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Childhood acute bacterial meningitis: risk factors for acute neurological complications and neurological sequelae

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Abstract

Objective: To assess acute neurological complications and neurological sequelae of childhood acute bacterial meningitis in order to determine possible warning signs.

Methods: This retrospective study evaluated children with acute bacterial meningitis (between 1 month and 14 years of age) admitted between 2003 and 2006.

Results: Of the 44 patients studied, 17 (38.6%) had acute neurological complications. Seizure was the most frequent (31.8%) complication. Patients with acute neurological complications showed a higher frequency of lower neutrophil count ($p = 0.03$), seizure at admission ($p < 0.01$), and *S. pneumoniae* as the etiologic agent ($p = 0.01$). Risk factors for the development of acute neurological complications were *S. pneumoniae* (odds ratio [OR] = 6.4, confidence interval [CI] 1.7-24.7) and neutrophil count < 60% ($p < 0.01$). Of the 35 patients who were followed up, 14 had neurological sequelae (40%). Behavioral change (22.9%) was the most frequent sequela. Seizures at admission (OR = 5.6, CI 1.2-25.9), cerebrospinal fluid protein concentration > 200 mg/dL ($p < 0.01$), and cerebrospinal fluid glucose concentration/glycemia ratio ($p < 0.01$) were identified as risk variables for sequelae.

Conclusion: Neutrophil count < 60%, seizure at admission, and *S. pneumoniae* as the etiologic agent were identified as warning signs for acute neurological complications, while protein levels, cerebrospinal fluid glucose concentration/glycemia ratio, and seizure at admission were seen as risk factors for neurological sequelae.

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Introduction

Acute bacterial meningitis (ABM) is an inflammatory process of the leptomeninges and the subarachnoid space.[1] Despite intensive care and therapeutic developments, the condition is still responsible for a high rate of morbidity and mortality.[2-4] It is among the 10 major causes of mortality from infectious disease over the world, mainly in the pediatric population.[5]

There are few studies conducted in Brazil or in countries with similar conditions regarding morbidity and lethality of ABM. Furthermore, few national and international studies have evaluated the association between acute neurological complications and initial clinical presentation, management and progress of patients, with focus on neurological sequelae, considering acute neurological complications as neurological sequelae or symptoms.[6-10]

We highlight the importance of making an effort to identify children more prone to develop acute neurological complications and neurological sequelae, so that a

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multidisciplinary team may plan a long-term follow-up and assure an adequate rehabilitation of those patients.[3,4] The objectives of the present study were to evaluate the acute neurological complications and the neurological sequelae resulting from ABM of unknown etiology, to characterize these children from a clinic and laboratory point of view, and to identify clinical/laboratory variables with potential to predict neurological sequelae and complications.

Methods

This was a cross-sectional, observational study conducted using a retrospective and analytical approach to evaluate the risk factors associated with neurological sequelae and acute complications in childhood ABM. The sample included 44 children between 1 month and 14 years of age, hospitalized at the Hospital de Clínicas of Universidade Federal do Paraná (HC-UFPR), Curitiba, state of Paraná, Brazil, between 2003 and 2006. They had ABM of known etiology and were selected from 458 cases reported as meningitis to the hospital surveillance unit. The inclusion criteria were ABM cases with agent identified from blood culture and/or bacterioscopy and/or cerebrospinal fluid culture and/or Latex, which were hospitalized and followed up by the pediatric infectious disease unit and which presented data available for the analysis of the medical records. We excluded ABM cases of other etiologies or of unknown etiology, cases of meningococcemia without meningeal involvement, presence of immunological or neurological conditions, previous neurosurgery, and posttraumatic meningitis. The dependent variables studied were acute neurological complications and neurological sequelae; the independent variables included the onset period and symptomatology, findings of general physical and neurological examination, laboratory test, and cerebrospinal fluid examination. We established a significance level of 5%, error type II of 10%, and magnitude effect of 15% for the sample calculation. Statistical treatment was performed with Statistica (Statsoft®), in which we used the Fischer's exact test for the study of categorical variables; and the Student's *t*-test and the Mann-Whitney test for the study of continuous variables of symmetric and asymmetric distribution, respectively. Multivariate logistic regression analysis model was used to identify the risk variables for the development of complications and/or neurological sequelae. For all the tests, we considered a minimum significance level of 5%, with power of 95%.

This study was approved by the Human Research Ethics Committee of the HC-UFPR.

Results

The study sample included 44 children, between 2 months and 145 months of age (median of 40 months), and 63.6% of them were male. The most frequent etiology agents were *Neisseria meningitidis* (56.8%) and *Streptococcus pneumoniae* (38.6%). Seventeen patients (38.6%) had acute neurological complications, and 64.7% of them were male, between two and 145 months of age (median of 8 months). The most frequent initial clinical manifestations among patients with neurological complications are listed in Table 1. The symptoms that presented significantly different frequencies between the groups were seizure ($p < 0.001$) and alteration of the level of consciousness ($p = 0.02$).

Regarding the findings in the physical examination, the presence of petechiae was more frequent in the group of children without neurological complications ($p = 0.02$). In relation to infants, bulging fontanelle was predominant among those with neurological complications ($p = 0.01$) (Table 1).

In Table 2, we present the results of complementary examinations in both groups. The values of neutrophils (% and total account) were significantly different between the groups.

The etiologic agent most commonly identified was *S. pneumoniae* in six out of nine positive blood cultures among the children with neurological complications, and in two out of five positive blood cultures in the group without complications.

In Table 3, the characteristics of the cerebrospinal fluid examination are presented.

Duration of use of antibiotics was significantly superior among children with acute neurological complications (18 versus eight days; $p < 0.001$) and the need of intensive therapy was similar between the groups, occurring in about half of the cases ($p = 0.35$). The median of the period of hospitalization was 18 days (1-40 days) in the group with complications and nine days (3-14 days) among the children without complications ($p < 0.001$). Two patients were deceased, both with acute neurological complications.

The main acute neurological complications recorded were convulsive crisis (82.3%), cranial nerve compromise (52.9%), convulsive status epilepticus (41.2%), coma (41.2%), motor deficit (35.3%), ataxia (23.5%), and behavioral alterations (11.8%).

Patients with acute neurological complications presented higher frequency of neutropenia ($p = 0.03$), convulsive crisis at admission ($p < 0.01$), and *S. pneumoniae* as etiologic agent ($p = 0.01$). Other variables were focal neurological deficit ($p = 0.06$), shock ($p = 0.07$), irritability ($p = 0.08$), and the need of intermittent mechanical ventilation during hospitalization ($p = 0.05$).

We observed a tendency of inverse correlation between age and acute neurological complications ($p = 0.06$). Bacterial meningitis due to *S. pneumoniae* was selected as risk factor for the development of acute neurological complications (odds ratio [OR] = 6.4; confidence interval [CI] 1.7-24.7) and neutropenia < 60% ($p < 0.01$).

Thirty five patients attended at least one appointment after hospital discharge. The median of time of follow-up of these patients was 139 days (15-1,869 days).

Within this group of 35 patients, 14 (40%) presented neurological sequelae. The most frequent sequelae were behavioral alteration (22.9%), psychomotor development

Table 1 - Acute neurological complications: onset period, symptoms and signs

	Acute neurological complications			
	Yes (n = 17)	**No (n = 27)**	**p***	**OR**
Onset				
< 24 h	9 (52.9%)	16 (59.3%)	0.76	0.7 (0.2-2.6)
< 48 h	11 (64.7%)	19 (70.4%)	0.74	0.7 (0.2-2.8)
Symptoms (%)				
Fever	15 (88.2%)	24 (88.8%)	1.00	0.9 (0.1-6.3)
Alteration of consciousness	15 (88.2%)	14 (51.8%)	0.02	7.0 (1.3-36.5)
Adynamia	14 (82.3%)	17 (63.0%)	0.19	4.1 (0.7-21.9)
Vomit	13 (76.5%)	24 (88.8%)	0.40	0.5 (1.0-3.1)
Seizures	9 (52.9%)	1 (3.7%)	< 0.001	33.4 (3.6-310.3)
Irritability	8 (47.0%)	5 (18.5%)	0.08	4.4 (1.1-17.5)
Anorexia	6 (35.3%)	10 (37.0%)	1.00	0.7 (0.2-2.5)
Migraine	5 (29.4%)	16 (59.3%)	0.06	0.3 (1.0-1.1)
Irritability	8 (47.1%)	5 (18.5%)	0.08	4.4 (1.1-17.5)
Signs				
Shock	7 (41.2%)	4 (14.8%)	0.07	2.3 (0.5-10.0)
Focal neurol. involvement	4 (23.5%)	1 (3.7%)	0.06	6.5 (0.7-63.4)
Hyperthermia	4 (44.4%)	11 (55.0%)	0.69	0.4 (0.1-1.7)
HR > 100 bpm	12 (75.0%)	21 (80.8%)	0.71	0.7 (0.2-2.7)
Neck stiffness	11 (64.7%)	16 (59.3%)	0.76	1.3 (0.3-4.4)
Kernig's sign +	0 (0.0%)	4 (14.8%)	0.14	0.4 (0.0-4.0)
Brudzinski's sign +	0 (0.0%)	3 (11.1%)	0.27	0.6 (0.0-6.5)
Laségue's sign +	0 (0.0%)	1 (3.7%)	1.00	2.0 (0.1-34.5)
Petechiae	2 (11.8%)	13 (48.1%)	0.02	0.1 (0.0-0.6)
Bulging fontanelle (9 infants)	6 (35.3%)	3 (11.1%)	0.01	3.3 (0.4-24.4)

bpm = beats per minute; HR = heart rate; OR = odds ratio.
* Fisher's exact test.

Table 2 - Acute neurological complications: laboratory tests

	Acute neurological complications		
	Yes (n = 17)	**No (n = 27)**	**p**
Total leukocyte (count)	8,700 (2,780-36,610)	17,000 (2,500-35,300)	0.07*
Neutrophils (%)	67.4 + 16.0	78.9 + 14.6	0.01†
Neutrophils (count)	5,046 (1,155-23,715)	12,702 (1,175-32,476)	0.03*
Lymphocyte (%)	26 (4-63)	13 (4 - 53)	0.06*
Lymphocyte (count)	1,955 (210-12081)	2,058 (402-11,925)	0.76*
Platelets (thousand)	280 (176-539)	271 (96-664)	0.71*
Glycemia	127.4 + 57.9	123.7 + 40.2	0.81†
CRP	9 (64.3%)	4 (23.5%)	0.03‡

CRP = C-reactive protein.
* Mann-Whitney test.
† Student's *t*-test.
‡ Fisher's exact test.

delay (17.1%), mental retardation (14.3%), epilepsy (14.3%) and cranial nerve involvement (14.3%). Other sequelae found in this study are presented in Table 4. Regarding cranial nerve involvement, there were two cases of oculomotor nerve involvement and three of vestibulocochlear nerve.

The median age of the group of patients with neurological sequelae was 14.5 months (4-87 months), considering that in 50% of the cases, the patients were less than 1 year of age. As for the gender, 71.4% were male.

Regarding the therapeutic, all the patients of both groups received empiric treatment with ceftriaxone. However, we noticed a higher need of combined antibiotic therapy in patients with neurological sequelae ($p = 0.01$). All the 35 patients received corticosteroids intravenous in the first day of hospitalization.

Patients with neurological sequelae presented higher frequency of acute neurological complications, such as cranial nerve involvement ($p < 0.01$), motor deficit ($p = 0.02$), convulsive crisis ($p = 0.03$), convulsive status epilepticus ($p = 0.02$), and coma ($p < 0.01$). The levels of cerebrospinal fluid protein were significantly different between those with and without neurological sequelae (224.9 versus 119.2, $p < 0.01$), as well as the values of the relation cerebrospinal fluid glucose/glycemia (0.01 versus 0.37, $p < 0.01$).

Table 3 - Acute neurological complications: cerebrospinal fluid examination

	Yes (n = 17)	No (n = 27)	p*
Muddy aspect/hemorrhagic	13 (76.5%)	21 (80.8%)	0.68
Total leukocytes	720 (58-49,493)	1315 (4-18,600)	0.75
Monomorphonuclear cells (%)	14 (3 101)	12 (0-53)	0.50
Monomorphonuclear cells (count)	56 (12-1,979)	86 (0-1,164)	0.95
Polymorphonuclear ells (%)	88 (30 101)	87 (47-100)	0.96
Polymorphonuclear cells (count)	600 (27-47,513)	1179 (3-18,228)	0.53
Protein	192 (20-1,220)	138 (17-583)	0.11
Glucose	2 (0-177)	24 (0-92)	0.25
Bacterioscopy	12 (70.6%)	13 (50.0%)	0.21
Culture	11 (73.3%)	20 (74.1%)	1.00
Latex	9 (75.0%)	12 (46.1%)	0.16
Cerebrospinal fluid glucose/glycemia ratio	0.21 (0.00-1.24)	0.41 (0.00-0.83)	0.55

* Mann-Whitney test.

Table 4 - Neurological sequelae caused by childhood acute neurological meningitis

Neurological sequelae	Final sample (n = 35)	Group with neurological sequela (n = 14)	OR
Behavior alteration	8 (22.9%)	8 (57.15)	0.2 (0.0-0.8)
NPMD delay	6 (17.1%)	6 (42.9%)	0.3 (1.0-1.1)
Cranial nerve involvement	5 (14.3%)	5 (35.7%)	0.3 (1.0-1.3)
Oculomotor	2 (5.7%)	2 (14.3%)	
Vestibulocochlear	3 (8.6%)	3 (21.4%)	
Epilepsy	5 (14.3%)	5 (35.7%)	0.3 (1.0-1.3)
Mental retardation	5 (14.3%)	5 (35.7%)	0.3 (1.0-1.3)
Motor deficit	4 (11.4%)	4 (28.6%)	0.3 (1.0-1.5)
Hemiplegia	1 (2.9%)	1 (7.1%)	
Quadriplegia	2 (5.7%)	2 (14.3%)	
Double hemiplegia	1 (2.9%)	1 (7.1%)	
Speech delay	4 (11.4%)	4 (28.6%)	0.3 (1.0-1.5)
Learning disability (mental retardation excluded)	3 (8.6%)	3 (21.4%)	0.3 (1.0-2.0)
Hearing impairment	3 (8.6%)	3 (21.4%)	0.3 (1.0-2.0)

NPMD = neuropsychomotor development; OR = odds ratio.

Convulsive crisis in hospitalization (OR = 5.6; CI = 1.2-25.9) and cerebrospinal fluid protein > 200 mg/dL ($p < 0.01$) were selected as risk variables for the development of neurological sequelae in the multivariate analysis.

Discussion

In the present study, we observed a predominance of male both in the general sample and within the group of patients with acute neurological complications and/or neurological sequelae, which has already been indicated by other authors.[11,12] Because the initial clinical manifestations in the groups with and without acute neurological complications were unspecific, they corroborate the high suspicion of bacterial meningitis in pediatric patients.[13-15] Regarding the etiologic agent, we noticed predominance of *N. meningitidis* and *S. pneumoniae* instead of *H. influenzae* type B, possibly due to the Hib vaccine high coverage and efficacy.[12,16-18]

The recent literature indicates that childhood ABM is associated with a high risk of complications and neurological sequelae, with a percentage of approximately 40%,[6,19] besides a considerable mortality rate, which can reach 4% to 10%.[13] In the present study, this frequency was 38.6%, with a mortality rate of 4.5%, a finding similar to the one found in the studies by Sáez-Llorens & McCracken and Chávez-Bueno & McCracken[13,14] and lower than other data recorded in Brazil[2,11] and in other developing countries.[19] In a recent literature review (1970 to 2010), about 50% of ABM survivors (1 month to 18 years of age) had neurological sequelae after 5 years of follow-up.[20]

The group of patients with acute neurological complications had a higher frequency of hospitalization in the intensive care unit and underwent more imaging studies and electroencephalography. These findings might suggest more serious cases of ABM, which required the use of a larger amount of medical and technological resources. The same reason can explain the extended duration of antibiotic therapy in these patients.

Regarding acute neurological complications, the frequency of seizure episodes and cranial nerve involvement found in the present study corroborate recent studies.[14,20]

In our sample, the warning signs for acute neurological complications were: presence of seizure episodes at admission, neutropenia < 60%, low age group, and *S. pneumoniae.* Because the absence of alteration in the level of consciousness and the presence of petechiae indicated potential infection with *N. meningitidis*, they showed a more favorable evolution of the patients. Our warning signs for morbidity resulting from ABM are compatible with the literature.[3,13,15,16,21,22] There was only a divergence regarding laboratory findings, since in the present study, neutropenia, instead of leucopenia,[16] was suggested as a warning sign for acute neurological complication.

Although focal neurological alteration and irritability as clinical onset are not usually pointed out as bad prognostic factors, in the present study, they tended to be more frequent in the patients with acute neurological complications.

The most frequent sequelae found in our study were behavior alteration, delayed psychomotor development, mental retardation, epilepsy, and cranial nerve involvement, which is in agreement with other authors' findings.[3,12,22]

It is important to highlight that several studies have reported hearing impairment as one of the most important and frequent sequelae in childhood ABM.[3,12,19,22,23] This information was not confirmed in the present study, once only 11 audiological evaluations were recovered among the 35 patients who were followed-up, from which two presented conductive hearing impairment. It is worth mentioning that all patients used intravenous corticosteroids on the first day of treatment, because this is a routine procedure at our institution based on evidence of the efficacy of intravenous corticosteroids in the prevention of deafness in controlled studies.[24]

Regarding age, some authors have suggested that infants with less than 12 years of age are at a higher risk of developing sequelae.[12] In the present study, the median age among patients with sequelae was 14.5 months (4-87) and, among the infants without sequelae, the median age was 53 months (3-145).

Although it has been reported in the literature that alteration of level of consciousness is a risk factor for the development of sequelae,[12,21] in the present study, there was no significant difference in relation to this variable between the groups with or without sequelae. According to Roine et al. (2008), the level of consciousness is a major predictor of a poor prognosis.[4,21] However, in our sample, we found a difference only when the presence of coma was taken into consideration. This fact was demonstrated by Shingi et al. (2007), who concluded that a Glasgow Coma Scale lower than eight at admission is an independent predictor of neurological sequelae.[4]

Several authors have reported the presence of seizure episodes as an important factor of poor prognosis.[3,4,11,12,24,25] According to the study by Natalino & Moura-Ribeiro (1999), neurological sequelae were detected in 36% of the patients who had epileptic manifestations.[11] In agreement with these findings, in the present study, the presence of seizure at admission was considered a risk variable for the development of neurological sequelae.

According to Grimwood et al. (1995 and 2000) and Koomen et al. (2005), the risk of sequelae is higher in those individuals who have acute neurological complications during the course of the disease.[6,8,26] This is in agreement with the present study, since the patients with neurological sequelae had higher frequency of acute neurological complications. Therefore, it is important to stress the relevance of the

factors pointed out by the present study as being associated with acute neurological complications, once they are closely related to neurological sequelae.

An association between meningitis caused by *S. pneumoniae* and unfavorable evolution has been suggested in the literature.[13,27,28] In our study, no statistical difference was found when the etiologic agents were compared regarding the presence of sequelae. However, we found a difference when comparing the agents in term of presence of acute neurological complications; thus infection with *S. pneumoniae* was considered a risk factor for acute neurological complication.

Unfavorable evolution has been being associated with low cerebrospinal fluid cell count.[16] Cerebrospinal fluid cell counts lower than 1,000/mm³ [12] and lower or equal to 200/mm³ [28] have been related to a poor prognosis in ABM. Furthermore, cerebrospinal fluid protein concentration higher or equal to 330 mg/dL was considered as a risk factor for a worse prognosis by Tsai et al.[28] The levels of cerebrospinal fluid protein concentration and the values of the ratio of cerebrospinal fluid glucose concentration to blood glucose were significantly different between the infants with or without neurological sequelae, considering that cerebrospinal fluid protein concentration > 200 mg/dL was selected as a risk variable for the development of neurological sequelae.

Based on results of the present study, it is possible to conclude that the warning signs for acute neurological complications and neurological sequelae should be used in medical practice involving infants with ABM. Neutrophil count < 60%, seizure episode at admission, and *S. pneumoniae* as the etiologic agent were identified as warning signs for acute neurological complications, while cerebrospinal fluid protein concentration > 200 mg/dL and seizure episodes were risk factors for neurological sequelae.

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