RESEARCH WORK

Bacterial Meningitis and Microbiological Profile in Neonates with Suspected Sepsis: A Two Year Retrospective Study at Two Tertiary Care Centers in Lebanon. Between January 2017 to December 2019

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ABSTRACT

Background and Objectives: Sepsis is a major concern in neonates. Central nervous system infections (CNS) causing sepsis usually denotes a poor prognosis. Data on their epidemiology is lacking in Lebanon. The purpose of this project was to determine the prevalence of CNS infections in septic neonates; by identifying the causing organisms and their effects on mortality and morbidity; and by assessing the factors associated with a CNS infection. **Subjects and Methods:** A cross-sectional retrospective study was conducted in Beirut at Rafic Hariri University Hospital and Sahel General Hospital including neonates presenting for sepsis. Data was collected from their medical files and included: the prevalence of CNS infections and its etiology, mortality, the occurrence of seizures and the need for intubation, the mode and term of delivery, post-partum hospitalization, differences in C-reactive protein (CRP) levels and body temperature between neonates with and those without a CNS infection. Data was analyzed using SPSS software for Windows, version 20 (IBM, Armonk, USA). **Results:** CNS infections accounted for 3.9% of neonatal sepsis. *Klebsiella Pneumonia* was mostly isolated (37.5%). Mortality (25%), intubation (25%) or seizures (12.5%) were not increased in CNS infections compared to other causes of sepsis (P-value = 0.08, 0.62 and 0.24, respectively). The type of delivery, its term and a history of a hospitalization were not found to be associated with a CNS infection (P-value = 0.96, 0.50 and 0.20, respectively). CRP levels did not differ between neonates with a CNS infection and those without one causing their sepsis (32 mg/dl vs. 16.95 mg/dl, P-value = 0.12). The same held true for body temperature (37.11°C vs. 36.75°C, P-value = 0.52). **Conclusion:** CNS infections are a rare cause of sepsis. They do not increase mortality or morbidity. *Klebsiella Pneumonia* is the most isolated germ causing CNS infections. Body temperature and CRP levels do not differ significantly between sepsis of CNS infection and other causes.

Key words: Cerebrospinal Fluid (CSF), Central Nervous System (CNS), C-reactive protein (CRP).

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INTRODUCTION

Sepsis continues to present a major concern in neonates, due to their immature immune system. A low threshold should be kept for evaluation and treatment of sepsis due to high morbidity and mortality among newborns (1). Despite several attempts of researchers to improve prognostic and diagnostic abilities, neonatal sepsis continues to pose a challenge to the medical world globally. In 2013, up to 44% of deaths in children under the age of five occurred during the neonatal period increasing from 37% in 1990 (2). The concurrent occurrence of central nervous system (CNS) infection with neonatal sepsis is not unusual, with meningitis coexisting with up to 25% of neonates presenting with bacteremia (3). The prevalence of neonatal viral infection occurs at much lower rates, led primarily by herpes simplex virus 1 and 2, having an incidence of 1.6 to 50 per 100000 live births (4). Unfortunately, coinciding presence of central nervous system infection in neonatal sepsis causes deterioration of the infant prognosis. The morbidity of neonatal meningitis reaches substantial rates of 20% to 60%. As a part of full diagnostic evaluation in neonatal sepsis, a lumbar puncture should be performed if the infant is able to endure the procedure. However, only 30% to 50% of infants assessed for sepsis in the neonatal intensive care unit undergo lumbar puncture. Furthermore, 75% of the lumbar puncture procedures are performed after commencement of broad-spectrum antibiotics (5).The diagnosis of CNS infections is aided by epidemiological considerations, an understanding of the presenting clinical syndrome and analysis of the cerebrospinal fluid (CSF) (6). Data on the epidemiology of CNS infections in Lebanon is scarce in the literature. Since the understanding of the microbiology and the patterns of resistance are key in determining the initial empiric therapy (7), there is an interest in investigating the issue of CNS infections in sepsis in Lebanon.

OBJECTIVES

Primary objective

To determine the prevalence of CNS infections in neonatal sepsis.

Secondary objectives

To identify the microbial etiology of CNS infections; to assess the effects of CNS infections on mortality and morbidity;and to verify if the level of CRP and the body temperature differ between sepsis due to CNS infections and other causes.

SUBJECTS AND METHODS

A cross-sectional retrospective study was conducted in Beirut at Rafic Hariri University Hospital and Sahel General Hospital during the period from January 2017 till December 2019. These hospitals serve mainly the population of Beirut and suburbs as well as other regions of Lebanon where cases are referred to these university hospitals. The study targets all neonates presenting with sepsis.

Inclusion Criteria

All neonates from birth till 30 days of age and presenting with a diagnosis of sepsis are eligible for inclusion in the study.

Exclusion Criteria

Patients with severe intraventricular hemorrhage.

Data Collection

For each patient included in the study, information's were collected from the patient's medical records. It included: age, sex, presence of underlying diseases, temperature on presentation, term, mode of delivery, history of post-partum hospitalization, CRP level on admission, need for intubation, occurrence of seizures, CSF culture and analysis results and the final outcome (survival or death). The patients were then divided into two groups: one with a confirmed CNS infection and the other without a CNS infection.

Statistical Analysis

Using SPSS software for Windows, version 20 (IBM, Armonk, USA), we determined the prevalence of CNS infections among the patients admitted with a diagnosis of sepsis. We also determined the microbial etiology of the CNS infection. A chi-square test was used to determine if there is a significant association between a diagnosis of CNS infection and mortality. The same test was used to check for association between CNS infection and the occurrence of seizures or the need for intubation. A logistic regression analysis was conducted to ascertain the effects of the mode of delivery, term of delivery and history of post-partum hospitalization on the occurrence of CNS infections. An independent-sample t-test was used to check for significant differences in the CRP level and body temperature between neonates with and those without CNS infections. A P-value of < 0.05 is considered significant.

Ethical Considerations

The study was based on data collected from the medical records from the hospitals. Confidentiality was protected by

having the provided medical records stripped from any patient identifiers (name, address, cell numbers…). Furthermore, no photos of medical imaging were collected. An Institutional Review Board (IRB) approval was obtained from the relevant hospitals before proceeding with data collection.

RESULTS

General Description of the Population

The study included 207 newborns with 132 males (63.8%) and 75 females (36.2%). The male to female ratio was 1.76. The mean age was 2.9 days (± 4.23 days). Three quarters of the newborns were born at term (154; 74.4%) with 53 preterm babies (25.6%). More than half of the deliveries were by C-section (110; 53.1%) with only 97 natural vaginal deliveries (NVD) (46.9%). In this sample, only 12 newborns had underlying medical conditions (5.8%). The average time to presentation to the emergency department (ER) was 0.52 days (± 1.56 days). Early sepsis (in the first 3 days of life) was present in 174 patients (84.1%), late sepsis (in days 4 to 21 of life) in 27 patients (13%) and late late sepsis (after 21 days) in 6 patients (2.9%). The results are presented in (Figure 1).

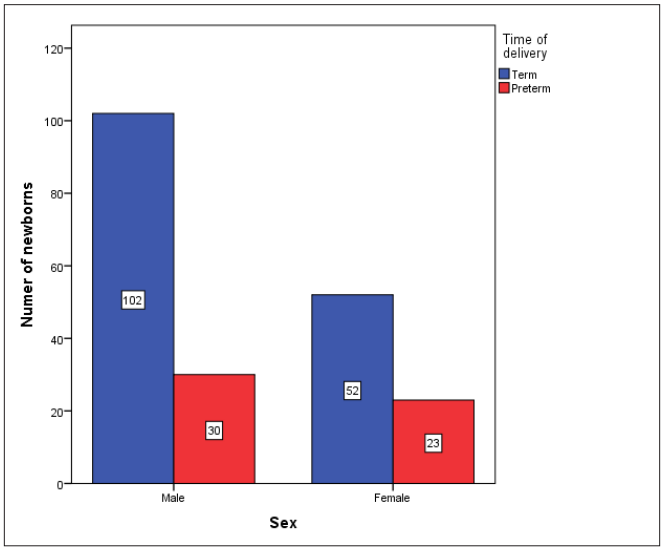

Figure 1: Chart showing the distribution of sex and time of delivery in the studied population

Prevalence of CNS Infections in Neonatal Sepsis

Among the 207 newborns with sepsis included in our study, 8 had a CNS infection (3.9%). Most of them presented with early sepsis (4 patients; 50%); 3 patients presented with late sepsis (37.5%) and 1 patient with late late sepsis (12.5%). The most commonly isolated pathogen in the cerebrospinal fluid (CSF) was *Klebsiella Pneumonia* (3 isolates; 37.5%). All the other isolates had a prevalence of 12.5% (1 case each): *Enterobacter Cloacae, Escherichia Coli, coagulase negative Staphylococcus, Streptococcus type B* and one negative CSF culture (presumed viral infection). The results are presented in (Figure 2).

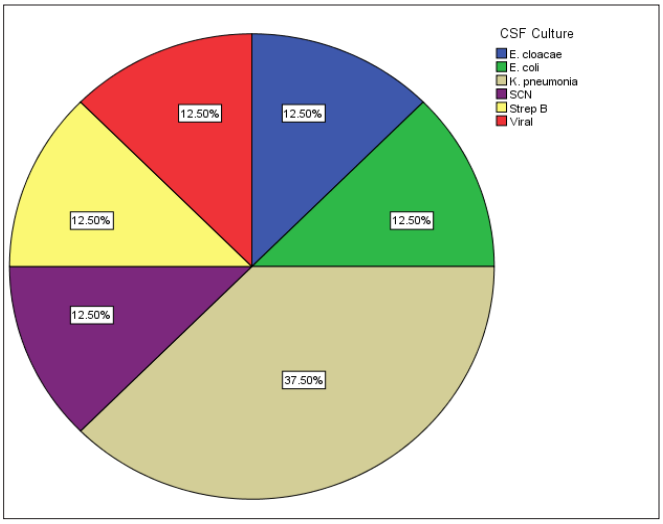

Figure 2: Results of CSF cultures

Effects of CNS Sepsis on Morbidity and Mortality

Of the newborns with CNS infection, 2 were intubated (25%). This proportion is similar to that observed in the population without CNS infection where 33 were intubated (16.6%). A chi-square test was performed to check if this observed difference is statistically significant. The test showed no correlation between CNS infection and the rate of intubation (P-Value = 0.62).A similar test was carried out to check for correlation between seizures and CNS infection. Here, again, none was found (P-value = 0.24). The group with CNS infection included 1 patient with seizure (12.5%) whereas the group without CNS infection had 6 patients with seizures (3%). This difference was not found to be statistically significant.As for mortality, there were 13 deaths in our sample. Eleven patients without CNS infection died (5.5%) while 2 patients with CNS infection died (25%). This difference was not found to be statistically significant (P-value = 0.08) (Table 3).

Table 3 shows that no association was seen between CNS infections and intubation, seizures or death. The numbers represent the count of cases. The percentages represent the proportion of the count from the total of the column. Fisher's exact test values were reported since some expected counts were less than 5.

Table 3: Association of CNS infections with intubation, seizure and death

		CNS infection				χ^2	Exact test
		Present (8)		Absent (199)			
Intubation	Yes (35)	2	(25.0%)	33	(16.6%)	0.38	0.62^{ns}
	No (172)	6	(75.0%)	166	(83.4%)		
Seizure	Yes (7)	1	(12.5%)	6	(3.0%)	2.11	0.24^{ns}
	No (200)	7	(87.5%)	193	(97.0%)		
Outcome	Survival (194)	6	(75.0%)	188	(94.5%)	4.95	0.08^{ns}
	Death (13)	2	(25.0%)	11	(5.5%)		

ns: non-significant

Factors Associated with CNS Infections

Using a logistic regression analysis, we investigated the association CNS infections with type of delivery, prematurity and a history of hospital admission post-partum. The logistic regression model was not statistically significant ($\chi 2$ = 2.32; P-value = 0.50). The multivariate analysis showed no association between any of these variables with CNS infection. The results are presented in (Table 4).

Table 4: Association of preterm, delivery mode and prior hospitalization with CNS infections

Independent variable	P-value	Odds (95% CI)
Type of delivery	0.96 *ns*	1.03 (0.24-4.35)
Term of delivery	0.50 *ns*	0.47(0.05-4.15)
Prior hospitalization	0.20 *ns*	2.62 (0.58-11.79)

ns: non-significant

Table 4 shows that no correlation exists between the type or term of delivery, a history of post-partum hospitalization and a CNS infection.

CPR and Body Temperature in CNS Infections

In CNS infection, the average temperature at presentation was 37.11°C (± 0.63) while in newborns without CNS infection the mean temperature was 36.75°C (± 1.56). An independent-sample t-test showed that this difference was not statistically significant (t= 0.63; P-Value = 0.52).In the group with CNS infection, the average CRP level on presentation was 32 mg/dl (± 34.91). In the group without CNS infection, it was 16.95 mg/dl (± 26.80). The independent-sample t-test showed that this difference was not statistically significant (t= 1.53; P-Value = 0.12).Therefore, CNS infections were not associated with significantly higher temperatures at presentation or higher CRP levels.

DISCUSSION

Our study showed a 3.9% prevalence of CNS infection among newborns admitted to the hospital for sepsis. The most isolated pathogen was *Klebsiella Pneumonia*. The presence of CNS infection did not affect with statistical significance the need of invasive mechanical ventilation. In addition, no correlation was found in patients with CNS infection and the occurrence of seizure episodes. Furthermore, the mortality difference was not seen to be statistically significant between neonates with or without CNS infection. A multivariate analysis showed no association between the mode of delivery, prematurity and the history of post-partum hospital admission with CNS infections. Finally, no statistically significant difference in temperature or CRP level was observed between septic patients with or without CNS infection. Neonatal CNS infections differ significantly from infections in older population due to a variety of age-specific factors related not only to the child, but also to the mother and specific pathogenic organisms. In our study, the prevalence of CNS infection was 3.9% in patients with sepsis, which is close to that found in another study reporting a 5 to 20% prevalence of meningitis in patients with early onset neonatal sepsis (4). In addition, one Australian study conducted in 1995 found that meningitis occurred in 23% of babies with early onset sepsis and in 10% of those with late onset sepsis. The mortality rate was around 15% in early onset sepsis population and 9% in late onset sepsis population (59). The lower rates observed in our study are most likely to be attributed to the under-diagnosis of CNS infections and empirical antibiotic treatment as well as the antibiotic era that extensively increased the usage of intrapartum antibiotics (5). In addition, the utility of CSF culture in patients suspected of having sepsis is debatable. Culture-proven bacterial meningitis affects around 0.25 out of every 1000 live births. Even though there is no agreement on whether a lumbar puncture should be performed in newborns with early neonatal sepsis, it should be done in infants with

blood culture positive and clinically suspected meningitis (35). Blood cultures are unable to reveal pathogenic germs in 15% to 50% of newborns with bacterial meningitis (8). The prevalence of culture-proven neonatal meningitis in developed countries is estimated to be 0.3 per 1000 live births, but this figure is likely to be underestimated (5). Only 30 to 50% of infants in the neonatal intensive care unit (NICU) who are evaluated for sepsis have a lumbar puncture, and it occurs in 75% of the time after the initiation of broad-spectrum antibiotics (66). The mortality rate of CNS infections ranges between 10% and 15%, and morbidity remains high (5). Up to 50% of infants who survive the illness develop chronic neurological sequelae, such as seizures, cognitive deficits, motor problems, and hearing and visual impairment (67). In our results, the mortality rate was 25% in patients with CNS infection. The difference with the mortality rate in neonates with sepsis without CNS infections did not reach a statistical significance. This higher rate of mortality in comparison with the Australian study is most likely attributed to the low number of patients with CNS infection and severe sepsis (8 patients) which could have resulted in a false increase in the percentage. In contrast, the reported mortality of neonatal meningitis is between 10% and 40% (5). Among the 207 newborns with sepsis, 8 patients had a CNS infection. *Klebsiella Pneumonia* was the most commonly isolated pathogen (37.5%), followed by the other pathogens (*Enterobacter Cloacae, Escherichia Coli, coagulase negative Staphylococcus, Streptococcus type B* and one viral meningitis). In contrast to our study, others found that *GBS* is the most common bacterial cause of early onset meningitis despite the decrease in its incidence due the initiation of intrapartum antibiotics to combat *GBS* infection. The next most common pathogen causing early onset meningitis was *E. coli* and has emerged as the most common cause of early-onset sepsis and meningitis among very low birth weight (less than 1500 g) infants (66). In late onset meningitis, *coagulation-negative Staphylococci and S. aureus* were the most common offenders, followed by *E. coli and K. pneumonia*. In addition, late onset disease included additional nosocomial organisms, particularly those found in NICU, such as *Pseudomonas Aeruginosa and methicillin-resistant Staphylococcus Aureus* (67). This discrepancy can be explained by the low number of patients in our study, and the low prevalence of *GBS* in our country due the extensive use of antibiotics intrapartum (68). In addition, the carriage rate of *GBS* in mothers in Lebanon is variable between studies ranging from 7.8% to 17.7% (68,69).Contrary to our results, many studies have reported that low birth weight (< 2500 g), preterm labor (< 37 weeks of gestation), premature and/or prolonged rupture of membranes are some of the risk factors for neonatal sepsis and meningitis (70–72). This difference is attributed directly to the lack of sufficient patients with CNS infections in our study. Our study found that no statistically significant difference in temperature or CRP level between patients with sepsis with or without CNS infection. This is in line with a study reporting that CRP is not a sensitive marker for the diagnosis of neonatal sepsis and that even high-sensitivity CRP needs more studies to explore its role in the diagnosis and approach to the patient (8). In addition, one study reported that the prevalence of fever in newborns is 1% with only 10% having culture proven sepsis which indicates directly to the lack of sensitivity of temperature measurement in diagnosing sepsis especially that not only hyperthermia but hypothermia can be present (15). Serial CRP tests have been demonstrated to improve sensitivity in the diagnosis of sepsis 24 to 48 hours after symptoms appear (73). In addition, testing CRP on regular basis is used in the assessment of antibiotic response (74). Although CRP serum levels rise mostly as a result of infections, they can also rise as a result of non-infectious reasons such as preterm membrane rupture, maternal fever, fetal distress, difficult delivery, and perinatal asphyxia. As a result, CRP has a limited specificity for early neonatal sepsis (75).

LIMITATIONS AND PERSPECTIVES

The small sample size made the statistical results not very reliable. This is due to the low incidence of sepsis and CNS infections newborns in the institutions. This could be corrected by extending the timeline of the study to increase the sample size. Our study is retrospective making it vulnerable to reporting bias. However, this study highlighted the possible prevalence of CNS infections in neonatal sepsis which was not clearly reported before in our country and provided and insight for future studies to detect and report CNS infections in newborns. As far as our knowledge, there is no local article discussed the prevalence of CNS infection in septic neonates with associated outcome and factors. We recommend increasing the time frame for any study related to the subject to increase the sample size, and increase the diversity of the sample to reflect the true prevalence in the population.

CONCLUSION

This study showed that CNS infections account for 3.9% of the causes of neonatal sepsis. Most of the patients had an early sepsis. The most commonly implicated organisms were *Klebsiella pneumonia*, followed by equal incidence of *E. Cloacae, E. Coli, coagulase negative Staphylococcus, Streptococcus type B* and viral infections. No difference

was observed in term of mortality, the need for intubation or the occurrence of seizures between the patients with and those without a CNS infection. The type of delivery and its term as well as a history of a hospitalization were not found to be associated with a CNS infection. CRP levels and body temperature did not differ between neonates with a CNS infection and those without one causing their sepsis. Unfortunately, our results do not reflect the Lebanese population for many reasons; one is the sample size which is considerably low, especially meningitis patients. Also, only two healthcare facilities were included, both in Beirut. However, we had noticed that the prevalence of meningitis patients is low; more studies should be done to confirm our results covering more healthcare institution.

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