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Serum and cerebrospinal fluid S100B concentrations in patients with neurocysticercosis

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Abstract

The clinical manifestations of neurocysticercosis (NC) are varied and depend on the number and location of cysts, as well as on the host immune response. Symptoms usually occur in NC when cysticerci enter a degenerative course associated with an inflammatory response. The expression of brain damage markers may be expected to increase during this phase. S100B is a calcium-binding protein produced and released predominantly by astrocytes that has been used as a marker of reactive gliosis and astrocytic death in many pathological conditions. The aim of the present study was to investigate the levels of S100B in patients in different phases of NC evolution. Cerebrospinal fluid and serum S100B concentrations were measured in 25 patients with NC: 14 patients with degenerative cysts (D), 8 patients with viable cysts (V) and 3 patients with inactive cysts. All NC patients, except 1, had five or less cysts. In most of them, symptoms had been present for at least 1 month before sample collection. Samples from 8 normal controls (C) were also assayed. The albumin quotient was used to estimate the blood-brain barrier permeability. There were no significant differences in serum (P = 0.5) or cerebrospinal fluid (P = 0.91) S100B levels among the V, D, and C groups. These findings suggest that parenchymal changes associated with a relatively small number of degenerating cysts probably have a negligible impact on glial tissue.

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- Neurocysticercosis
- S100B
- Cerebrospinal fluid
- Albumin quotient
- Glial marker

Introduction

Over the last decades, several neurobiochemical markers have been proposed as monitoring tools for brain damage associated with neurological disorders. Among them, those most extensively studied are neuron-specific enolase (NSE), creatine kinase isoenzyme BB, 14-3-3 protein, myelin basic protein, tau protein, polyamines, glial fibrillary acidic protein, and S100B protein (1-5).

Protein S100 is a calcium-binding dimeric protein composed of two immuno-

logically distinct subunits, α and ß. Its ßß dimeric form, which predominates in the central nervous system (CNS), is referred to as S100B (6). S100B is produced and released predominantly by astrocytes in physiological and pathological conditions. Depending on its extracellular concentration, S100B can play a trophic or toxic role in both neurons and glial cells (7).

Increased S100B levels in cerebrospinal fluid (CSF) and serum are related to reactive gliosis and astrocyte death (8). Therefore, S100B has been used as a marker of glial damage in several neurological disorders such as traumatic brain injury (2), stroke (9), cardiac arrest (10), cardiac surgery (11), and infectious diseases (12).

Neurocysticercosis (NC) is a major public health problem in several developing countries, and is occurring with increasing frequency in some developed nations due to migration and tourism (13). This parasitic disease is caused by cysticerci, which are the encysted larval form of the tapeworm *Taenia solium*. Humans acquire NC by ingesting food or water contaminated with eggs of *T. solium* shed in the feces of human carriers, or by fecal-oral autoinfection (14). Cysticerci may remain viable in the CNS for several years. In this phase, the parasite modulates the host immune response and rarely causes symptoms (15). Symptomatic disease usually occurs when cysticerci enter a degenerative course associated with the inflammatory response, but symptoms also depend on the number, size and localization of cysts within the CNS (15). Seizures, focal neurological signs, and intracranial hypertension are the most common clinical manifestations (16).

We have recently shown that serum and CSF NSE levels in patients with both active and degenerative forms of NC do not differ from those of normal controls, suggesting that the associated perilesional inflammatory reaction of degenerating cysts does not seem to provoke neuron-related damage (17). Alternatively, since NSE is a neuronal marker (4), its measurement may neglect injuries or alterations related to other types of CNS cells, particularly glial cells. Therefore, the aim of the present study was to investigate the possible role of S100B, a glial marker, in different evolutionary phases of the cysticercus and/or CSF inflammatory changes by measuring S100B levels in CSF and serum samples from patients with NC.

Subjects and Methods

Subjects

The study was approved by the Research Ethics Committee of the University of São Paulo School of Medicine at Ribeirão Preto, and written informed consent was obtained from all subjects before lumbar puncture (LP). All patients included in this study were chosen prospectively among patients who underwent LP due to medical indication. A total of 33 subjects, 16 men and 17 women ranging in age from 16 to 70 years (mean = 42, median = 40), were enrolled in the study. Twenty-five patients had NC and 8 normal subjects were included in the control (C) group.

The diagnosis of NC, definitive or probable, was determined by a combination of neuroimaging (computed tomography and magnetic resonance imaging), CSF analysis including a CSF enzyme-linked immunosorbent assay (ELISA) for NC, epidemiological data, and clinical findings (18). The definitive diagnosis of NC was made in 20 of 25 patients (80%), and a probable diagnosis was made in the remaining 5 patients (20%; 3 with the inactive form, 1 with the viable form and 1 with the degenerative form).

Patients were classified as proposed by Carpio et al. (19) and grouped according to the evolutionary phases of the cysticercus and/or CSF inflammatory changes as follows: viable (V), presence of one or more viable cysts without a CSF inflammatory

reaction; degenerative (D), presence of one or more degenerating cysts even in the presence of other viable or calcified cysts, or a positive CSF inflammatory reaction, even without the detection of cysts by neuroimaging; inactive, presence of only calcified cysts without CSF inflammatory changes.

Among the 25 NC patients studied, 8 had viable forms (V group; Table 1), 14 had degenerative forms (D group; Table 2) and 3 had inactive forms.

All NC patients presented <5 cysts, except patient D12, who had 30 cysts, and most of them were viable cysts. Only 2 patients in the D group had no detectable cysts by neuroimaging at the time of LP. The mean and the median number of cysts per patients were 3.6 and 2.0, respectively. The CSF ELISA for NC was positive in 10 of 14 patients (71%) in the D group and in 2 of 8 (25%) in the V group.

The following clinical data were analyzed: presence of seizures (partial or generalized) within 1 month before LP; the occurrence of clinical findings suggestive of intracranial hypertension (ICH, symptoms of headache, vomiting, with or without papilledema) confirmed by increased CSF pressure (>20 mmH_2O) and/or neuroimaging showing hydrocephalus or a mass effect, and use of corticosteroids by the time of enrollment. Six patients (5 from group D and 1 from group V, Tables 1 and 2) had chronic symptoms of ICH, all of them due to hydrocephalus. The hydrocephalus was mainly caused by arachnoiditis in the 5 patients from group D and by the presence of a cyst in the 4th ventricle in a patient from group V. Only 3 patients (from group D) needed to be treated with corticosteroids. Patient D6 had been using prednisone, 10 mg/day, for 2 months; patient D9 had been using dexamethasone, 4 mg/day, for 3 months, and patient D13 had been using prednisone, 5 mg/day, for 1 month.

Eight patients (3 from group V and 5 from group D, Tables 1 and 2) were treated with albendazole. In all of them, LP was performed on the 8th day of treatment (last day). None of these patients was using corticosteroids.

For the C group, we included patients without neurological or systemic disorders who underwent LP for spinal anesthesia for inguinal herniotomy or orthopedic surgeries, or patients with chronic headache who

Table 1. Serum and cerebrospinal fluid S100B concentrations, albumin quotient and clinical data in patients with viable (V) cysts.

Patient	Symp. Dur.	cS100B (ng/mL)	sS100B (ng/mL)	Qalb (x 10^{-3})	ICH	Seizures	Alben	Cort	Cells	CSF ELISA
V1	>1 month	2.25	0.03	4.95	Yes	No	No	No	2.0	Negative
V2	>1 month	4.18	0.04	3.53	No	No	Yes	No	1.0	Negative
V3	>1 month	0.90	0.00	2.00	No	Yes, PS (1 week)	Yes	No	3.0	Positive 1/64
V4	>1 month	36.17	0.02	0.74	No	No	No	No	2.0	Negative
V5	>1 month	0.86	0.04	4.96	No	Yes, PS (3 weeks)	No	No	1.6	Negative
V6	>1 month	3.39	0.06	2.33	No	No	Yes	No	1.3	Negative
V7	7 days	2.55	0.21	5.40	No	Yes, PS (1 week)	No	No	1.0	Negative
V8	>1 month	2.28	0.02	2.25	No	Yes, GS (5 h)	No	No	0.6	Positive 1/64
Mean		6.57	0.05	3.27					1.6	
Median		2.41	0.04	2.93					1.5	
SD		12.01	0.07	1.70					0.8	

Symp. Dur. = period of time since the onset of symptoms; cS100B = cerebrospinal fluid (CSF) S100B; sS100B = serum S100B; Qalb = albumin quotient; ICH = intracranial hypertension; Seizures = presence of seizures within 1 month before enrollment; PS = partial seizure; GS = generalized seizure; data in parentheses = time elapsed between the most recent seizure and CSF collection; Alben = albendazole use at the time of enrollment; Cort = corticosteroid use at the time of enrollment; Cells = number of CSF cells/mm^3; CSF ELISA = CSF enzyme-linked immunosorbent assay for neurocysticercosis.

had normal clinical examination, neuroimaging, CSF and other ancillary exams, and were finally diagnosed as having tension headache.

Cerebrospinal fluid and serum samples

CSF and peripheral blood samples were collected simultaneously and centrifuged for 10 min at 2500 *g*; 500 µL of the cell-free samples was immediately frozen and stored at -70ºC until analysis. These samples were collected at the same time as samples used in a previous NSE study (17). Hemolyzed serum samples and CSF samples containing erythrocytes were excluded. Control CSF samples were obtained at the time of LP performed for spinal anesthesia, before the anesthetic was injected. Quantitative determination of albumin by nephelometry (BN-100; Behring, Frankfurt, Germany) was also performed in serum and CSF samples. The CSF/serum albumin ratio (albumin quotient, Qalb) was used as a measure of blood-brain barrier permeability (20,21).

S100B protein concentrations were determined in a single series of measurements using a sensitive luminescence assay (BYK-Sangtec; Bromma, Stockholm, Sweden) as described (22). Briefly, this is a monoclonal two-site immunoassay that uses an antibody covalently bound to isoluminol as tracer. The samples were measured in duplicate and in those for which the coefficient of variation was above 10%, the measurement was repeated.

Statistical analysis

The Kruskal-Wallis test was used to compare age, CSF S100B (cS100B), serum S100B (sS100B) and Qalb among the D, V and C groups. The Mann-Whitney U-test was used to compare cS100B and sS100B between patients with or without ICH and between patients with or without seizures.

Table 2. Serum and cerebrospinal fluid S100B concentrations, albumin quotient and clinical data in patients with degenerative (D) cysts.

Patient	Symp. Dur.	cS100B (ng/mL)	sS100B (ng/mL)	Qalb (x 10^{-3})	ICH	Seizures	Alben	Cort	Cells	CSF ELISA
D1	>1 month	4.37	0.29	11.52	No	No	No	No	8.0	Negative
D2	>1 month	0.82	0.18	3.23	No	Yes, PS (2 h)	Yes	No	13.0	Positive 1/256
D3	>1 month	2.80	0.16	5.45	No	No	No	No	6.6	Negative
D4	>1 month	2.77	0.19	1.87	No	No	No	No	110.0	Positive 1/64
D5	20 days	3.56	0.03	8.72	No	Yes, PS (10 days)	Yes	No	24.3	Negative
D6	>1 month	10.62	0.03	5.96	Yes	No	No	Yes	43.0	Positive 1/256
D7	>1 month	2.17	0.15	2.35	Yes	No	Yes	No	40.0	Positive 1/1000
D8	>1 month	1.60	0.16	3.39	No	No	Yes	No	35.5	Positive 1/256
D9	>1 month	1.86	0.01	2.08	Yes	Yes, PS (2 days)	No	Yes	64.0	Positive 1/4000
D10	5 days	2.21	0.00	7.43	No	Yes, GS (5 days)	Yes	No	46.0	Positive 1/16
D11	>1 month	2.32	2.80	1.90	Yes	No	No	No	0.3	Positive 1/256
D12	7 days	1.87	0.01	6.92	No	No	No	No	2.3	Positive 1/16
D13	>1 month	2.02	0.11	4.63	Yes	No	No	Yes	15.3	Positive 1/1000
D14	>1 month	5.14	0.06	2.23	No	Yes, GS (3 weeks)	No	No	0.3	Negative
Mean		3.15	0.30	4.83					29.2	
Median		2.26	0.13	4.01					19.8	
SD		2.43	0.72	2.98					30.6	

Symp. Dur. = period of time since the onset of symptoms; cS100B = cerebrospinal fluid (CSF) S100B; sS100B = serum S100B; Qalb = albumin quotient; ICH = intracranial hypertension; Seizures = presence of seizures within 1 month before enrollment; PS = partial seizure; GS = generalized seizure; data in parentheses = time elapsed between the most recent seizure and CSF collection; Alben = albendazole use at the time of enrollment; Cort = corticosteroid use at the time of enrollment; Cells = number of CSF cells/mm^3; CSF ELISA = CSF enzyme-linked immunosorbent assay for neurocysticercosis.

Spearman's rank correlation coefficient was used to correlate S100B with age and several CSF and serum parameters. The level of significance was set at $P < 0.05$.

Results

There was no difference in age among persons in the V, D, and C groups (P = 0.54). S100B concentrations did not differ between males (cS100B: median = 3.02 ng/mL, interquartile interval, IQ: 2.12/4.16; sS100B: median = 0.04 ng/mL; IQ: 0.01/0.13) and females (cS100B: median = 2.28 ng/mL, IQ: 2.02/3.32; sS100B: median = 0.13 ng/mL, IQ: 0.03/0.19) (cS100B: P = 0.26; sS100B: P = 0.12). The values for the C group (N = 8) were: cS100B: median = 2.84 ng/mL, IQ: 2.11/3.40; sS100B: median = 0.08 ng/mL, IQ: 0.01/0.17; Qalb: median = 3.1×10^{-3}, IQ: $2.55 \times 10^{-3}/4.22 \times 10^{-3}$.

The 3 patients with the inactive form of the disease presented the following values: cS100B: median = 4.15 ng/mL, IQ: 3.74/4.57; sS100B: median = 0.14 ng/mL, IQ: 0.08/0.15; Qalb: median = 3.3×10^{-3}, IQ: $2.74 \times 10^{-3}/3.88 \times 10^{-3}$.

Comparisons among the V (Table 1), D (Table 2) and C groups did not demonstrate significant differences in cS100B (P = 0.91), Qalb (P = 0.55) or sS100B (P = 0.5) levels. There were no significant differences in S100B levels between NC patients with ICH (N = 6; cS100B: median = 2.21 ng/mL, IQ: 2.06/2.30; sS100B: median = 0.07 ng/mL, IQ: 0.03/0.14) and without ICH (N = 19; cS100B: median = 2.66 ng/mL, IQ: 1.80/3.71; sS100B: median = 0.05 ng/mL, IQ: 0.02/0.16) (cS100B: P = 0.47; sS100B: P = 0.98).

No differences were found between patients with seizures (N = 9; cS100B: median = 2.21 ng/mL, IQ: 0.90/2.55; sS100B: median = 0.03 ng/mL, IQ: 0.01/0.06) and without seizures (N = 16; cS100B: median = 3.06 ng/mL, IQ: 2.17/4.18; sS100B: median = 0.11 ng/mL, IQ: 0.03/0.16) (cS100B: P = 0.07; sS100B: P = 0.12).

There were no correlations between age and cS100B (r_s = 0.06; P = 0.72), CSF number of cells and cS100B (r_s = -0.27; P = 0.12), age and Qalb (r_s = 0.20; P = 0.24), cS100B and Qalb (r_s = 0.12; P = 0.49), sS100B and Qalb (r_s = 0.01; P = 0.94), or cS100B and sS100B (r_s = 0.17; P = 0.33).

Discussion

The immunological response that mediates both the viable and degenerative NC phases has been the subject of increasing research in recent years (23-28).

In the viable phase, the parasite prevents its elimination by modulating the host immune response (15). The early immune response associated with degenerating cysts seems to be mediated mainly by Th1 cytokines such as interleukin-2 (IL-2) and interferon-γ (29). Nevertheless, Th2 cytokines like IL-4 and IL-10, have also been detected in NC granulomas (30,31).

It has been proposed that Th1 cytokines, particularly ß IL-1 (IL-1ß) and tumor necrosis factor-α are toxic to the resident CNS cells (32,33), while the Th2 response is protective (34). Hence, one might expect that expression of brain damage surrogate markers would be increased in the degenerative phase of NC. However, in the present study, we found no differences in serum and CSF S100B levels between patients with both the viable and degenerative forms of NC and controls.

As suggested in our previous study concerning a marker for neuronal damage (NSE), which was shown to be within normal levels for all NC patients (17), no evidence of astrocytic-induced response/damage associated with degenerating cysts, assessed by the glial marker S100B, was found in this study as well. These results are also in agreement with data reported by Portela et al. (35) that revealed no changes in serum S100B levels in patients with epilepsy and chronic

NC. However, in their series only patients (N = 20) harboring inactive forms were considered. Hence, the present study extends these preliminary findings by including both serum and CSF analysis and by studying the other evolutionary phases of NC.

It is important to point out some limitations of our sample and experimental design, as also reported by us previously (17). First, the great majority of our patients had been symptomatic for at least 1 month before the LP, including the 6 patients with ICH (Tables 1 and 2). Some astrocytic damage may possibly have occurred at the onset of symptoms or at any time within this period, and at the time of LP, S100B levels had already returned to normal levels. It is not possible to verify this hypothesis since CSF collection was performed only when there was a clinical indication. In addition, there are obvious ethical reasons against the use of serial LP in NC patients. Second, studies regarding CSF abnormalities in NC almost always exclude patients with a large number of degenerating cysts (cysticercal encephalitis), in which LP is contraindicated due to brain edema.

In our study, only 3 patients were under corticosteroid therapy when serum and CSF samples were obtained. Since these patients also had normal S100B levels, we do not know whether or not corticosteroids affect S100B levels. To our knowledge, there is no conclusive experimental or clinical study describing the effect of corticosteroid treatment on S100B concentrations.

Regarding the treatment with albendazole, transient worsening of neurological symptoms can be expected during therapy. The aggravation of symptoms is probably not caused by the toxicity of albendazole, but rather by the host inflammatory response to the death of the parasite (14). In spite of this, we did not find any increase of S100B levels in our patients treated with albendazole, who were submitted to LP on the 8th day of treatment, suggesting that a putative increase in the inflammatory reaction was not sufficient to cause a glial response, at least in patients with a small number of cysts.

All patients in the present study had five or less cysts detected by neuroimaging, with the exception of one case from the D group (D12 in Table 2), who had 30 cysts (most of them viable forms) and also had normal S100B levels. The small number of cysts is this study is in agreement with the profile found in most NC patients (36,37). Two studies also performed in Latin America have indicated a small number of cysts per patient, one showing a range from 1.9 to 5.0 cysts, and the other a mean of 3.7 cysts (38,39).

In conclusion, we found normal levels of serum and CSF S100B in patients in different phases of NC. These findings suggest that the impact of cysticercotic lesions on glial tissue seems not to be sufficient to cause changes in S100B levels, at least in patients with a low cyst burden.

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