Research Article

Is Bacterial Meningitis Associated With Specific Microorganism in Neonatal Sepsis?

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Abstract

Background: Neonatal infections including meningitis are among the major reasons of neonatal death in the region. Timely and prompt diagnosis and treatment is required to prevent its complications. Aim of this study was to find out the association between etiological agents of meningitis and sepsis in neonates.

Methods : It was a cross sectional descriptive study done at Neonatology department, the Children's Hospital Lahore, with effect from 1st March till 31st August 2018. One hundred and seventy-five neonates with blood culture positive sepsis were enrolled in the study. All patients underwent CSF tap. Thirteen neonates with congenital anomalies, deranged coagulation profile and surgical problems were excluded. The information including age, gender, weight, type of microorganisms, CSF analysis and outcome of the patients was collected on a predesigned proforma. SPSS version 20 was used for statistical analysis to look for association between pathogens causing sepsis and meningitis. Significance was calculated by using Chi-square test and logistic regression methods. Significant p-value was less than 0.05.

Results: Total included neonates were 162. Male to female ratio was 2:1. EOS cases were 53 (32.70%) while LOS cases were 109 (67.30%). Gram negative microorganism was more common in both blood cultures (n=127, 78.39%) and CSF cultures (n=41 80.40%). Meningitis was found in 103/162 (63.5%) neonates. A significant number of septic babies due to Pseudomonas, E. coli, Klebsiella and CONS were found to have meningitis.

Conclusions: Meningitis is common in blood culture positive sepsis due to Pseudomonas, E. coli, Klebsiella and CONS species.

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Introduction

Mortality in neonates is major health issue worldwide and contributes 47% to overall under five years mortality rate (U5MR).[1] Neonatal mortality rate has been reported to be 18 per 1,000 live births worldwide while for Pakistan it is 44. Major causes include infections, prematurity and birth related events (Asphyxia).[2]

Neonatal mortality due to neonatal sepsis is high (upto 50%) in developing countries as compared to developed world (upto15%), while it is 28% in Pakistan.[3-5] Neonatal sepsis is a clinical syndrome comprising of infection and systemic inflammatory response syndrome[6]. Because of diversity in presen-

tation, it requires high index of suspicion and multiple investigations for diagnosis. Blood culture remains the gold standard.[7] The common organisms implicated in developing countries are Klebsiella, Coagulase-negative Staphylococcus (CONS), Staphylococcus aureus, Escherichia coli, Pseudomonas and Enterobacter species.[8]

Acute inflammation of the meninges is called meningitis. Meningitis in the neonates can be classified as early onset if presented in less than 72 hours and late onset in more than 72 hours of age.[9] In the developed countries culture-proven neonatal meningitis is estimated at 0.3 per 1000 live births and leads to 10-15% deaths in neonates. While the incidence of neonatal meningitis in developing countries is much higher at 0.8– 6.1 per 1000 live births, with a death rate of up to 30%.[9-12]

Globally, Group-B Streptococcus (GBS) is responsible for more than 40% and Escherichia coli in 30% cases of meningitis in all early-onset infections.[8] While Coagulase-negative staphylococci and Staphylococcus aureus are the leading gram-positive pathogens and E. coli and Klebsiella spp. are the leading gram-negative pathogens which cause meningitis in late onset sepsis.[12]

Bacterial isolates causing neonatal infections in Pakistan include Escherichia coli, Klebsiella spp., Staphylococcus aureus, Pseudomonas aeruginosa and Staphylococcus epidermidis.[13]

Early diagnosis and prompt treatment of meningitis can prevent its complications and mortality. We have planned this study as limited data is available to find out the predisposition of a specific microorganism to cause meningitis in a septic newborn.

Aims & Objectives

Aim was to find out the association between etiological agents of meningitis and blood culture positive sepsis.

Objective was to improve the index of suspicion, early diagnosis and timely appropriate managent with ultimate reduction in morbidity and mortality.

Methods

This cross sectional descriptive study was done between 1st March 2018 and 31st August 2018 in the department of Neonatology at the Children's Hospital, Lahore. Consent from the local Institutional Review Board was taken before the study. Parents or guardians were taken on board with written consent before inclusion in the study. One hundred and sixty two neonates admitted in Neonatology department through OPD/ emergency were included in the study that presented with or acquired sepsis in hospital and their blood culture was positive. Blood sample under aseptic technique for gram staining, culture and sensitivity were sent on admission before starting antibiotic and during the admission in babies who developed sepsis in hospital. Sepsis presented in neonates with less than 72 hours of age was taken as early onset sepsis. While sepsis in neonates more than 72 hours of life was taken as late onset sepsis.[14] Meningitis in neonates is defined by the CSF white cell count of more than 20/mm3, CSF protein level of more than150 mg/dl and CSF glucose of less than 50 mg/dl or a CSF/serum glucose ratio of less than 0.5, with or without positive CSF culture. It was taken as early onset if presented in neonates within 72 hours of life while in neonates after 72 hours of age it was taken as late onset meningitis.[9] Non probability purposive sampling technique was done. After clinical assessment the neonates were subjected to lumber puncture under aseptic technique (for CSF cytology, biochemistry and culture) while other investigations were done where required and treated as per standard management guidelines. The neonates with congenital anomalies making lumber puncture (LP) practically impossible, deranged coagulation profile and surgical problems were excluded from the study.

Sample size was calculated by applying the formula; $n = z^2 (p) (1-p) / d^2$. Sample size was found by sample size calculator through internet by "raho soft sample size calculator." The information including age, gender, weight, type of microorganisms, CSF analysis and outcome of the patients was noted on a predesigned proforma. SPSS version 20 was used for statistical analysis to look for association between pathogens causing sepsis and meningitis. Significance was calculated by using Chi-square test and logistic regression methods. Independent sample t test was used to find significance for association of microbiological profile of blood with CSF culture.

Significant p-value was less than 0.05.

Results

Initially 175 neonates were registered for the study. Thirteen cases were excluded on the basis of refusal for LP (n=7), deranged coagulation profile (n=3), congenital malformations (n=2) and surgical problems (n=1). After excluding 13 patients finally included number of septic neonates was 162 with positive blood cultures and their information was used for this study.

The analysis of gender showed that 108 (66.66%) were male while 54 (33.33%) were female. Ratio for male to female was 2:1. They presented from 7 hours to 25 days of age at admission (mean 14.14 days ± 1.42) and weight 1.4 – 3.7 kg (mean 2.75 Kg ± 0.48). The gestational age ranged from 31 – 41 weeks and among them 90 (55.55%) were term while 72 (44.45%) were preterm with a term to preterm ratio of 1.2:1. (Table-1).

Out of a total of 162 cases, 53 (32.70%) were early onset sepsis (EOS) and 109 (67.30%) were of late onset sepsis (LOS). A significant number (n=81, p = 0.004) of LOS neonates developed meningitis. Blood culture results showed that Gram negative organisms (n=127, 78.39%) were significantly more in number than Gram positive organisms (n=35, 21.06%) (p = 0.003). Gram negative bacteria included Pseudomonas species (n=42), Klebsiella (n=29), E. coli (n=24), Enterobacter (n=14), Acinetobacter (n=11), Proteus (n=4), Citrobacter (n=2) and Serratia species (n=1). Coagulase negative Staphylococcus (n=14) predominates among the Gram positive microorganisms followed by Staphylococcus aureus (n=11), Streptococcus species (n=9) and Staph epidermidis (n=1). The detailed results are given in table-2.

Table 1: *Demographic Data (n=162)*

DEMOGRAPHIC DATA			RATIO
Gender	Male	108 (66.66%)	2 : 1
	Female	54 (33.33%)	
Age	0-3 days	53 (32.71%)	1 : 2
	4-28 days	109 (67.28%)	
G/A	[illegible]	90 (55.55%)	1.2 : 1
	<37 weeks	72 (44.44%)	
Weight	≥2.5kg	99 (61.11%)	1.5 : 1
	<2.5kg	63 (38.88%)	

Table 2: *Microbiological Profile of Blood Culture Positive Sepsis (n=162)*

Sr. No.	Microorganism	Blood Culture Positive (n)
1	Pseudomonas	42
2	Klebsiella	29
3	E. coli	24
4	CONS	14
5	Enterobacter	14
6	Staph aureus	11
7	Acinetobacter	11
8	Streptococcus	9
9	Proteus	4
10	Citrobacter	2
11	Staph epidermidis	1
12	Serratia mercecens	1
	Total	162

Meningitis was found in 103/162 (63.5%) neonates on the basis of clinical signs & symptoms, CSF cytology and biochemistry examination. CSF culture was found to be positive in 51/103 (49.5%) babies. Gram negative organisms were found in significantly higher number (n=41, 80.39%) than Gram positive organisms (n=10, 19.60%) (p = 0.001). Pseudomonas (19) was the most common microorganism among the Gram negative organisms followed by Klebsiella (n=10), E. coli (n=8), Enterobacter (n=2), Acinetobacter (n=1) and Proteus species (n=1) while CONS

Table 3: *Association of Microbiological Profile of Blood with CSF Culture*

Sr. No.	Microorganism	Positive blood culture (n)	Positive csf culture(n)	p-value
1	Pseudomonas	42	19	0.003
2	Klebsiella	29	10	0.02
3	E. coli	24	8	0.01
4	CONS	14	5	0.02
5	Enterobacter	14	2	0.20
6	Staph aureus	11	3	0.15
7	Acinetobacter	11	1	0.86
8	Streptococcus	9	2	0.17
9	Proteus	4	1	0.11
10	Citrobacter	2	0	-
11	Staph epidermidis	1	0	-
12	Serratiamercecens	1	0	-
	Total	162	51	

(n=5) was leading among the Gram positive organisms followed by Staphylococcus aureus (n=3), and Streptococcus (n=2).

In babies with Pseudomonas (p=0.003), E. coli, Klebsiella and CONS sepsis, incidence of meningitis is significant while with other microorganism its incidence is statistically not significant. The detailed results are given in table-3.

Among included cases, 115 (70.98%) neonates were discharged home after treatment, 7 (4.32%) got LAMA due to their personal reasons and 40 (24.69%) expired.

Discussion

Neonatal sepsis is among the leading causes of neonatal deaths around the globe.[1,2] Different microorganisms are implicated in its etiology. In developing countries, Klebsiella, coagulase-negative Staphylococcus (CONS), Staphylococcus aureus, Escherichia coli, Pseudomonas and Enterobacter species have been shown to be the common causative microorganisms.[8]

During literature search to find the ability of a specific organism to cause meningitis, we could not find any study that showed association between a microorganism causing sepsis and meningitis. Present study was designed to fill in this gap.

Neonatal sepsis is more common in males. Immunological difference between males and females due to polymorphism in genes for Lysosomal Binding Protein may be reason for male predominance in neonatal sepsis. Difference in response to inflammation due to sepsis between the two genders is responsible for the decrease incidence of neonatal sepsis in females.[15, 16] Same inference was made in another study done by Muhammad and Sheikh.[17,18] In our study we found twice the number of male babies was admitted with sepsis as compared to females which is in conformity to above studies. In addition gender bias towards male babies, which is known to be a universal phenomenon, can also be a reason for their larger proportion in our study.[19]

Late onset sepsis is more common as compared to early onset sepsis. Our study has shown same observations. A study conducted in Peshawar shown the similar results[20] and the similarity may be because of same infection causing pathogens and affected population. Studies conducted in Europe described identical situation where the pattern of culture-proven neonatal sepsis is more common after three days of life like a study done in United Kingdom. The similarity may be due to the reasons that cut-off limit taken to define the late onset infections is the same as taken in our study.[21]

Neonatal sepsis is a bloodstream infection which is seen in the first month of life. Both Gram negative and Gram positive bacteria are involved in its etiology, Gram negative being more common. Same was the inference by Najeeb et al in his study conducted in Pakistan.[20] In addition the study conducted in Egypt showed similar results.[22] We had comparable observation in our study which may be due to similar geographical situation/population and type of infections. In a study done in Netherland Gram positive bacteria were found to be the main contributors to neonatal sepsis. Its difference with our study and other studies done in our region may be due to difference in prevalence of microorganisms related to geographical distribution of microorganisms[23].

Meningitis is associated with sepsis and tends to develop more frequently in late onset sepsis. A study done by Izeta Softic found that 61% of babies with late onset sepsis developed meningitis.[24] Although our study showed similar results where larger proportion of cases of late onset sepsis developed meningitis, our percentage was higher (78.43%) as compared to above mentioned studies. This difference may be due to the reason that in other studies all the babies were inborn while in our study all the babies were out-born. In a study done in Tehran by Nasreen Khaleesi[25] CSF culture was positive in 25% of cases of septic newborns, while in our study CSF culture was positive in 49.5% of septic babies with positive blood culture. This yield of CSF culture could be due to administration of antibiotics prior to admission in our hospital.

Causative organisms for bacterial meningitis differ according to the population investigated, and geographic area.10 A study done in USA found Group B Streptococcus and E. coli as more common microorganisms than others.[10] while in a study conducted in Pakistan common bacterial isolates were E. coli and Klebsiella.[17] In another study in Pakistan major pathogens were Staph. aureus, E. coli, Klebsiella and Acinetobacter.[18] In our study although Pseudomonas is the predominant organism but Klebsiella, E. Coli and CONS are also among the statistically significant organisms causing meningitis in neonates. In our set up all the babies are out-born and major proportion had previous history of admission in another health facility, hence the reason of Pseudomonas being commonest in our study.

Neonatal mortality due to neonatal sepsis is high (upto 50%) in developing countries as compared to developed world (upto15%), while it is 28% in Pakistan.[3-5] The culture proven neonatal meningitis in

developed countries leads to mortality of 10-15%[13-15] while it is responsible for upto 30 % mortality in developing countries.[14,15] In our study it came out to be 24.69% that correlates to these studies.

Limitations of the study were that in our set up all the babies were out-born and major proportion had previous history of admission and administration of antibiotics from other health facility which can change the pattern of culture and sensitivity.

Conclusion

Meningitis is common in blood culture positive sepsis due to Pseudomonas, E. coli, Klebsiella and CONS species.

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