usefulness of serum measurement of NSE in patients with functioning and nonfunctioning (NF) pituitary adenomas.

We studied 36 patients (24 women, 12 men, ages 20–84 years, mean 47 years) with pituitary adenomas. Nineteen tumors secreted prolactin (PRL) and six growth hormone (GH), and 11 were NF adenomas. Control subjects (28) included 9 females and 19 males, ages 12–69 years (mean 36 years) without known pituitary disorders. The procedures followed for the use of these subjects were in accordance with the Helsinki Declaration of 1975, as revised in 1983.

Tumor patients were given a complete pituitary function test, including measurements of serum PRL, GH, corticotropin and (or) cortisol, thyrotropin, free thyroxine, luteinizing hormone, testosterone or estradiol-17β, and follicle-stimulating hormone. For serum NSE determination, venous blood samples were drawn without hemolysis from the antecubital vein, and centrifuged after 30 min. Each serum aliquot was stored frozen at −20°C until assayed with a commercial kit (Pharmacia, Saint Quentin en Yvelines, France). Normal NSE values were ≤12.5 μg/L.

Statistical analysis was performed with the nonparametric Mann–Whitney U-test and Spearman rank correlation. A P value <0.05 was considered significant.

The mean (±SD) serum NSE concentration was significantly higher in tumor patients than controls [7.5 ± 2.9 μg/L (range 1.0–16.5 μg/L) vs 5.0 ± 1.5 μg/L (range 2.3–9.9 μg/L) (P <0.001)]. In patients with tumors, serum NSE concentrations were within the reference interval in all but one subject. The mean serum NSE concentration was also significantly higher (P <0.003) in each subgroup of pituitary tumor group when compared with the control group. In patients with PRL, GH, and NF tumors, values were 6.9 ± 2.6 μg/L (range 1.0–12.0 μg/L), 8.1 ± 1.7 μg/L (range 5.7–10.0 μg/L), and 8.3 ± 3.7 μg/L (range 4.5–16.5 μg/L), respectively. Mean serum NSE concentrations were similar among the three subgroups of tumor patients. No significant correlation was found between serum PRL and NSE concentrations in patients with PRL adenoma.

We conclude that serum NSE is not a useful marker of pituitary adenomas and cannot distinguish among PRL, GH, and NF tumors.

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References


Age- and Sex-Related Changes of S-100 Protein Concentrations in Cerebrospinal Fluid and Serum in Patients with No Previous History of Neurological Disorder, Øystein Nygaard, Bodil Langbakken,1 and Bertil Ronner* (Depts. of Neurosurgery and 1Clin. Chem., Univ. Hosp. of Tromso, 9038 Tromso, Norway; *author for correspondence: fax + 47 77 62 70 52)

S-100 is a calcium-binding protein synthesized in astroglial cells in all parts of the central nervous system (CNS). It is present in the body in different subchains, of which the beta form (96%) predominates in the brain [1]. S-100 protein is normally not detectable in serum [1], but previous studies have demonstrated that increased S-100 concentrations in cerebrospinal fluid (CSF) are an index of the active phase of cell injury in patients with acute multiple sclerosis exacerbations, intracranial tumours, acute encephalomyelitis, and spinal cord compression [2]. High CSF concentrations of the S-100 protein have also been demonstrated in patients with glioblastoma, cerebral compression, polynuropathy, hydrocephalus, subarachnoid hemorrhage, encephalitis, meningitis, and cerebral infarction [3–8]. A previous study demonstrated age-related reference values for S-100 protein in CSF in children and adults with distinct neurological disorders [9].

We sampled serum and CSF from 75 men and 35 women undergoing various surgical procedures in spinal anesthesia. The patients had no actual or previous history of neurological disease. The study was performed to establish reference intervals of S-100 protein in CSF and serum.

From August 1995 to June 1996, serum and CSF samples were obtained from 110 patients undergoing surgery in spinal anesthesia. Before inclusion in the study, the patients answered a questionnaire concerning known neurological symptoms or diseases, and their hospital records were investigated. The inclusion criteria were as follows: no history of previous neurological symptoms or disease, no previous investigation in a neurological department, no present symptoms indicating any neurolog-
ical disease, no evidence of malignant disease, age between 20 and 89 years, and signed informed consent form. The patients were divided into three age groups: 20–39 years, 40–59 years, and 60–89 years.

To determine S-100 protein concentration, 1 mL of CSF was taken from the spinal needle (gauge 25) immediately before the spinal anesthesia was performed. Simultaneously, 5 mL of serum was taken from a venous cannula. The samples were stored at −70 °C within 10 min for later analysis.

The concentrations of S-100 protein in CSF and serum were analyzed by using a commercially available two-site IRMA kit (Sangtec Medical, Bromma, Sweden). Calibrators (1, 5, 10, and 20 μg/L), controls (high and low), and diluent (also used as zero calibrator) were delivered from Sangtec Medical. CSF and serum samples were diluted with phosphate buffer and subsequently incubated with a plastic bead coated with monoclonal anti-S-100 antibody. After a 1-h incubation, the beads were washed to remove any unbound material. 125I-labeled anti-S-100 antibody was added, and after a 2-h incubation and subsequent washing, the amount of radioactive label bound to immobilized S-100 was measured in a gamma counter.

The sensitivity was 0.13 μg/L S-100 protein, and the precision (CV) was: low concentration, 10%; high concentration, 5%.

The same calibration curves were used for CSF and serum, and each sample was analyzed in duplicate.

The procedure of collecting CSF from the 110 patients undergoing surgery in spinal anesthesia was approved by the ethical committee at the University Hospital of Tromso.

The scatter diagrams of S-100 protein contained one clear outlier (10.2 μg/L), which was excluded, resulting in a normal distribution of values. P-values for sex dependency were calculated by using a two-tailed Student’s t-test. The relation between age and S-100 protein in CSF in men and women was evaluated by using simple regression analysis. The median values and distribution percentiles in three age groups of men and women were estimated.

The mean age for men (n = 75) was 48 ± 15 years and for women (n = 35), 47 ± 15 years. The frequency distribution of age in men and women was equal.

S-100 protein was not detectable in any serum samples. There was a significant difference between men and women in S-100 protein concentrations in CSF (mean 1.9 ± 0.7 vs 1.5 ± 0.5 μg/L, P = 0.0026). Fig. 1 illustrates the S-100 protein concentrations as a function of age (years) in both sexes. Concentrations of S-100 protein in CSF increased with age in both sexes, but this relation was less pronounced in women.

Table 1 lists age-related percentiles for the distribution of S-100 protein concentrations in men and women.

This is the first report of reference values of S-100 protein in CSF in patients with no previous history of neurological disorder. In 1992, van Engelen et al. [9] reported age-related changes of S-100 protein concentrations in CSF from children and adults undergoing neurological examination but without evidence of an organic neurological disease. The present report confirms their results, demonstrating an increase of S-100 protein concentrations in CSF with age from 21 to 84 years. Furthermore, we found sex-related dependency of S-100 protein in CSF, with significantly higher concentrations in men than in women.

There are several explanations for an age-related increase in S-100 protein in CSF: (a) The age dependency reflects increasing myelin loss with age; (b) the S-100 protein concentrations in the cells increase with age, whereas the turnover of the cells remains constant; or (c) the increase could be a result of increased half-life attributable to a reduced CSF bulk flow at older age [9–12].

S-100 protein was not detectable in serum in the present material including only neurologically healthy patients. Detectable serum S-100 protein indicates damage to glial cells and a reduced integrity of the blood–brain barrier (BBB). Ingebrigtsen et al. [13] reported increased serum concentrations of S-100 protein in patients with minor
head injury. The protein was detectable in serum within 12 h after the injury, indicating a BBB dysfunction.

Persson et al. [6] demonstrated increased CSF concentrations of S-100 protein in ischemic stroke patients between 18 h and 4 days after the stroke. Thus, normal values of S-100 protein in CSF or serum do not exclude neurological disease, and serial measurements can elucidate the dynamics of the pathological process in relation to therapy.

The commercially available IRMA kit for analysis of S-100 protein in CSF and serum estimates values as low as 0.2 μg/L with an acceptable precision. In one sample, the calibrators and controls showed higher concentrations of the protein than described from the manufacturer. Consequently, a consistent use of local laboratory controls in addition to the ordinary delivered calibrators and controls is recommended.

Recently, Lamers et al. [7] evaluated the value of neuron-specific enolase, S-100 protein, and myelin basic protein in CSF in patients who underwent a diagnostic lumbar puncture for a clinical indication such as CNS infection or another neurological disorder. In patients with cerebrovascular accidents such as minor cerebral infarcts, a significant increase in S-100 protein in CSF was demonstrated. The authors conclude that the concentrations of proteins in CSF depend on several factors, such as the distance between the affected brain area and the CSF compartment, the severity and extent of brain damage, the regional variability of these proteins in the brain, and the possible degradation of these proteins by macrophages and (or) proteinases either locally or in the CSF.

Consequently, normal or increased concentrations of CSF-specific proteins in individual patients must be evaluated with caution. Although S-100 protein and other nervous-system-specific proteins are very sensitive indices of pathology [14], normal serum or CSF values do not exclude CNS disease.

The present study underlines the importance of considering both age and sex when S-100 protein concentrations in CSF are evaluated in patients with different neurological disorders.

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References

Serum Osteocalcin in 1634 Healthy Children, Michele Cioffi,* Anna Maria Molinari, Patrizia Gazzero, Bruno Di Finizio, Mario Fratta, Angela Deufemia, and Giovanni Alfredo Puca (Ist. di Patol. Generale e Oncol., Seconda Univ. degli Studi di Napoli, Larghetto S. Aniello a Caponapoli, 2, 80138 Napoli, Italy; *author for correspondence: fax +81/566-5695)

Osteocalcin or bone Gla protein (BGP) is a vitamin K-dependent, low-molecular-mass (5800 Da) 49 amino acid peptide synthesized by osteoblasts [1, 2]. Osteocalcin con-

Table 1. Percentiles for the distribution of S-100 protein concentrations (μg/L) in CSF in three age groups of patients with no previous history of neurological disorders.

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Men</th>
<th>Women</th>
</tr>
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<tbody>
<tr>
<td>P10</td>
<td>P25</td>
<td>P50</td>
</tr>
<tr>
<td>20–39</td>
<td>1.0</td>
<td>1.1</td>
</tr>
<tr>
<td>40–59</td>
<td>1.2</td>
<td>1.3</td>
</tr>
<tr>
<td>60–89</td>
<td>1.4</td>
<td>1.9</td>
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10th to 90th percentiles (P = percentile).