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CLINICAL AND CEREBROSPINAL FLUID (CSF) PROFILE AND CSF CRITERIA FOR THE DIAGNOSIS OF SPINAL CORD SCHISTOSOMIASIS

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ABSTRACT - *Objectives*: To describe the clinical and CSF findings among patients with presumptive neuroschistosomiasis (NS) and to suggest a classification for the CSF diagnosis of presumptive NS. *Method*: The charts of all patients whose CSF exam was performed at the CSF Lab, José Silveira Foundation, Salvador, Brazil, from 1988 to 2002 were reviewed. Those with clinically suspected NS whose indirect fluorescent antibody test (IFA) and or hemagglutination-inhibiting antibodies test (HAI) were positive to *S. mansoni* were identified. *Results*: Of 377 patients, 67.9% were males; the median age was 36 years (mean 37 $\pm$ 16 yrs, range 3-82 yrs). The most frequent complaints were paraparesis (59.9%), urinary retention (36.2%), lower limb pain (22.8%). WBC of CSF (count/mm^3) was > 4 in 66.0% (mean 83 $\pm$ 124, median 40, range 4.3-1,100), protein (mg/dl) was > 40 in 84.6% (mean 185 $\pm$ 519, median 81, range 41-6,800) and eosinophils were present in 46.9%. IFA and HAI were positive in 75.3%. WBC > 4 and presence of eosinophils were associated with IFA and HAI positive (67.3% *versus* 51.4%, p 0.014; 49.1% *versus* 23.0%, p 0.0001, respectively) and protein > 40 was not (85.4% *versus* 77.0%, p 0.09). Presence of WBC > 4, protein > 40 and eosinophils was associated with IFA and HAI positive (71.6% *versus* 38.2%, p 0.0003) but presence of eosinophils and any other combination of WBC and protein were not. *Conclusion*: NS should be considered as a possible diagnosis in patients who had had contact with schistosome-infected water and present with spinal cord compromising. Presence of IFA and HAI positive to *S. mansoni*, WBC > 4, protein > 40 and presence of eosinophils in the CSF may be considered as a criterium of highly probable presumptive diagnosis.

KEY WORDS: neuroschistosomiasis, cerebrospinal fluid, CSF diagnosis, myelitis, myeloradiculitis, *Schistosoma mansoni.*

Aspectos clínicos e liquóricos e critérios para o diagnóstico liquórico de esquistossomose medular

RESUMO - *Objetivos*: descrever aspectos clínicos e liquóricos de pacientes com diagnóstico presuntivo de neuroesquistossomose (NE) e sugerir uma classificação para o diagnóstico liquórico presuntivo da NE. *Método:* as fichas de todos os pacientes cujo exame de líquor (LCR) foi realizado no Laboratório de Líquor, Fundação José Silveira, Salvador, Brazil, entre 1988 e 2002, foram revistas. Aqueles com suspeita clínica de NE e teste de imunofluorescência indireta (IFI) e ou inibição da hemaglutinação (IHA) positivos para *S. mansoni* foram identificados. *Resultados*: dos 377 pacientes, 67,9% eram do sexo masculino, a mediana da idade foi 36 anos (média 37 $\pm$ 16 anos, variação 3-82 anos). As queixas mais freqüentes foram paraparesia (59,9%), retenção urinária (36,2%), dor em membros inferiores (22,8%). A celularidade do LCR (células/mm^3) foi > 4 em 66,0% (média 83 $\pm$ 124, mediana 40, variação 4,3 – 1.100), a proteína (mg/dl) foi > 40 em 84,6% (média 185 $\pm$ 519, mediana 81, variação 41-6.800) e eosinófilos estavam presentes em 46,9%. IFI e IHA foram positivas em 75,3%. Celularidade > 4 e presença de eosinófilos estiveram associadas com IFI e IHA positivas (67,3% *versus* 51,4%, p 0,014; 49,1% *versus* 23,0%, p 0,0001, respectivamente) e proteína > 40 não foi (85,4% *versus* 77,0%, p 0,09). Celularidade > 4, proteína > 40 e eosinófilos estiveram associados com IFI e IHA positivos (71,6% *versus* 38,2%, p 0,0003) mas a presença de eosinófilos e qualquer outra combinação de celularidade e proteína não estiveram. *Conclusão*: NE deve ser considerada uma possibilidade diagnóstica em pacientes que tiveram epidemiologia positiva para *S. mansoni* e desenvolveram uma mielopatia. A presença de IFI e IHA positivos para *S. mansoni*, celularidade > 4, proteína > 40 e presença de eosinófilos no líquor pode ser considerado critério de alta probabilidade para o diagnóstico presuntivo da NE.

PALAVRAS-CHAVE: neuroesquistossomose, líquor, diagnóstico liquórico, mielite, mielorradiculite, *Schistosoma mansoni.*

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Schistosomiasis infects over 200 million people worldwide, primarily children and young adults, being prevalent in Central and South Americas, Africa and Asia, where it has been considered an important issue of public health[1]. The specie *Schistossoma mansoni* infects around 12 million people in Brazil, where 30 more million people are exposed to schistosome-infected water, characterizing this country as an endemic area[2]. Out of the digestive system, the nervous system is the most common localization of the mansonic schistosomiasis[3]. Among the several presentations of the Neuroschistosomiasis (NS), the meningomyelorradiculitis is the most frequent[4]. Previous studies have reported an incidence of 5% to 6% of spinal cord schistosomiasis (SCS) among patients with non-traumatic or non-neoplastic myelopathy[5,6]. From post-mortem studies, it has been estimated that between 20% and 30% of patients with mansonic schistosomiasis have compromising of the nervous system and that the incidence of asymptomatic NS is 3 to 4 times higher the frequency of symptomatic NS[7-9].

Difficulties in recognizing NS have been described and attributed as one of the causal factors of the low frequency of diagnosis[10]. Some of these difficulties are the scarce knowledge about this illness among physicians, the incomplete or oligosymptomatic or transient evolution of some cases with little functional disturbances, and the operational difficulties at the health institutions regarding investigation and diagnosis[11]. It is important to highlight the necessity of thinking about SCS when any patient reporting contact with schistosome-infected water with non-traumatic myelopathy looks for health assistance[10], because the treatment is highly composed by oral medication and the prognosis is extremely favorable, if the disease is diagnosed and treated at an early stage[12-17].

The purposes of the present investigation are to describe the clinical and CSF findings among patients with presumptive SCS and to suggest a classification for the CSF diagnosis of presumptive SCS.

METHOD

The charts of all patients whose CSF exam was performed at the CSF Lab, José Silveira Foundation, in Salvador, Northeast Brazil, from September 1988 to May 2002, were reviewed. Those with clinically suspected SCS, who reported contact with schistosome-infected water, whose indirect fluorescent antibody test (IFA) and or hemagglutination inhibiting antibodies test (HAI) to *S. mansoni* were positive plus negative ELISA to HTLV-1 were identified. When the CSF samples had been collected before the availability of ELISA to HTLV-1, this test was performed by using frozen (-20°C) samples kept in the CSF base. All patients presented *S. mansoni* eggs in feces or in a biopsy specimen from the rectum.

Data collection was based on a questionnaire which asked for demographic and clinical features and on the CSF findings that were registered on the CSF Lab charts. Specific items were asked to those patients submitted to lumbar tap at the CSF Lab. Some samples of CSF were received in the CSF Lab accompanied by the syndromic diagnosis. The CSF examination was performed by the same person (OAMC), at the same Lab and included, in all samples, CSF WBC (white blood cell) and differential cell counts, concentration of protein, glucose, chloride, AST (glutamic-oxaloacetic transaminase) and LDH (lactate dehydrogenase), bacteriologic and mycologic exams (cultures for aerobic bacteria, fungus and *Mycobacterium tuberculosis* and specific stained-smears), IFA and HAI to *S. mansoni*, *Toxoplasma gondii* and *Cisticerccus cellulosae*, VDRL, FTA-ABS and HAI to *Treponema pallidum*, ELISA to *C. cellulosae* and HTLV-1. Whenever the protein concentration was > 160mg/dl, the CSF sample was diluted to the protein concentration equal to 80mg/dl. The IFA to *S. mansoni* was performed by using adult worm included in paraffin, when IgG antibodies were searched. Hypercytosis was defined as WBC count > 4 cells/mm^3 and protein concentration increase was defined as protein concentration > 40mg/dl. For this investigation, just the first CSF examination of each patient was considered. All taps were performed on the lumbar region.

Statistical analyzes were performed by using the Statistical Package for the Social Sciences (SPSS 9.0). Differences in proportions were assessed by the Pearson Chi Square test or Fisher's exact test, as appropriate. Means of continuous variables were compared by Mann-Whitney U. Confidence interval (95%) was reported for mean difference. The statistical tests were two tailed, with a significance level of 0.05.

RESULTS

Of 522 identified patients, ELISA to HTLV-1 was performed in 401 and was negative in 377, all of them also had negative tests to cysticercosis, syphilis and toxoplasmosis and constituted the group of patients for this study. Cancerous cells were also searched in all samples and were not identified in any of them.

There were 256 (67.9%) males and 121 (32.1%) females. Of 362 patients whose age was reported, the median age was 36 years (range 3 to 82 years, mean 37 $\pm$ 16 years). The distribution of age in strata is shown in Table 1. The frequency of clinical findings or syndromic diagnosis and respective duration are shown in Table 2. Hypercytosis was present in 249 (66%) of the samples (median WBC count 40 cells/mm^3, mean 83 $\pm$ 124, range 4.3 to 1,100 cells/mm^3).

Protein concentration increase was identified in 319 (84.6%) of the samples (median 81mg/dl, mean 185±519 mg/dl, range 41 to 6,800 mg/dl) and eosinophils were present in 177 (46.9%) (median 6%, mean 8%±10%, range 1% to 54%). The concentration of glucose, chloride, AST and LDH were under normal limits in all samples as well as all bacteriologic and mycologic exams were negative.

In order to search IgG antibodies to *S. mansoni*, IFA and HAI were performed in 368 (97.6%) and 309 (82.0%) of the CSF samples, respectively, both of them were performed in 300 (79.6%) and both were positive in 226 (75.3%). IFA was positive in 325 (86.2%) and HAI in 278 (73.7%). The comparison of the proportions and means of isolated CSF aspects with the positiveness of IFA and HAI to *S. mansoni* in CSF samples is presented in Tables 3 and 4, respectively. The association of combined CSF aspects

Table 1. Distribution of age of pacients with presumptive diagnosis of Spinal Cord Schistosomiasis, Salvador, 1988-2002.

Age stratum (years)	N	%
≤ 9	6	1.7
10-19	10	9.9
20-29	86	23.8
30-39	86	23.8
40-49	71	19.6
50-59	38	10.5
60-69	31	8.6
70-79	5	1.4
≥ 80	3	0.8

N, absolute number.

Table 2. Frequency of clinical findings or syndromic diagnosis and respective durations among pacients with presumptive spinal cord schistosomiasis, Salvador, 1988-2002.

Clinical Findings	N	%	Duration (days)					
			N	Median	Mean	SD	Minimum	Maximum
Paraparesis	226	59.9	208	45	317	905	3	21 years
Urinary retention	144	36.2	139	30	197	698	1	20 years
Lower limb (LL) pain	86	22.8	82	90	271	429	5	6 years
LL Paresthesia	77	20.4	65	90	208	360	4	6 years
Lumbar pain	56	14.9	53	30	144	304	3	4 years
Paraplegia	51	13.5	43	30	163	435	3	7 years
Tetraparesia	11	2.9	10	135	197	231	7	2 years
Mielorradiculitis	11	2.9	1	15	15	-	15	15
Sexual disfunction	9	2.4	7	730	472	331	21	2 years
Polineuropathy	4	1.1	3	730	1643	1741	548	10 years
Atrophy of 1 LL	4	1.1	4	730	881	734	240	5 years
Abdominal pain	3	0.8	3	90	88	63	25	150
Thoracic pain	3	0.8	2	55	55	49	20	90
4 limbs pain	3	0.8	3	120	167	180	15	365
Tetraplegia	2	0.5	2	53	53	52	16	90
Transverse mielitis	2	0.5	1	20	20	-	20	20
Thoracic and abdominal pain	1	0.3	1	30	30	-	30	30
Plegia of 1 LL	1	0.3	1	5	5	-	5	5

Table 3. Association between isolated CSF aspects with the positiveness of IFA and HAI S. mansoni in CSF (X^2).

	IFA and HAI			
	Two positive	One positive		
CSF Aspect*	(N=226)	(N=74)	Total (N=300)	p
Hypercytosis	67.3 (152)	51.4 (38)	63.3 (190)	0.014
Presence of Eosinophils	49.1 (111)	23.0 (17)	42.7 (128)	0.0001
Protein > 40 mg/dl	85.4 (193)	77.0 (57)	83.3 (250)	0.09
Protein > 60 mg/dl	62.4 (141)	45.9 (34)	58.3 (175)	0.01

*Results in % (n).

Table 4. Comparison between means of isolated CSF aspects with the positiveness of IFA and HAI to S. mansoni in CSF. †

	IFA and HAI			
CSF Aspect	Two positive	One positive	p	95% CI mean difference
WBC count	90 ± 142	46 ± 75	0.001	10, 77
Presence of Eosinophils	8 ± 10	6 ± 8	0.069	-2, 7
Protein > 40 mg/dl	216 ± 624	84 ± 64	0.001	42, 222

† Mann-Whitney U.

Table 5. Association between the presence of eosinophils and combined CSF aspects with the positiveness of IFA and HAI to S. mansoni in CSF.

	IFA and HAI			
CSF Aspect*	Two positive	One positive	Total	P
WBC > 4, protein > 40	71.6 (96/134)	38.2 (13/34)	64.9 (109/168)	0.0003†
WBC ≤ 4, protein ≤ 40	6.7 (1/15)	7.7 (1/13)	7.1 (2/28)	1‡
WBC > 4, protein ≤ 40	44.4 (8/18)	25.0 (1/4)	40.9 (9/22)	0.616‡
WBC ≤ 4, protein > 40	10.2 (6/59)	8.7 (2/23)	9.8 (8/82)	1‡

WBC = white blood cell. *Result in % (n/N), †X^2, ‡Fisher's exact test

and the positiveness of the immunologic tests to *S. mansoni* is shown in Table 5.

DISCUSSION

To the best of the authors' knowledge, this investigation presents the greatest number of studied patients with presumptive SCS. The second greatest study was published by Peregrino et al., when 80 patients were analyzed[18]. This characteristic may be explained by some factors: this study was conducted in Salvador, Northeast Brazil, an endemic zone of mansonic schistosomiasis[19], the study included patients submitted to lumbar tap during a 14-year period and the data were collected from the data base of the CSF Lab – José Silveira Foundation, where many patients seen at several Services of Neurology or Infectious Diseases in the state of Bahia and in other neighbouring states are sent to in order to be submitted to CSF examination.

The predominance of males and the age range from 20 to 50 years (Table 1) is according to the results previously reported in several other studies[4,10,18,20-22]. The predominance of males is attributed to a great exposition in the environment[23], added to professional activities that increase the intra-abdominal pressure[4]. The increase of the intra-

Table 6. Classification for the CSF diagnosis of NS.

Gold standard diagnosis depends on the development and standardization of a test that identify the antigens of *S. mansoni* in the CSF;

Presumptive diagnosis

highly probable when there are 2 positive immunologic reactions plus hypercytosis plus presence of eosinophil cells plus protein concentration increase;

probable when there are 2 positive immunologic reactions plus either hypercytosis and presence of eosinophil or hypercytosis and protein concentration > 60mg/dl or presence of eosinophil and protein concentration > 60mg/dl;

possible when there are 1 or 2 positive immunologic reactions plus either hypercytosis or presence of eosinophil cells or protein concentration increase.

abdominal and of the intra-spinal pressures concurrent with the maintenance of negative pressure in the epidural space predisposes to the migration of eggs or worms to the spinal cord by Batson's plexus[24]. It is important to highlight the little importance of portal hypertension in the pathogenesis of SCS[4], and the age in which the incidence of this illness is higher, compromising young adults, during the most productive phase of life, factors that emphasize the importance of the study of SCS.

The most frequent clinical findings, paraparesis, lower limb pain and urinary retention, and the frequency of paraplegia (13.5%), (Table 2) are consequences of the commonest location of the lesion of SCS, that is, *conus medullaris* and equine cauda[4,20]. The functional disturbances may be restrictive or disabling. In the present study, the clinical findings varied from 1 day up to 21 years, being the predominant duration ≤ 45 days at the time of the lumbar tap (Table 2). The SCS is an inflammatory disease, where the delayed-type hypersensitivity in response to antigens (eggs, worms) is the responsible for the neurological damage in the spinal cord[18]. Therefore, it is important to ensure an early diagnosis and treatment, in order to warrant a better prognosis and the preservation or recuperation of neurological functions[4,10,18,20-22,25].

The gold standard for the diagnosis of SCS is the demonstration of the pathologic process after a biopsy or a necropsy[10]. Nevertheless, the surgery to collect clinical specimen for biopsy is an invasive procedure that may compromise by itself the neurological function of the patient, and must be kept for doubtful or unresponsive cases[4,18,26]. The standardization and availability of tests to identify *S. mansoni* antigens in the CSF, such as the Polymerase Chain Reaction, will be an advance in the SCS diagnosis. Nevertheless, in the meantime, it is recommended to establish criteria for presumptive diagnosis and to know their reliability. The most recommended study would consist in determining the predictive value of a positive and of a negative test which depends on the presence or absence of the disease as determined with the gold standard[27]. Such a study was not feasible because of the difficulties mentioned previously[4,18,26].

The CSF reflects the inflammatory process that compromises the spinal cord very reliably[18]. In 1985, Livramento et al. described the syndrome of CSF in NS[28], when the immunologic reactions to *S. mansoni* in the CSF were standardized. This syndrome included lymphomononuclear hypercytosis associated with the presence of eosinophil cells, protein concentration increase and the presence of antibodies to *S. mansoni*[28]. In the present investigation, the presumptive diagnosis was strengthened by the presence of IgG antibodies to *S. mansoni* in two different tests. From the data shown in Tables 3 and 4, it is possible to infer that the intensity of hypercytosis and of the increase in protein concentration influence the association of those CSF aspects and the positiveness of the immunologic tests to *S. mansoni*, and that this is not the case of presence of eosinophil cells. For this latter CSF aspect, the association remains on the presence of eosinophil cells *per si*, without any influence of the intensity of its presence. The permanence of the association of concomitant hypercytosis, protein concentration increase and presence of eosinophil cells, with the positiveness of IFA and HAI to *S. mansoni* in the CSF (Table 5) demonstrates the importance of all these aspects of the syndrome of CSF for the presumptive diagnosis of SCS. From the foregoing data, a classification for the CSF diagnosis of presumptive NS is proposed in Figure 1. The difference among those levels (Table 6) is based on the analysis of the CSF abnormal findings intensity that may represent different probabilities of SCS. The specific treatment to SCS must be considered at any of those levels (Table 6) because the prognosis is_extremely favorable, if the disease is diagnosed and treated at an early stage[12-17]. It is important to emphasize that two negative immunologic reactions do not necessarily exclude the diagnosis of NS.

Every patient included in this study had mansonic schistosomiasis and neurological complaints that

may not have been due to SCS. CSF antibodies may have crossed the blood-CSF barrier and the neurological findings may have been due to another disease. The cause-effect relationship could have been established if the serum/CSF index of specific antibodies had been studied along with the investigation of the integrity of the blood-CSF barrier[29]. These procedures were not performed. Information about other complementary exams was not computed because such information was not regularly registered on the charts of the CSF Lab. Therefore, a prospective study is highly recommended in order to confirm our results.

For every patient with history of previous contact with schistosome-infected water, with compromise of spinal cord, it is important to consider the SCS as a possible diagnosis. The definitive diagnosis relies on the histopathological demonstration of the inflammatory process around the eggs or the worm in the spinal cord. The presumptive diagnosis of SCS must rely on history of exposure to schistosome-infected water, clinical findings, demonstration of schistosome eggs in feces or in a biopsy specimen from the rectum, CSF findings and exclusion of other illnesses that can cause the same symptoms.

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