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Neonatal meningitis according to the microbiological diagnosis

A decade of experience in a tertiary center

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ABSTRACT

The aim of this study was to evaluate the incidence of and mortality due to meningitis and compare data according to microbiological diagnosis. This was a ten-year retrospective study conducted at a neonatal intensive care unit (NICU). Newborns with meningitis confirmed by positive CSF culture were included; those with congenital infection or malformations that made lumbar puncture impossible were excluded. The variables investigated were birth weight, gestational and postnatal age, procedures, hematological and CSF parameters, and complications. Parametric and non-parametric tests were used (statistical value $p<0.05$). The incidence of meningitis was 0.6% and mortality was 27%. Of the 22 cases, 59% involved Gram-negative bacteria; 36% Gram-positive and 5% fungi. The groups did not differ in relation to birth weight, gestational and postnatal age, procedures or hematological and CSF parameters. Sepsis, convulsions and deaths were frequent in both groups, without statistical difference. Gram-negative cases showed abscesses and higher frequency of ventriculitis and hydrocephaly. Meningitis was infrequent, but presented high mortality and frequent complications.

Key words: meningitis, newborn, central nervous system, sepsis.

Meningite neonatal de acordo com diagnóstico microbiológico: uma década de experiência em centro terciário

RESUMO

O objetivo do estudo foi avaliar incidência e mortalidade da meningite e comparar dados de acordo com o diagnóstico microbiológico. Estudo retrospectivo, de 10 anos, em UTI Neonatal. Incluídos RNs com meningite confirmada por cultura de líquor positiva; RN com infecção congênita ou malformações que impedem punção lombar foram excluídos. Variáveis: peso ao nascimento, idades gestacional e pós natal, procedimentos, parâmetros hematológicos e liquóricos, complicações. Testes paramétricos e não paramétricos foram utilizados (valor estatístico $p<0,05$). A incidência de meningite foi de 0,6% e mortalidade de 27%. Dos 22 casos, 59% foram por bactérias Gram-negativas; 36% por bactérias Gram-positivas e 5% por fungos. Grupos não diferiram quanto ao peso ao nascimento, idades gestacional e pós-natal, procedimentos e por parâmetros hematológicos e liquóricos. Sepse, convulsões e óbitos foram frequentes e não diferiram entre os grupos. Gram-negativos causaram abscessos e mais frequentemente ventriculite e hidrocefalia. Meningite não foi freqüente, mas apresentou alta mortalidade e complicações.

Palavras-chave: meningite, recém-nascido, sistema nervoso central, sepse.

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Neonatal meningitis is still a disease with high morbidity, although advances in perinatal care over the last few decades have been able to reduce its mortality rates to approximately 10%. Nevertheless, 20 to 58% of survivors show neurological sequelae. Another worrisome issue is the association of sepsis with meningitis, which has remained constant and rather frequent, showing rates of approximately 25%[1-3]. A recent review study on neonatal infections has reported meningitis incidence ranging from 0.8 to 6.1 cases in every 1,000 live newborns[4].

Meningitis occurring during the first week of life, particularly on the first two to three days, suggests that maternal transmission may be involved. Such cases are more frequently caused by group-B streptococci, *E. coli* and *Listeria monocytogenes*, whereas occurrences after this period suggest that nosocomial infection consisting of staphylococcal species and Gram-negative rods is the main etiological agent[2,3,5]. Studies in developed countries comparing neonatal meningitis data over the periods 1985-1987 and 1996-1997 showed little variation between etiological agents, and group-B streptococci were the agents most frequently isolated[2,6,7]. However, in developing countries, Gram-negative bacteria are the main causative agents of meningitis[8].

The hypothesis that meningitis caused by Gram-negative agents shows greater severity of progression, and the possibility that there might be characteristic findings in this group of patients that could help in the diagnosis, was the motivation for conducting this study. The aim was to evaluate the incidence of and mortality due to neonatal meningitis confirmed by culture, and to compare the clinical and laboratory characteristics of meningitis caused by Gram-negative and Gram-positive agents.

METHOD

A retrospective epidemiological study was conducted in the Neonatal Intensive Care Unit (NICU) of a tertiary center from January 1997 to December 2006 following approval from the institution's Medicine Ethics Committee.

All newborns admitted to the NICU (either born at this hospital or born elsewhere) who developed meningitis with positive cerebrospinal fluid (CSF) culture before the age of 28 days were included in the study. Newborns with clinical and serological evidence of congenital infection; central nervous system malformation that made lumbar puncture impossible; CSF contamination (more than one agent in the same culture); positive CSF culture for coagulase-negative staphylococci in the absence of concomitant positive blood culture for this agent); and cases in which it was not possible to obtain the protocol data were excluded.

Meningitis was defined laboratorially as the presence of a positive CSF culture, regardless of cytological and biochemical CSF abnormalities. Coagulase-negative staphylococci were considered to be the etiological agent of meningitis only when they was isolated in CSF and blood cultures at the same time. The indications for lumbar puncture followed the standard protocol at our service: suspected sepsis and/or meningitis, presence of positive blood culture and non-defined infectious focus. Among preterm infants older than 35 weeks that were born in situations of infection risk, and among newborns presenting fever, the puncture indication was individualized.

The patients were stratified into two groups, according to the microbiological diagnosis of meningitis (Gram-negative vs. Gram-positive), and were evaluated with regard to clinical and laboratory data. Because of the low incidence of fungal meningitis, such patients were considered only in relation to estimations of incidence and mortality.

The study began with an assessment of all positive CSF cultures from newborns admitted to the NICU during the study period. The CSF cultures were obtained from the hospital's microbiology laboratory. An automated method (BACTEC Peds Plus F) was used in this laboratory. After obtaining the culture registration numbers, the patients' charts were selected for filling out the protocols.

Variables studied

Maternal and gestational: Age; prenatal follow-up; premature rupture of membranes ≥18 hours; chorioamnionitis (maternal fever associated with at least two signs among the following: uterine hypotonia, fetid amniotic fluid, maternal leukocytosis, maternal or fetal tachycardia); premature labor and delivery.

Neonatal: Gender, birth weight, gestational and postnatal age, Apgar<7 at the fifth minute and congenital malformation.

Care procedures: Vascular catheters, parenteral nutrition, mechanical ventilation, previous antibiotic therapy and ventriculoperitoneal shunt.

Hematological parameters: Leukocyte count, platelets, immature-to-total neutrophil ratio; immature-to-segmented neutrophil ratio, Rodwell scoring system[9] and positivity of C-reactive protein (CRP). In the initial years of the study, CRP levels were determined using a semiquantitative method, but since the year 2000, it has been determined using turbidimetry. A CRP level >1 mg/dl is considered abnormal.

CSF parameters: Leukocyte count, red cells, glucose and protein.

Cultures: Agents isolated in blood and CSF.

Laboratory-confirmed sepsis was defined as clinical evidence of infection associated with alterations in temperature and/or heart rate and/or respiratory rate and/or leukocyte count, with signs of poor tissue perfusion and a positive blood culture.

Clinical course: Meningitis associated with sepsis or complicated with convulsions; ventriculitis; abscess; hydrocephaly diagnosed by means of the imaging examinations routinely performed on all newborns with meningitis (preferably cranial ultrasound); and death during hospitalization.

Continuous data were described in terms of either means and standard deviations or as medians and interquartile ranges (percentiles 25 and 75), while categorical variables were expressed in terms of the number and proportion of events. Comparisons between the groups were performed using the t test or Mann Whitney test for numerical variables, and using the chi-square or Fisher's test for categorical variables. Results were considered to be significant when $p<0.05$.

RESULTS

Among the 3,910 newborns (NB) admitted to the NICU of the University Hospital over the 10-year study period, 24 presented meningitis that was confirmed by positive CSF culture. Two patients were excluded (due to congenital infection and not obtaining the protocol variables). Considering the 22 newborns included, the incidence of meningitis was 0.6% and the mortality rate was 27% (6 NB). The overall mortality rate at the NICU over this period was approximately 12%.

In only one case did meningitis occur within the first three days of life. In this case, the agent isolated from CSF was group-B streptococci, and the patient died. The other episodes occurred after the first week of life.

Among the 22 patients studied, meningitis due to Gram-negative bacteria predominated, with this finding in 59% of the cases (13 NB). Infection occurred particularly during the first five years of the study, and the bacteria most frequently observed were *Pseudomonas aeruginosa* (3 NB), *Burkholderia cepacea* (2 NB) and *Klebsiella sp* (2 NB). *E. coli* was not isolated in any of the cultures. In the cases of meningitis due to Gram-positive bacteria (36%), the most frequent agents were *S. aureus* (2 NB), coagulase-negative staphylococci (2 NB) and group-B streptococci (2 NB). There was only one case (5%) of fungal meningitis (*Candida sp)*, which was diagnosed on the 22nd day of life of a septic 28-week premature infant with birth weight of 1,000 g. No cases of coagulase-negative staphylococci meningitis were excluded due to contamination.

The demographic data and hematological and CSF findings from newborns with meningitis according to the microbiological diagnosis are shown in Tables 1, 2 and 3.

It is noteworthy that most of the newborns were premature, had low birth weight and were diagnosed with meningitis in the third week of life. Malformation in the central nervous system corresponded to two cases of hydrocephaly and one of Dandy-Walker cyst, which were not excluded because it was possible to perform the lumbar puncture.

When comparing the groups based on etiological agents, no difference was observed in relation to maternal or neonatal variables, except for male gender, which was more frequent among the cases of meningitis due to Gram-negative agents.

Vascular catheters, parenteral nutrition, mechanical ventilation and previous antibiotic therapy were the most common procedures, but without differences between the groups. The mean and median values of the hematological tests were found to be normal and also did not differ between the groups, except CRP positivity, which was significantly higher in cases of meningitis caused by Gram-negative agents (Table 2).

The high CSF values for leukocytes and proteins, as well as the low glucose concentrations in both groups, without differences between Gram-positive and Gram-negative agents (Table 3), are also noteworthy.

Blood cultures were positive in 46% of the cases of Gram-negative meningitis and in 50% of the Gram-positive cases.

The clinical course of Gram-negative meningitis was worse, with a larger number of patients developing ventriculitis and hydrocephaly. Abscess occurred only in the Gram-negative meningitis group. Mortality was high, particularly among patients infected with Gram-positive agents; however, no difference was observed between the groups (Table 4). By analyzing deaths according to study periods (every five years), it was observed that mortality dropped from 50% to 22% over the last five years studied.

DISCUSSION

This study on confirmed cases of meningitis at a tertiary university center aimed to learn about the realities of this devastating disease, which is difficult to diagnose during the neonatal period and is responsible for high mortality rates. The hypothesis that there might be clinical and/or laboratory findings that could differentiate between meningitis infections due to Gram-negative and Gram-positive agents, along with the scarcity of data on this disease in Brazilian publications, was the motivation for conducting this study. Given the controversy regarding clinical and laboratory meningitis confirmations[1,10,11], it was decided to use a gold-standard-based diagnosis, i.e. positive CSF culture.

The incidence of meningitis confirmed by culture was not high (0.6%). An American multicenter study found a rate of 1%[11], and another review has recently shown that, in newborns with late-onset infection, meningitis prevalence ranged from 1.3% to 3.5%[12].

In this study, the mortality rate was 27% among new-

Table 1. Demographic data from newborns with confirmed meningitis, according to microbiological diagnosis.

Demographic data	Gram-negative agents (n=13)	Gram-positive agents (n=8)	Statistics p
Birth weight (g)	2770 (1155-2915)	2607 (1470-3120)	0.443
Gestational age (weeks)	35 (32-38)	33 (32-37)	0.302
Postnatal age (days)	17 (11-28)	17 (8-25)	0.852
Males (%)	9 (69)	4 (50)	0.010
Vaginal birth (%)	6 (46)	3 (37)	0.251
Apgar < 7 at the 5th min (%)	4 (31)	3 (37)	0.798
Central nervous system malformation (%)	2 (15)	1 (12)	0.895

Table 2. Hematological parameters of newborns with confirmed meningitis, according to microbiological diagnosis.

Hematological parameters	Gram-negative agents (n=13)	Gram-positive agents (n=8)	Statistics p
Leukocytes (mm^3)	15210±11980	13090±5090	0.646
Platelets (×10^3 /mm^3)	244 (103-355)	293 (100-525)	0.483
Immature-to-segmented neutrophil ratio	0.03 (0.02-0.20)	0.10 (0.06-0.20)	0.684
Immature-to-total neutrophil ratio	0.02 (0.01-0,20)	0.09 (0.05-0.11)	0.717
Rodwell score	1.8±1.5	1.0±1.1	0.200
C-reactive protein (%)	88	64	<0.001

Table 3. CSF parameters of newborns with confirmed meningitis, according to microbiological diagnosis.

CSF parameters	Gram-negative agents (n=13)	Gram-positive agents (n=8)	Statistics p
Leukocytes (mm^3)	837 (207-3336)	111 (9-5680)	0.203
Red cells (mm^3)	166 (13-1680)	50 (10-690)	0.563
Glucose (mg%)	10 (10-27)	10 (10-38)	0.817
Protein (mg%)	398±272	415±376	0.914

Table 4. Clinical course of newborns with confirmed meningitis, according to microbiological diagnosis.

Clinical course	Gram-negative agents (n=13)	Gram-positive agents (n=8)	Statistics p
Association with confirmed sepsis; positive blood culture (%)	6 (46)	4 (50)	0.671
Convulsions (%)	8 (61)	5 (62)	1.000
Ventriculitis (%)	10 (77)	5 (62)	0.032
Abscess (%)	2 (15)	0	0.015
Hydrocephaly (%)	10 (77)	5 (62)	0.032
Death (%)	3 (23)	3 (37)	0.068

borns with meningitis, which was twice as high as the general rate for the NICU during this period. However, it is noteworthy that in the last five years of the study, the mortality rate was reduced from 50% to 22%. The literature reports a decrease in mortality rate, which went down from 50% in the 1950s to the current figures of approximately 20%[1,2]. British studies comparing two periods, 1985-87 and 1996-97, showed a reduction in mortality among confirmed meningitis cases from 29% to 10%[6,7].

The detection of only one case of early meningitis corroborates the finding of low rates of positive cultures due to early infection that was observed in this NICU by Silva. This author studied early sepsis over a five-year period (1999 to 2003) and found positive blood cultures in only 1.5% of the cases[13]. Factors such as delay in performing lumbar puncture due to hemodynamic instability and use of antibiotics preceding the puncture may interfere with bacterial growth[11].

The agents causing meningitis differ according to regional and care-provision characteristics and may be the same as those causing sepsis. In developed countries, it has been reported that 30 to 40% of meningitis cases are Gram-negative, and that *E. coli* is the most frequent bacterium[1,2]. In developing countries, Gram-negative meningitis is more frequent[4,14]. The predominance of Gram-negative bacteria in the present study reflected the bacteriological pattern in the NICU in the late 1990s and early 2000s[13]. From 2001 onwards, after implementation of infection control measures, empirical therapy protocols for nosocomial infection and restrictions on the use of third-generation cephalosporin and vancomycin, coagulase-negative staphylococci became the causative agent of late sepsis in more than 60% of the cases[13], a pattern that is also found in CSF cultures.

In Gram-positive meningitis, group-B streptococci were not common. Staphylococci predominated among the Gram-positive agents and they are currently the main agents causing late-onset sepsis[4,14]. A multicenter study involving 134 very low birth weight premature infants with confirmed meningitis showed that Gram-positive agents were responsible for 63% of the episodes, with occurrences of coagulase-negative staphylococci in 29% of the cases. When the sepsis cases with meningitis were evaluated, coagulase-negative staphylococci were the agents responsible for 44% of the cases[15] .

In the present study, the newborns were mostly premature, but without low birth weight. The literature warns about occurrences of meningitis in premature infants with higher weight and older gestational age at birth, as documented in the study by Holt et al., in which only 15% of the newborns were premature and less than 33 weeks of gestational age, and 17% weighed less than 2,000 grams at birth[7]. Krebs and Taricco studied 50 newborns with bacterial meningitis at the Children's Institute in São Paulo and showed that the medians for gestational age and weight at birth were 36 weeks and 2,577 g respectively, with a postnatal age of 13 days at the time of meningitis diagnosis[16]. At present, there is great concern about premature infants of gestational age greater than or equal to 34 weeks that show physiological and developmental immaturity and greater morbidity-mortality[17-19]. Studies on ontogeny and maturation sequence are being developed in an attempt to explain these patients' greater susceptibility to infection[20,21] .

The hypothesis that Gram-negative meningitis would be more devastating and that there could be some characteristic finding in its development that would help in early identification of this condition was the motivation for comparing the two groups of agents. The association of meningitis and sepsis with positive blood cultures was high: 46% for Gram-negative and 50% for Gram-positive agents. An association between sepsis and meningitis has been described in approximately 25% of the cases[22], but these figures may vary. A multicenter study in the National Institute of Child Health on 134 very low birth weight newborns with confirmed meningitis showed that the pathogens responsible for meningitis were similar to those associated with sepsis, and that one third of these newborns did not have positive blood cultures[15]. In a multicenter study, Ansong et al. showed that 20% of infants with group-B streptococcal meningitis had negative blood cultures[23]. In another multicenter study on 9,111 newborns with gestational age greater than or equal to 34 weeks who underwent lumbar puncture, 95 patients with meningitis were detected, and of these, 62% showed positive blood culture. The authors pointed out that meningitis frequently occurs in the absence of bacteremia and, for that reason, lumbar puncture is an important part of the diagnostic investigation in cases of suspected sepsis, since it may be the only positive test[11].

Another study conducted in São Paulo on 87 newborns with meningitis diagnosed by cytological and biochemical alterations reported that 39% of the cases had positive CSF cultures and only 17% showed positive blood cultures[24].

Hematological tests have not been shown to be useful for differentiating between the agents and are unspecific in relation to infection and meningitis diagnosis[22].

Concerning the analysis of cytological and biochemical CSF parameters, the expectation that they would be able to help with diagnosis based on the etiological agents was not confirmed. Increased leukocyte and protein levels and decreased glucose concentrations occurred in both groups. These data differ from the results obtained by Smith et al.[5] in a multicenter study, in which leukocyte counts were significantly higher in cases of Gram-negative meningitis, without differences in other parameters. The larger number of patients included in that multicenter study must be emphasized, as it could explain the differences found. Garges et al.[11] evaluated the correlation between CSF culture, blood culture and CSF parameters and observed that, for the meningitis cases confirmed by culture, a leukocyte count greater than 0/mm^3 showed sensitivity of 97% and specificity of 11%. A leukocyte count greater than 21/mm^3 reduced the sensitivity to 79% but increased the specificity to 81%, and the glucose and protein values were not useful for the diagnosis. The authors concluded that it was difficult to diagnose meningitis based on changes to CSF parameters: this method did not distinguish between the agents, and no parameter alone could rule out meningitis. Therefore, cultures are essential for diagnosis. Smith et al. analyzed more than 4,000 lumbar punctures in premature infants with less than 34 weeks of gestational age and identified

95 cases of meningitis. The accuracy obtained was 0.80 for leukocyte count, 0.63 for glucose and 0.72 for protein. Thus, caution must be used in interpreting CSF values for meningitis diagnosis in premature infants, since the accuracy of these parameters is low[25].

In agreement with data in the literature, complications such as ventriculitis, hydrocephaly and abscesses were more frequent in Gram-negative meningitis. Ventriculitis may occur in 40 to 90% of the cases, particularly when bacteria persist in the CSF, while hydrocephaly is usually associated with ventriculitis and hemorrhage[24]. The frequency of abscesses was rather high (15%) in comparison with the rates of 1% to 3.4% reported in the literature[24,26]. Abscesses may develop slowly, and they are not always easily seen, which hinders diagnosis. They are often only detected in necropsies.

The high frequency of complications detected in this study points towards another worrisome aspect of neonatal meningitis: the risk of sequelae over time. Although this was not the objective in the present study, the literature shows that Gram-negative meningitis is especially responsible for sequelae such as delayed motor and mental development, auditory and visual deficits and behavioral problems, thus increasing the social and economic costs and compromising patients' and their relatives' quality of life[1,27].

Another relevant point was the high mortality rate among Gram-positive agents (one death caused by group-B streptococci, one by *S. aureus* and another by coagulase-negative staphylococci). This was also shown in the multicenter study by Heath et al., which reported death rates of 12 to 24% among meningitis cases due to group-B streptococci and of up to 36% among other Gram-positive agents, whereas mortality caused by Gram-negative agents ranged from 0 to 50%[2].

The present study has limitations, since it was retrospective, only involved a single center and only included a small number of subjects. However, it reflects the reality of a reference center for caring for high-risk newborns over a period of one decade. It is the first Brazilian study to focus on confirmed cases of meningitis by comparing groups of agents. It may contribute towards improving the knowledge on this severe disease, which despite technological advances in perinatal care, continues to present high morbidity and sequelae rates worldwide.

In conclusion, neonatal meningitis is infrequent, but shows high morbidity and mortality rates, particularly among premature infants with low birth weight. CSF parameters do not help in differentiating between agents. The clinical course of Gram-negative meningitis is more severe and shows a higher frequency of ventriculitis, hydrocephaly and abscesses.

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