S-100 protein as marker of the blood-brain barrier disruption in children with internal hydrocephalus and epilepsy - a preliminary study

Sendrowski K[1], Sobaniec W[1], Sobaniec-Łotowska ME[2], Lewczuk P[1]

[1]Department of Child Neurology & Rehabilitation, [2]Department of Clinical Pathomorphology,
Medical University of Bialystok, Poland

Abstract

S-100 is a structural protein of the central nervous system. An elevated level of S-100 in CSF is generally considered to be a marker of nervous tissue damage. The presence of this protein in blood serum points to the functional and/or morphological disruption of the blood-brain barrier. We measured S-100 in the cerebrospinal fluid and blood of children with two of the most often observed pathological states in child neurology - internal hydrocephalus and epilepsy. High levels of S-100 in CSF were detectable in children with internal hydrocephalus. Increased blood levels of S-100 protein were detectable in both groups of paediatric patients. Our preliminary results indicate neuronal damage in internal hydrocephalus and morphological and/or functional disturbances of the blood-brain barrier (their increased permeability) in both above mentioned disabilities.

Key words: S-100 protein, blood-brain barrier, epilepsy, hydrocephalus.

Introduction

S-100 is a set of small, acidic, calcium-binding dimer proteins of approximately 20 kDa which are widely distributed in different tissues. The S-100 protein was first discovered by Moore in 1965 [1]. Dimeric combination of the α- and β-chain form three known subtypes: S-100ao (αα), S-100a (αβ) and S-100b (ββ). S-100b is regarded as nervous-system-specific protein and is present mainly in glial cells and Schwann cells [2]. The function of S-100 in the central nervous system (CNS) is only poorly understood. It is known that S-100 plays a role in neuronal plasticity and long-term potentiation processes [3, 4]. This protein is generally considered to be a marker of CNS damage [5]. Increased levels of S-100 in CSF or serum were measured after a variety of cerebral lesions and injuries, including stroke, severe head trauma, brain tumours, or multiple sclerosis.

Brain has its own unique and effective protective system that controls the process of active transport of chemical substances from blood to neurons and CSF. This system, known as the blood-brain barrier (BBB), is formed by complex tight junction of the brain capillary endothelial cells and segregates the circulating blood from interstitial fluid in the brain [6]. In normal conditions, S-100 does not cross the BBB. Levels of this protein in plasma are extremely low and approximately one third of the levels, found in the cerebrospinal fluid (CSF) [5]. Thus, opening the blood-brain barrier (BBB) would be expected to markedly increase plasma S-100 levels. Kapural et al. [7] suggest that S-100β is an early marker of BBB disruption that is not necessarily related to neuronal damage. We measured S-100 in children with two of the most often observed pathologic states in child neurology - internal hydrocephalus and epilepsy. Studies on the blood levels of S-100 protein in paediatric patients are very rare.

Material and methods

Two groups of patients: Group H - children with internal hydrocephalus and Group E - children with epilepsy were involved into the study.

Group H amounted to 4 patients in whom the shunt implantation was necessary. The CSF and blood samples were obtained just before the implantation. The control group included 5 healthy children, in whom only blood samples were taken to the study. Some level of S-100 protein has been detected at the Klinikum Grosshadern in Munich (Germany), using an

ADDRESS FOR CORRESPONDENCE:
Krzysztof Sendrowski
Department of Child Neurology & Rehabilitation
Medical University of Bialystok
Waszyngtona 17, 15-274 Bialystok, Poland
e-mail: krsen@mp.pl

Table 1. S-100 concentrations in CSF and serum in children with internal hydrocephalus.

Patient's number	S-100 in serum (μg/L)	S-100 in CSF (μg/L)
1.	0.065	0.790
2.	0.210	7.700
3.	0.140	11.500
4.	0.248	0.660

Table 2. S-100 concentrations in CSF and serum in children with epilepsy.

Patient's number	S-100 in serum (μg/L)	S-100 in CSF (μg/L)
1.	0.204	0.650
2.	0.280	0.620
3.	0.260	0.570
4.	0.230	0.340
5.	0.230	0.320
6.	0.134	0.300

immunofluorometric sandwich assay. Details of this method are described in [8]. In group E, there were 6 epileptic patients in whom lumbar puncture was performed to exclude infection of CNS. The CFS and blood samples were taken within 12 h after the seizure. The control group constituted 12 healthy children, in whom only blood samples were obtained. Levels of S-100 protein were measured, using the radioimmunometric assay (Sangtec, Sweden).

Results

Group H: The results, obtained Group E, are presented in Table 1. The range of S-100 concentration in CSF was 0.660-11.500 mg/ and. in blood serum - 0.065 - 0.248 μg/L respectively. In the healthy children, the median serum level of S-100 protein was 0.033 μg/L. The obtained data suggest that CSF levels of S-100 can be almost 8 times higher than those in serum of the same patients and that the concentration of S-100 in serum of children with hydrocephalus can be 8 times higher too than that in control group.

Group E: The results, obtained in Group E, are presented in Table 2. The range of S-100 concentration in CSF was 0.320 - 0.650 μg/L. In blood serum - 0.134 - 0.280 μg/L respectively. In all 12 cases of children in the control group, the level of S-100 in serum was lower than 0.010 μg/L. The obtained data suggest that CSF level of S-100 is 2-3 times higher than that in serum of the same epileptic children and that the concentration of S-100 in serum of epileptic children is15-20 times higher than that in control group.

Discussion

Several groups have reported increased CSF levels of S-100 protein in patients with lesions of the CNS [i.e. 9, 10] and a relationship between cell damage in the CNS and the concentration of S-100 in CSF [11]. There is evidence that CSF levels of S-100 may serve as quantitative markers of the extent of brain damage. However, especially in patients with intracranial pressure, lumbar puncture is contraindicated, due to the risk of transtentorial herniation. For these reasons, S-100 which is released from brain cells during brain damage, must be detectable in blood if it is to serve as a useful tool in clinical medicine. Otherwise, S-100 level in blood increased significantly when the BBB is disrupted and that is not necessarily related to neuronal damage [7]. Our study shows that CSF concentration of S-100 was only 2-3 times higher, compared to serum levels in the group of epileptic children. Similar results were found in healthy volunteers [5]. This fact does not point to any severe neuronal damage in epilepsy. Our results indicate an increased permeability of BBB in epilepsy and, in a less degree, in internal hydrocephalus. The obtained data can have practical meaning, especially in children affected by hydrocephalus [12]. Periodic controls of S-100 protein levels in blood may be a useful indicator of shunt function.

Conclusions

Increased blood levels of S-100 protein were detectable both in children with internal hydrocephalus and in those with epilepsy. Our results indicate morphological and/or functional disturbances of BBB (their increased permeability) in both above mentioned disabilities. Very high CSF levels of S-100 in Group H point to severe damage of the CNS tissues in children with internal hydrocephalus. There is no evidence of S-100 levels in CSF to the neuronal damage in epileptic children. We concluded that measuring the blood levels of S-100 protein may be a reproducible and less invasive method for determining the integrity of the BBB in children with internal hydrocephalus and epilepsy.

References

1. Moore BW. A soluble protein characteristic of the nervous system. Biochem Biophys Res Commun, 1965; 19: 739-44.
2. Isobe T, Takahashi K, Okuyama T. S-100a0 (alpha alpha) protein is present in neurons of the central nervous system. J Neurochem, 1984; 43: 1494-6.
3. Gerlai R, Wojtowicz JM, Marks A, Roder J. Overexpression of a calcium binding protein, S-100β, in astrocytes impairs synaptic plasticity and spatial learning in transgenic mice. Learn Mem, 1995; 2: 26-31.
4. Whitaker-Azmitia PM, Murphy R, Azmitia EC. Astroglial 5-HT1A receptors and S-100β in development and plasticity. Perspect Dev Neurobiol, 1994; 2: 233-8.
5. Grocott HP, Laskowitz DT, Newman MF. Markers of cerebral injury, In: The Brain and Cardiac Surgery, Newman SP, Harrison MJG [Eds] Harwood Academic Publishers, Amsterdam, 2001; pp. 113-42.
6. Reese TS, Karnovsky MJ. Fine structural localization

of a blood-brain barrier to exogenous peroxidase. J Cell Biol, 1967; 34: 207-17.

7. Kapural M, Krizanac-Bengez Lj, Barnett G, Perl J, Masaryk T, Apollo D, Rasmussen P, Mayberg MR, Janigro D. Serum S-100β as a possible marker of blood-brain barrier disruption. Brain Res, 2002; 940: 102-4.

8. Missler U, Wiesmann M. Measurement of S-100 protein in human blood and cerebrospinal fluid: analytical method and preliminary clinical results. Eur J Clin Chem Clin Biochem, 1995; 33: 743-8.

9. Mokuno K, Kato K, Kawai K, Matsuoka Y, Yanagi T, Sobue I. Neuron-specific enolase and S-100 protein levels in cerebrospinal fluid of patients with various neurological diseases. J Neurol Sci, 1983; 60: 443-51.

10. Persson L, Hardemark HG, Gustafsson J, Rundstrom G, Mendel-Hartvig I, Esscher T, Pahlman S. S-100 protein and neuron-specific enolase in cerebrospinal fluid and serum: markers of cell damage in human central nervous system. Stroke 1987; 18: 911-8.

11. Rosen H, Rosengren L, Herlitz J, Blomstrand C. Increased serum levels of the S-100 protein are associated with hypoxic brain damage after cardiac arrest. Stroke 1998; 29: 473-7.

12. Sendrowski K, Wiesmann M, Sobaniec W, Lewczuk P. The analysis of S-100 protein in CSF and serum in children with internal hydrocephalus (abstract). 71. Jahrestagung Deutsche Gesellschaft für Neurologie mit Fortbildungsakademie, München, 2-6 September 1998.