Risk factors associated with the development of early neurological complications in purulent meningitis in a pediatric population

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Abstract

Objective: *To determine the risk factors associated with the development of early neurological complications in purulent meningitis in a pediatric population.* **Methods:** *This was a case-control study including 78 children aged one month to 16 years with purulent meningitis divided into two groups: cases, with early neurological complications (defined as those presenting < 72 hours from initiation of clinical manifestation), and controls, without early neurological complications. Clinical, serum laboratory, and cerebrospinal fluid (CSF).* **Results:** *Seventy-eight patients were included: cases, n = 33, and controls, n = 45. Masculine gender, 19 (57%) vs. feminine gender, 28 (62%) (p = 0.679). Median age in months, 36 months (range, 1-180) vs. 12 months (range, 1-168) (p = 0.377). Factors associated with neurological complications: convulsive crises on admission, p = 0.038, OR, 2.65 (range, 1.04-6.74); meningeal signs, p = 0.032, OR, 2.73 (range, 1.07-6.96); alteration of the alert state, p = 0.003, OR, 13.0 (range, 1.64-105.3); orotracheal intubation, p = 0.000, OR, 14.47 (range, 4.76-44.01); neurological deterioration, p = 0.000, OR, 9.60 (range, 3.02-30.46); turbid CSF, p = 0.003, OR, 4.20 (range, 1.57-11.20); hypoglycorrhachia, < 30 mg/dl, p = 0.001, OR, 9.2 (range, 3.24-26.06); and positive CSF culture, p = 0.001, OR, 16.5 (range, 1.97-138.1).* **Conclusions:** *The factors associated with early neurological complications included convulsive crises on admission, meningeal signs, alteration of the alert state, need for orotracheal intubation, turbid CSF, hypoglycorrhachia, and positive CSF culture.*

KEY WORDS: *Neurological complications. Meningitis purulent meningitis. Meningoencephalitis.*

Introduction

Meningitis is an acute inflammatory process of the leptomeninges and can be caused by bacteria, viruses, fungi or parasites[1]. Bacterial meningitis is one of the infections that can be more serious in infants and older children[2]. This infection is associated with a high frequency of acute complications and with an elevated risk of long-term morbidity[3,4]. The World Health Organization considers it to be a serious threat for health, since 171,000 deaths per year are estimated to occur worldwide[5]. These infections represent the third or fourth cause of pediatric intensive care admissions, with a lethality rate of 15-30%[6].

Clinical manifestations are unspecific, especially in infants younger than 1 year; sometimes, first there are minimal symptoms that suggest central nervous system involvement. The clinical picture generally manifests itself as 4 syndromes: infectious, endocranial hypertension, meningeal irritation and neuronal damage, as well as infection in other organs and systems[1,6]. Most common signs and symptoms are fever, poor feeding, nausea, vomiting, irritability or

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headache in older children, and altered state of alertness (signs of cerebral edema)[2], somnolence and irritability in infants. About 3% to 11% of patients can exhibit stupor or coma, hypertensive anterior fontanelle and neck or back pain[8].

One third of patients can present with focal or generalized seizures at diagnosis; in 15-20% of cases, these occur within the first 24-48 hours of hospitalization (early seizures). Difficult to control seizures or those that occur after the second hospitalization day are associated with higher risk of neurological complications[7]. Late-occurring seizures may indicate the presence of electrolytic or structural alterations, subdural collection, parenchymal abscesses, thrombosis or hydrocephalus[6,7].

Several studies have been conducted with the purpose to identify risk or prognostic factors associated with neurological complications or mortality in children with bacterial meningitis[8]. De Jonge et al.[3], in a multicenter study, reviewed 31 articles with regard to risk factors for complications and prognostic factors of mortality. They identified an association of *Streptococcus pneumoniae* infection and cerebrospinal fluid (CSF) low glucose level and hearing loss; leukopenia and a high rate of protein in the CSF, with coma and death; fever with 7-day or longer evolution was found to be an important risk factor for neurological sequels in general; and the presence of symptoms for more than 48 hours and seizures for more than 12 hours after hospital admission were associated with an unfavorable prognosis[3].

Kin et al.[9], in a series of cases, identified subdural empyema as a complication in 2.7%, and as predisposing factors, otitis or sinusitis in 93%, and neurological focalization, such as paresthesias, focal seizures or contralateral dysesthesia, in 75-82%. *S. pneumoniae* was the etiologic agent in 93% of patients. Surgical treatment was required in 5 patients because they presented with midline shift. They evolved with complications such as seizures, focal neurological abnormalities and hearing loss[9].

In the same sense, Davenport et al.[4] identified *S. pneumoniae* as a risk factor for the development of acute complications in 60% of cases, with a p-value of 0.028. In addition, hyperproteinorachia, hypoglycorrhachia and blood and CSF positive cultures were significantly associated with the development of complications[4].

Other authors, such as Namani et al.[11], found that age younger than 12 months and the presence of alertness state alteration, seizures or focal neurologic deficit prior to hospital admission were related to higher incidence of neurological complications. It was predominant in patients who received dexamethasone and in those in whom and initial scheme with two antibiotics was implemented.

The purpose of the study was to determine the risk factors associated with the development of early neurological complications (ENC) in purulent meningitis in a children's population.

Methods

This was a case-control study carried out from 2012 to 2015, which had as study universe pediatric patients admitted to the pediatric infectology department with a diagnosis of purulent meningitis for their management at the CMNO UMAE Pediatrics Hospital in Guadalajara, Mexico.

Patients older than 1 month and younger than 16 years admitted for their management to the department of pediatric infectology, with clinical diagnosis of purulent meningitis, confirmed by laboratory and imaging, were included. Cases were defined as those patients with ENC and, as controls, those patients without ENC. Patients with complications after the first 72 hours, underlying neurological conditions, ventricle-peritoneal bypass carriers, immunocompromised subjects, those with incomplete information in the medical file or moved to another hospital prior to relevant clinical information recollection completion were excluded; newborn patients younger than 28 days were also excluded.

Acute purulent meningitis was defined as presence of the condition for less than 5 days, with an acute febrile clinical picture, accompanied by neurological anomalies: irritability, mood swings, meningeal signs, seizures, status epilepticus, focal neurological deficits or signs of endocranial hypertension. CSF alterations with purulent data: turbid aspect, leukocytosis > 50 cells/mm^3 with plymorphonuclear predominance, hypoglycorrhacia < 40 mg/dL or < 50% with regard to the serum glucose value, and hyperproteinorachia > 50 mg/dL. Those cases where the infectious agent could be identified by means of Gram staining, co-agglutination or CSF culture were classified as bacterial meningitis[7,12].

Those lesions caused by purulent meningitis over the course of the first 72 hours of the infectious process onset (immediate phase) were characterized as ENC, including cerebral edema, endocranial hypertension, seizures, status epilepticus, endocranial

Table 1. Pediatric patients per group according to the presence of early neurological complications in meningitis

Characteristics	Cases (n = 33)	Controls (n = 45)	p
Male/female gender, n (%)*	19 (57)/14 (43)	28 (62)/17 (38)	0.679
Age, median (range)†	36 (1-180)	12 (1-168)	0.377
1 month to 2 years, n (%)*	15 (45)	25 (55)	
3 to 5 years, n (%)‡	4 (12)	9 (20)	
6 to 12 years, n (%)*	7 (21)	7 (15)	
> 12 years, n (%)‡	7 (21)	4 (9)	
H. influenzae vaccination, n (%)*	28 (85)	40 (89)	0.306
S. pneumoniae vaccination, n (%)*	28 (85)	40 (89)	0.306

*Chi-square test.
†Mann Whitney U-test.
‡Fisher's exact test.

hemorrhage or cerebral death. The diagnosis of these complications was established after a full neurological clinical assessment, in addition to an imaging study (cranial computed tomography [CT], CT brain angiography or transfontanellar ultrasonography in the case of small infants) by the pediatric neurology department of this hospital center[11].

The descriptive analysis of qualitative variables was carried out with frequencies and percentages; quantitative variables, with medians and ranges (upper and lower range). Inferential statistics was used for the comparison of proportions with the chi-square test or Fisher's exact test. The comparison of quantitative variables was performed with Mann Whitney U-test, owing to a non-symmetric data distribution curve. Risk association was determined by means of the odds ratio (OR). The statistical package SPSS 21.0 for Windows was used, and a p-value < 0.05 was considered as a statistically significant difference.

Calculation was made with the formula for two proportions, where $\alpha < 0.01$ and $\beta = 0.95$, according to the results of the study by Kirimi et al.[8], with a sample size of 33 patients per group being determined. A proportion of patients with neurological complications of 69% was considered, in comparison with 46% for the group without neurological complications.

Ethical considerations

The study took into account the general research principles established by the 1965 declaration of Helsinki. This was a category I study, free of risk, according to the general Statute of Health, and no informed consent was therefore required. The work was approved by the local committee of research and ethics of the hospital with document number R-2015-1302-25.

Results

Seventy-eight patients were included in two groups: with early neurological complications (n = 33) and without early neurological complications (n = 45), with a 1 to 1.3 ratio.

Table 1 shows similar demographic characteristics for both groups. History of *Haemophilus influenzae* and *S. pneumoniae* vaccination was similar in both groups.

Clinical alterations of included patients per group are shown in table 2. The presence of fever was assessed at admission, and was corroborated by health personnel, since history referred by the mother was unspecific and non-quantified. Fever duration in both groups was 4 days, ranging from 0 to 15. Main respiratory data were cough and rhinorrhea. Two patients from each group had symptoms of acute otitis media. Among the gastrointestinal symptoms, vomiting was predominant in 19 children of the group of cases and 18 controls. Neurologically, intense headache, predominantly frontal or holocranial, stood out. Five patients (15%) of the study group and 4 of the control group (9%) had neurologic deficit. Predominant seizures were generalized tonic-clonic convulsions. Status epilepticus was found at admission in 3 patients; one of them was secondary to *Neisseria meningitidis* with infarction area on the CT scan, and died within 72 hours of admission; in the other 2 cases, no causative agent was isolated and had cerebral edema as complication. Only one control had status epilepticus, and no hygromas or subdural collections were corroborated by CT. Two controls were reported with ataxia at admission (one of them with spasticity); no infectious agent could be isolated and they had no ENC. One case had dysarthria at disease onset, which was

Table 2. Clinical characteristics by group according to the presence of early neurological complications in meningitis

	Cases (n = 33)	Controls (n = 45)	p
Febrile at admission, n (%)*	6 (18)	5 (11)	0.375
Fever duration, median (range)†	4 (0-15)	4 (0-15)	0.855
Upper respiratory tract infection, n (%)‡	20 (61)	24 (53)	0.522
Cough, n (%)*	14 (42)	14 (31)	0.303
Rhinorrhea, n (%)*	13 (39)	14 (31)	0.447
Gastrointestinal symptoms, n (%)*	23 (70)	26 (21)	0.282
Diarrhea, n (%)*	5 (15)	9 (20)	0.581
Abdominal pain, n (%)‡	4 (12)	5 (11)	0.890
Neurological symptoms‡	6 (2-12)	4 (1-8)	0.110
Intense headache, n (%)*	12 (36)	8 (18)	0.704
Baseline Glasgow, median (range)†	15 (3-15)	10 (9-15)	0.486
Seizures, n (%)*	20 (61)	27 (69)	0.957
Generalized tonic-clonic seizures, n (%)*	12 (36)	18 (40)	0.744
Tonic or clonic partial seizures, n (%)*	8 (24)	9 (20)	0.748
Status epilepticus, n (%)‡	3 (9)	1 (2)	0.174
Neurological deficit, n (%)‡	5 (15)	4 (9)	0.392
Hemiparesis, n (%)‡	1 (3)	1 (2)	0.823

*Chi-square test.
†Mann Whitney U-test.
‡Fisher's exact test.

Table 3. Laboratory results by group according to the presence of early neurological complications in meningitis

	Cases (n = 33)	Controls (n = 45)	p
Result at admission			
Anemia, n (%)	14 (42)	16 (36)	0.81
Thrombocytosis, n (%)	3 (9)	2 (4)	0.64
Thrombocytopenia, n (%)	3 (9)	4 (8)	1
Leukopenia, n (%)	1 (3)	3 (7)	0.63
Leukocytosis, n (%)	11 (33)	6 (13)	0.05
Neutropenia, (%)	0 (0)	0 (0)	-
Hyperglycemia, n (%)	10 (30)	10 (22)	0.44
Hyponatremia, n (%)	1 (3)	5 (11)	0.23
Hypernatremia, n (%)	3 (9)	2 (4)	0.64
Hyperpotassemia, n (%)	3 (9)	4 (8)	1

Median comparison: Mann Whitney U-test.

referred by the mother, but at emergency department admission, only nuchal rigidity and fever were found, and another patient of the cases group had facial paralysis; in both kids, no causative agent was isolated and had cerebral edema as complication.

Laboratory data are referred in table 3, and they are very similar in both groups, with no relevant statistical differences; only in the leukocyte count was there a difference found when comparing the medians of 16,000 in the group of cases and 12,350 in the controls (p = 0.004). Similarly, the number of neutrophils was higher in cases (10,900) than in controls (7590) (p = 0.014).

Table 4 shows the study's bacteriology, with very similar data in both groups and no significant differences in CSF Gram staining. A higher number of infectious agents (11; 33%) were identified in the group of cases in comparison with the control group (3; 4%) (p = 0.005). Identified agents were, in the group of cases, 3 *S. pneumoniae*, 4 *Streptococcus agalactiae*, 1 type b *H. influenzae*, 1 *N. meningitidis*, 1 *Pseudomonas aeruginosa* and 1 *Citrobacter freundii*. In the group of controls, only 1 *S. pneumoniae*, 1 *S. agalactiae* and 2 *N. meningitidis* were isolated.

Table 5 concentrates the CSF cytochemical characteristics, and the turbid aspect in the group of cases stands out when compared with the water clear aspect in the control group (p = 0.004 and 0.003, respectively). Cellularity, glucose and proteins showed statistically significant differences as well.

Table 6 shows the most relevant variables associated with risk of ENC, with CSF culture positivity, endotrachial intubation, alteration of the state of alertness, neurological deterioration, glucose < 30 mg/mL,

Table 4. CSF microbiological findings by group according to the presence of early neurological complications in purulent meningitis

	Cases (n = 33)	Controls (n = 45)	p
CSF positive Gram staining, n (%)*	3 (9)	2 (4)	0.408
CSF Gram staining result			
Gram-positive cocci, n (%)*	2 (6)	2 (4)	0.749
Gram-negative bacilli (%)*	1 (3)	0	0.240
Positive CSF co-agglutination, n (%)*	5 (15)	3 (7)	0.222
Positive CSF culture and co-agglutination, n (%)*	11 (33)	3 (4)	0.005
S. pneumoniae, n (%)	3 (9)	1 (2)	0.3
S. agalactiae, n (%)	4 (12)	1 (2)	0.15
Type b H. influenzae, n (%)	1 (3)	0	0.42
P. aeruginosa, n (%)	1 (3)	0	0.42
N. meningitidis, n (%)*	1 (3)	1 (2)	0.61
C. freundii, n (%)	1 (3)	0	0.42

*Fisher's exact test.

Table 5. CSF cytochemical analysis characteristics by group according to the presence of early neurological complications in purulent meningitis

	Cases (n = 33)	Controls (n = 45)	p
CSF characteristics	11 (33)	30 (67)	0.004
Water clear, n (%)*	18 (54)	10 (22)	
Turbid, n (%)*			
CSF cells, cells/mm^3, median (range)†	700 (50-18,720)	96 (50-21,600)	0.005
51-1000, n (%)*	20 (60)	40 (80)	0.003
> 1001, n (%)‡	13 (39)	5 (11)	
CSF polymorphonuclear cells, cells/mm^3, median (range)†	73 (35-100)	73 (35-100)	0.623
35-50%, n (%)‡	6 (18)	4 (9)	0.220
> 51%, n (%)*	27 (81)	41 (91)	
CSF glucose, mg/dL, median (range)†	20 (9-77)	39 (10-68)	0.001
5-30, n (%)*	23 (70)	9 (20)	0.001
> 31, n (%)*	10 (30)	36 (79)	
CSF proteins, mg/dL, median (range)†	300 (32-1431)	76 (9-460)	0.000
30-100, n (%)*	7 (21)	13 (29)	0.010
> 31, n (%)*	27 (82)	20 (44)	

*Chi-square test.
†Mann Whitney U-test.
‡Fisher's exact test.

turbid CSF and presence of meningeal signs and seizure at admission standing out; values are presented with their respective ORs and confidence intervals.

Discussion

Different authors have identified some clinical situations, such as being an infant, having fever for at least 7 days, alterations of the state of alertness, seizures prior to admission or neurologic deficit, coma, shock and respiratory distress, as well as some significant laboratory findings such as leukopenia, proteinorachia, initial pleocytosis > 5000, hypoglycorrhagia, blood and CSF positive cultures and *S. pneumoniae* infection, as risk factors associated with neurological complications[3,4,13].

Kirimi et al.[8] found depression of the level of consciousness as a risk factor for acute neurological complications. In our case, a higher number of patients were found with neurological deterioration or status epilepticus requiring orotracheal intubation prior to hospital admission.

The Glasgow score assigned at emergency department admission had a median of 11 for cases and 13 for controls; however, it should be noted that in the majority of cases where orotracheal intubation was required, it was not documented in the medical file, and statistical significance was therefore not reached.

Table 6. Risk factors by group according to the presence of early neurological complications in purulent meningitis

Variable	OR	95% CI
Positive culture	16.5	1.97-138.1
Orotracheal intubation	14.47	4.76-44.01
State of alertness alteration	13.0	1.64-105.3
Neurological deterioration	9.60	3.02-30.46
Glucose range 5-30	9.2	3.24-26.06
Turbid CSF	4.20	1.57-11.20
Meningeal signs	2.73	1.07-6.96
Seizures at admission	2.65	1.04-6.74
Three doses of *H. influenzae* vaccine	0.129	0.02-0.61
Partial tonic seizures at admission	4.77	0.89-25.4
Water-clear CSF	0.25	0.09-0.64
CSF leukocytes 30-500 mm^3	0.18	0.06-0.50
CSF glucose 31-60 mg/dL	0.071	0.02-0.21
CSF proteins 301-600 mg/dL	6.06	0.64-57

Similarly to De Jonge et al.[3] and Namani et al.[11], we observed that the majority of patients in the group of controls presented with alertness state alteration at admission, with somnolence being the main symptom.

As for clinical manifestations at onset of the condition, fever was found to be the predominant symptom. De Jonge et al.[3] referred in their study that the presence of fever for at least 7 days prior to hospital admission is a risk factor for neurological sequels; it was a relevant factor in our population as well. Respiratory tract symptoms are common in both groups and cough was the most referred symptom.

Isolation of the infectious agent was achieved in 18% of cases. The presence of bacteria in the CSF reached statistical significance. Namani et al.[11] reported higher frequency of microbiological confirmation, with 74% of cases in their study carried out in population of Pristina, capital city of Kosovo, in Europe. Davenport et al.[4], in another study conducted in Argentina, identified the etiology in 18% of cases, similar to findings in our population. Namani et al.[11] reported that *N. meningitidis* was the most common causative agent, followed by *S. pneumoniae*. Davenport et al.[4] found *S. pneumoniae* at first place, followed by *N. meningitidis*. Ercan et al.[8], in Turkey, identified *Staphylococcus aureus* as the main isolated agent, followed by *S. pneumoniae*. Curiously, in this study, the most commonly isolated agent was *S. agalactiae*, which is generally implicated in sepsis and early and late meningoencephalitis of the newborn in other countries such as the USA and some countries of South America. In our study, all patients who had *S. agalactiae* isolated were younger than 3 months, which was the predominant group, and this is therefore the attributed cause for this agent being the most commonly isolated one. In the case of *S. pneumoniae*, one of the patients was 15 years old and the second almost 6, and both had incomplete vaccination schedules (only one dose against pneumococcus). Only in one of the controls, a 2-month-old infant, was *S. pneumoniae* identified by co-agglutination, and the culture was negative; because of his/her age, the infant had only received one dose of pneumococcal vaccine, and a serotype not included in current pneumococcal vaccine cannot therefore be highly suspected as the cause of these infections. One type b *H. influenzae* isolate was found in a 4-month-old patient who had received a single dose of vaccine against this agent. The cases with *P. aeruginosa* and *C. freundii* were a 3-month-old patient and another of 1 month of age; the first one had serious cerebral edema, endocranial hypertension and ventricle-peritoneal bypass insertion; the second one had cerebral edema and hygroma as complications. No additional risk factors were identified in these patients, although the purpose of the study was not to identify previous history of hospital stay in neonatal intensive therapy areas or not previously diagnosed immunodeficiency that might have contributed to gram-negative microorganisms' infection acquisition.

The risk factors associated with neurological complications found in different international studies are mainly age younger than 12 months, altered mental state, seizures prior to admission, presence of neurological deficit at admission, proteinorachia, initial pleocytosis > 5000 and hypoglycorrhachia[11], blood and CSF positive cultures, state of coma, state of shock, respiratory distress, leukopenia, fever for at least 7 days, age younger than 2 years and infection with *S. pneumoniae*[1]. In our study, we did not find any socio-demographic variable or clinical characteristics at disease onset as risk factor; the presence of seizures and meningeal signs at admission was associated with neurological complications (as for the type of meningeal sign, only nuchal rigidness had statistical significance), and alteration of the state of alertness, need for orotracheal intubation and neurological deterioration at admission are the factors that were more highly associated with neurological complications. The presence of turbid CSF increased 4-fold the probability to suffer a neurological complication; CSF glucose < 30, increased

9.2-fold the risk; and finally, one of the most important variables, having a positive CSF culture, increased 17-fold the probability to experience an ENC.

The study shows some limitations. Among them, since this was a retrospective analysis, the collected information is dependent on data documented in medical records; the sample size is small; the ratio between groups was 1:1.3 because, in some cases, medical records were not found, and in other the information was partial, which might have limited the establishment of a significant risk ratio; in addition, confidence intervals were found to be very broad owing to the sample size.

Reported mortality varies in different studies: Kirimi et al.[9] found a mortality of 12%; Namani et al.[8], of 3%; and Davenport et al.[4], of 4%. In our study population, a mortality of 9% was found; of these cases, 86% had cerebral death, and adolescents were the most affected group, with no associated factors being identified. Other important aspects should be investigated, such as mobilization opportunity and conditions in foreign cases, which should be emphasized in other type of studies.

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Conflicts of interests

The authors declare not having any conflicts of interests.

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