs, largely agree with figures reported by others, although some authors demonstrated higher concentrations of NSE.

A conspicuous finding of the present study was that the concentrations of S-100 and NSE in lumbar or ventricular CSF varied according to time after the onset of symptoms. In ischemic stroke patients, concentrations of the markers were increased in CSF between 18 hours and 4 days after the ictus. The concentrations of the markers during this period appeared to reflect the severity of the disease.

It should be pointed out that of the 30 patients with CI, TIA, or ICH studied, only 1 died (of intercurrent disease); no patient became vegetative, and only 4 became severely disabled. Thus, the resulting brain damage in these patients was, as a whole, probably rather restricted, yet concentrations of the markers were increased in most cases if sampled during the 18 hours-to-4 days period. This suggests that both S-100 and NSE are sensitive markers of brain damage. A few patients with small lesions and low concentrations of S-100 and NSE suffered a poor outcome, probably because the lesion was located in a vulnerable area of the brain.

In the SAH patients, S-100 and NSE also seemed to be sensitive markers of brain damage, and their concentrations in CSF appeared to reflect the clinical course and severity of the disease. In some of the SAH patients, increased concentrations were also noted later than 4 days after ictus; this may be attributed to secondary brain damage (i.e., vasospasm). The dynamic changes in CSF concentrations of S-100 and NSE are further illustrated by the 2 cases of SAH in whom the markers were consecutively measured.

One rationale for analyzing both these markers is the possibility of differentiating between gray and white matter damage because S-100 is present mainly in glial cells and NSE mainly in neurons. In most of our
patients, both proteins were elevated in CSF if sampling was done within a certain time period. This is probably because most of the lesions (ischemic, traumatic, or other) involved both gray and white matter. In some cases, there was preponderance of one of the markers. In the patients with CI, concentrations of both S-100 and NSE as a rule increased, but in general the increase in S-100 concentration was greater than that of NSE. This contrasts with the findings in the TIA patients, in whom elevation of CSF NSE concentration dominated. The reason for the difference between CI and TIA is unclear, but it is well established that neurons are the cells in the CNS most sensitive to ischemia. Assuming that TIA represents the mildest form of recognizable cerebral ischemia, the preponderance of NSE in the CSF of such patients may reflect a selective vulnerability of neurons. Although TIA by definition is a reversible state, the presence of NSE and S-100 in CSF indicates that structural brain damage occurs in TIA.

When the concentrations of the markers in CSF from patients with ischemic stroke were related to CT and
brain scintigraphy findings instead of to clinical entities such as CI and TIA, a difference between S-100 and NSE emerged. In principle, NSE concentration was increased in patients with both visible and nonvisible lesions, whereas S-100 concentration was predominantly increased in patients with visible lesions. This suggests that the markers might distinguish between patients with larger (i.e., visible) infarcts on one hand, and patients with smaller (i.e., nonvisible) infarcts and TIA on the other.

S-100 and NSE can also be detected in serum. In ischemic stroke patients, the levels of the markers during the first days were related to the severity of the lesion. It should also be pointed out that the serum concentrations of S-100 and NSE were in the same range as or lower than the CSF concentrations found in patients with ischemic stroke. Thus, the increased concentrations of these markers in CSF were probably derived from damaged cerebral tissue rather than from serum.

In conclusion, the findings presented here indicate that early determination of CSF and serum S-100 and NSE concentrations in patients with cerebral lesions may reflect the extent of brain damage and that repeated measurements may be useful to follow the course of brain ischemia.

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References


KEY WORDS • S-100 protein • neuron-specific enolase • cerebrovascular disease • cerebrospinal fluid • subarachnoid hemorrhage
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