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CLINICAL OUTCOME OF NEONATAL BACTERIAL MENINGITIS ACCORDING TO BIRTH WEIGHT

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ABSTRACT - *Objective:* To describe the clinical outcome and the complications of bacterial meningitis according to birth weight of out born neonates admitted in intensive care unit during an 11 year-period. *Method:* Eighty-seven newborns were studied. Thirty-four infants were low birth weight newborn and 53 presented birth weight ≥2500 g. The clinical data were obtained through the analysis of patients' files. Fisher's exact test, the χ^2 and the Mann-Whitney test were applied. *Results:* Neurological symptoms were more common in infants weighed ≥2500 g (p<0.05). Complications affected half of the cases in both groups. Complications affected half of the cases in both groups, with an overall mortality rate of 11.5%. *Conclusion:* The rate of complications was high in both groups, regardless of the birth weight. No association was observed between the occurrence of death and birth weight. Infants with positive CSF culture had a poorer prognosis.

KEY WORDS: newborn, neonatal meningitis, central nervous system.

Evolução clínica da meningite bacteriana neonatal de acordo com o peso de nascimento

RESUMO - *Objetivo:* Descrever a evolução clínica e as complicações da meningite bacteriana de acordo com o peso de nascimento em recém-nascidos admitidos em unidade de terapia intensiva externa durante o período de 11 anos. *Método:* Foram estudados 87 neonatos, dos quais 34 foram recém-nascidos de baixo peso e 53 apresentaram peso ≥2500 g. Os dados clínicos foram obtidos por análise dos prontuários médicos. Foram realizados teste exato de Fisher, teste do χ^2 e teste de Mann-Whitney. *Resultados:* Os sintomas neurológicos foram mais comuns em neonatos com peso ≥2500 g (p<0,05). As complicações ocorreram na metade dos casos em ambos os grupos, com mortalidade global de 11.5%. *Conclusão:* A freqüência de complicações foi alta em ambos os grupos, independentemente do peso de nascimento. Não houve associação entre óbito e peso de nascimento. Os neonatos com cultura de líquor positiva apresentaram pior prognóstico.

PALAVRAS-CHAVE: recém-nascido, meningite neonatal, sistema nervoso central.

Low birth weight newborns present a 3-fold increased risk of acquiring meningitis when compared to those whose birth weight is ≥2500 g[1]. Among very low birth weight neonates (<1500 g) the risk is a 10 to 17-fold higher[2-4]. In addition to the immaturity of the immunological system, these neonates frequently present risk factors for infection related to maternal diseases or neonatal conditions[1,3,5].

The objective of this study was to describe the clinical outcome and the complications of bacterial meningitis according to birth weight of out born neonates admitted in intensive care unit during an 11 year-period.

METHOD

Eighty-seven newborns with bacterial meningitis who were admitted to the Neonatal Intensive Care Unit (NICU) of the Instituto da Criança, Hospital das Clínicas, University of São Paulo, from January 1st, 1994 to December 31st , 2004 were studied. Thirty-four of the newborn were low birth weight newborn (<2500 g) and 53 presented birth weight ≥2500 g. Neonates with meningomyelocele, hydrocephalus, perinatal asphyxia, congenital infection, nonbacterial infection and those with a prior history of surgical procedure in the central nervous system were excluded from the study. The clinical data were obtained through the analysis of patients' files.

The diagnosis of meningitis was based on either the presence of bacteria in the cerebrospinal fluid (CSF) or CSF with an increase in the number of cells (>20 cells/mm^3), predominance of neutrophils, increase in the concentration of protein (>100 mg/dL) and reduction in the concentration of glucose (<50% of the concomitant glycemia)[6,7].

Ampicillin and third-generation cephalosporins were administered immediately after the lumbar puncture was performed. When necessary, therapy was changed based on the result of cultures and maintained for at least 21 days.

Fisher's exact test, the chi-square and the Mann-Whitney test were applied for statistical analysis. p values <0.05 were considered statistically significant.

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The study was approved by the Research and Ethics Committee of the Department of Pediatrics of São Paulo University School of Medicine and by the Ethics Committee for the Analysis of Projects and Research of the Hospital das Clínicas.

RESULTS

Among the 87 neonates with bacterial meningitis, 53 (61%) presented birth weight ≥2500 g and 34 (39%) were low birth weight newborns, including 15 very low birth weight (<1500 g) infants. The age at diagnosis, duration of treatment and gender are shown in Table 1. There was no statistically significant difference in the duration of the treatment between the newborns presented birth weight ≥2500 g and the low birth weight newborns (p=0.196).

Fever, irritability, seizures and a bulging fontanel were significantly more frequent among newborns whose birth weight was ≥2500g, whereas abdominal distension, apnea, jaundice and blood count abnormalities were predominant among low-birth weight newborns (Table 2).

Etiological agents identified at the CSF and blood cultures are shown in Table 3. Bacteria in the CSF were identified in 34 (39%) of the newborn, 17 (50%) were gram-positive and 17 (50%) gram-negative bacteria, with no difference regarding the type of bacteria and birth weight (p=0.688).

Table 1. Age at diagnosis, duration of treatment and gender in 87 newborns with bacterial meningitis according to birth weight.

	Birth weight (g)		
Variables	<2500 (N=34)	≥2500 (N=53)	Total (n=87)
Age at diagnosis (d) *	7.4 (0-29)	12.9 (1-28)	10.8 (0-29)
Duration of treatment (d)	29.1 (2-98)	21.6 (1-48)	24.5 (1-98)
Female	22 (25%)	25 (32%)	50 (57%)
Male	12 (14.7%)	25 (29%)	37 (43%)

d, days; *mean (minimum-maximum).

Table 2. Comparision of the clinical signs in 87 newborns with bacterial meningitis according to birth weight.

	Birth weight (g)			
	<2500 (n=34)	≥2500 (n=53)		Total (n=87)
Clinical signs*	n (%)	n (%)	p	n (%)
Fever	16 (47.1)	39 (73.6)	55 (63.2)	0.012
Irritability	3 (8.8)	24 (45.3)	27 (31.0)	<0.001
Seizures	4 (11.8)	22 (41.5)	26 (29.9)	0.003
Lethargy	9 (26.5)	14 (26.4)	23 (26.4)	0.995
Food refusal	7 (20.6)	13 (24.5)	20 (23.0)	0.670
Bulging fontanel	3 (8.8)	16 (30.2)	19 (21.8)	0.019
Moaning	4 (11.8)	14 (26.4)	18 (20.7)	0.100
Tachypnea	8 (23.5)	7 (13.2)	15 (17.2)	0.214
Cyanosis	6 (11.6)	8 (15.1)	14 (16.1)	0.752
Abdominal distension	8 (23.5)	2 (3.8)	10 (11.5)	0.012
Vomiting	3 (8.8)	7 (13.2)	10 (10.3)	0.734
Apnea	7 (20.6)	2 (3.8)	9 (8.0)	0.025
Jaundice	6 (17.6)	1 (1.9)	7 (8.0)	0.013
Skin lesions	2 (5.9)	4 (7.5)	6 (4.6)	1.000
Opisthotonos	1 (2.9)	2 (3.8)	3 (3.4)	1.000
Diarrhea	0 (0.0)	3 (5.7)	3 (3.4)	0.277
Hypothermia	2 (5.9)	0 (0.0)	2 (2.3)	0.150
Digestive bleeding	1 (2.9)	0 (0.0)	1 (1.1)	0.391
Metabolic disorder	1 (2.9)	0 (0.0)	1 (1.1)	0.391

*Neurological findings in 36.8% of the newborns.

Table 3. Etiological agents identified at the cerebrospinal fluid (CSF) and blood cultures of 87 newborns with bacterial meningitis.

	CSF culture		Blood culture	
	Birth weight (g)		Birth weight (g)	
	<2500	≥2500	<2500	≥2500
Bacteria	n (%)	n (%)	n (%)	n (%)
Streptococcus B	0 (0.0)	6 (11.3)	1 (2.9)	2 (3.8)
Staphylococcus aureus	2 (5.9)	2 (3.8)	1 (2.9)	3 (5.7)
Staph. coagulase negative	0 (0.0)	0 (0.0)	2 (5.9)	4 (7.5)
Klebsiella sp	1 (2.9)	2 (3.8)	3 (8.8)	1 (1.9)
Acinetobacter sp	2 (5.9)	1 (1.9)	1(2.9)	0 (0.0)
Neisseria meningitidis	1 (2.9)	2 (3.8)	1 (2.9)	0 (0.0)
Escherichia coli	0 (0.0)	2 (3.8)	0 (0.0)	1 (1.9)
Streptococcus pneumoniae	0 (0.0)	2 (3.8)	0 (0.0)	0 (0.0)
Streptococcus viridans	1 (2.9)	1 (1.9)	0 (0.0)	0 (0.0)
Pseudomonas sp	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)
Enterobacter sp	0 (0.0)	1 (1.9)	0 (0.0)	1 (1.9)
Serratia marcescens	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)
Proteus sp	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)
Enterococcus fecalis	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)
Citrobacter sp	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)
Streptococcus pyogenes	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)
Streptococcus mitis	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)
Alcaligenes sp	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)
Gram-negative bacilli	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)
Total	8 (23.5)	26 (49.1)	10 (2.9)	12 (22.6)

Table 4. Comparision of the frequency of complications in 87 newborns with bacterial meningitis according to birth weight.

	Birth weight (g)			
	<2500 (n=34)	≥2500 (n=53)	Total (n=87)	p
Complications	n (%)	n (%)	n (%)	n (%)
Seizures	4 (11.8)	22 (41.5)	26 (29.9)	0.003
Intracranial hemorrhage	9 (26.5)	5 (9.6)	14 (16.1)	0.035
Hydrocephaly	6 (17.6)	6 (11.3)	12 (13.8)	0.526
Death	5 (14.7)	5 (9.4)	10 (11.5)	0.503
Ventriculitis	4 (4.8)	5 (9.4)	9 (10.3)	0.732
Brain abscess	1 (2.9)	2 (3.8)	3 (3.4)	1.000
Sagittal venous sinus thrombosis	0 (0.0)	3 (5.7)	3 (3.4)	0.277
Cerebral infarction	0 (0.0)	3 (5.7)	3 (3.4)	0.277
Inappropriate ADH* secretion	0 (0.0)	2 (3.8)	2 (2.3)	0.518
Total without complications	17 (50.0)	27 (50.9)	44 (50.6)	1.000
Total with complications	18 (50.0)	25 (49.1)	43 (49.4)	1.000

*Antidiuretic hormone

The bacteria most frequently identified in the CSF were *Enterobacteria* (41% of the cases, Table 3), followed by *Streptococcus* B (17.5%), non-B-type strain *Streptococcus* (17.5%), *Staphylococcus aureus* (11.7%), *Neisseria meningitidis* (8.8%) and *Enterococcus faecalis* (3%).

Among the neonates with a positive CSF culture, mortality rate was 20.5% *versus* only 5.6% among those with a negative CSF culture, showing an association between the presence of bacteria in the CSF and complications (p=0.008) or death (p<0.043). The frequency of neurological complications were similar in the two groups, regardless of the birth weight (Table 4).

DISCUSSION

The most frequent clinical findings were non-specific, confirming the difficulty of attaining an early diagnosis of neonatal meningitis, due to the absence

of neurological signs in the acute phase of the infectious process[8,9]. Fever, irritability, seizures and a bulging fontanel were significantly more frequent among newborns whose birth weight was ≥2500g, whereas abdominal distension, apnea, jaundice and blood count abnormalities were predominant among low birth weight newborns. It is possible that the neonates whose birth weight is ≥2500g present seizures more often due to the relative maturity of the central nervous system, when compared to the low-birth weight neonates. The low frequency of neurological findings makes diagnosis of bacterial meningitis more difficult in low birth weight newborns that in infants whose birth weight was ≥2500 g.

Suspicion of bacterial infection is usually confirmed, although not consistently by positive results of cultures of CSF or blood. The identification of the bacteria in the CSF culture is considered the most accurate method for diagnosing bacterial meningitis. The CSF culture was positive in 39% of the neonates and the blood culture obtained at the same day from the CSF sample was positive in 17.2% of the cases. These results support the findings of Garges et al.[9], which report a considerable number of neonates with a positive CSF culture and a negative blood culture. In 26.4% of the infants, only CSF was positive, with negative blood culture. According these authors, if the spinal tap had been carried out only in patients with a positive blood culture, 61% of the newborn would have gone undiagnosed.

As for the etiological agent, there was no association between the type of bacteria (gram-positive or gram-negative bacteria) and birth weight. The etiological agents most commonly identified in patients with a positive CSF culture were enterobacteria (41%), followed by *Streptococcus* B (17.6%) and other *Streptococcus* (17.6%). *Streptococcus* B was not identified in low-birth weight newborns, suggesting that in this group of neonates, meningitis was more associated to nosocomial infection than to vertical transmission. *Neisseria meningitidis*, considered a rare agent of CNS infection in the neonatal age, was found in 3 cases (8.8%). The predominance of enterobacteria in our patients is supported by other studies[10,11], which show that these microorganisms are the main etiological agents of bacterial meningitis in the neonatal period in developing countries.

Complications affected half of the cases in both groups, with an overall mortality rate of 11.5 %. Differently from what would be expected, no association was observed between the occurrence of complications or death and birth weight, although the percentage of low birth weight newborns who died (14.7%) was higher than the percentage found in infants whose birth weight was ≥2500 g (9.4%).

Despite the decrease in mortality rate compared to prior studies conducted at the same Service, which showed mortality rates of 29%[10] and 26%[12], the complications affected 50% of the patients in both groups. Others authors have emphasized the high morbidity of neonatal bacterial meningitis[11-13], regardless of the decrease in the mortality. A surveillance study carried out in 2000 and 2001 revealed a mortality rate of 12.4% for meningitis due to *B Streptococcus* infection in England and Ireland and of 8% in the USA[13]. Despite the decline in mortality, morbidity did not change significantly between 1970 and 1990. The frequency and severity of the complications in the surviving neonates demonstrated the importance of prevention in this group of patients.

The main complication observed was seizure, mainly among newborns whose birth weight was ≥2500g (p=0.003). It is possible that the increased frequency of seizures in this group is related to the relative maturity of their CNS compared to low birth weight infants.

Neonates with birth weight <1500 g presented a significantly higher frequency of intracranial hemorrhage. Because this group, whose brain is extremely vulnerable, presents several risk factors for intracranial hemorrhage, we considered it difficult to accurately assess the role of bacterial meningitis in the genesis of the hemorrhagic process.

Ventriculitis is a frequent complication of neonatal meningitis and is reported in 40 to 90% of the cases[14], especially in infants with persistent bacteria in the CSF. The frequency of ventriculitis observed in our patients (10,3%) was relatively low, which suggests that the antibiotic used in the treatment was effective. Hydrocephaly is often associated with ventriculitis or intraventricular hemorrhage.

The association between positive CSF culture and the presence of complications or death has been reported by other authors[9,12]. It is likely that the presence of bacteria or their products in the CSF is related to the maintenance of the inflammatory cascade and central nervous system injury. Fifty per cent of the deaths occurred in neonates with a positive culture for enterobacteria, which is supported by other studies that show a variation in mortality according to the type of microorganism isolated from the CSF, with enterobacteria being the most virulent[15,16]. Krebs et al.[8] observed significantly higher levels of IL-6 in the CSF

of neonates with meningitis due to gram-negative bacteria, suggesting a higher intensity of the inflammatory process in these newborns.

The brain abscess, reported in literature in 1% of meningitis cases caused by gram-negative bacteria[17], was observed in 3,4% of our patients. It is known that the abscess may have a slow evolution and reach great proportions until it is detected. Sagittal sinus thrombosis and acute brain infarct are severe complications which are rarely diagnosed *in vivo* in cases of neonatal meningitis and, in most of the cases, they are reported as necropsy findings[18]. The higher incidence of these complications in our casuistic reflects the importance of conducting image exams systematically when examining neonates with bacterial meningitis.

The incidence of inappropriate ADH secretion, reported in up to 30% of neonates with meningitis[10], was low in our patients.

There was no statistically significant difference in the duration of the treatment between the newborns presented birth weight ≥2500 g and the low birth weight newborns. Treatment of meningitis in the neonatal period is longer than therapy provided to all the other age groups because of the high severity of the disease in the newborn and the elevated risk of recurrence, which might affect 7 to 21% of the cases, even after a full treatment course[15,16]. The authors recommend that the antibiotic therapy is maintained for at least 14 to 21 days after CSF culture becomes negative[12,16]. Additionally, we recommend the systematic CSF analysis before treatment withdrawal.

We conclude that the low frequency of neurological findings makes diagnosis of bacterial meningitis more difficult in low birth weight newborns that in infants whose birth weight was ≥2500 g. The rate of complications was high in both groups, regardless of the birth weight. No significant association was observed between the occurrence of death and birth weight, although the mortality rate of low birth weight newborns was higher than the mortality rate found in infants whose birth weight was ≥2500 g. Infants with positive CSF culture had a poorer prognosis.

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