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CLINICAL TRIAL STUDY

Bacterial Meningitis Profile in Newborns: Is the Epidemiology Changing?

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Abstract:

Objective:

The aim of the study was to determine the epidemiological characteristics of bacterial meningitis observed in neonates.

Materials and Methods:

A retrospective study of all cases of meningitis, hospitalized in the neonatal intensive care unit, Mohamed VI University Hospital, from January 2016 to December 2016.

Results:

Twenty of 794 neonates admitted (2.5%) developed meningitis,with a male predominance (12 boys). The mean age of symptom presentation was 5 days. All patients were symptomatic. The most common clinical features were: fever, respiratory distress and seizure. Microbiological analysis of cerebrospinal fluid was positive in 14 cases and resulted in the isolation of several unusual species such as, *Streptococcus pneumoniae* (4 cases), Coagulase-negative *Staphylococci* (3 cases), *Enterococci* (2 cases), *Acinetobacter baumannii* (2 cases) and one case each of *Escherichia coli* , *Neisseria meningitidis* and *Klebsiella pneumonia.* Interestingly, the two *A. baumannii* cases were nosocomially-acquired, while the origins of the other infections were community-acquired. Gram-positive bacteria were more frequently responsible (9/14, 64%). All cases were treated with a combination of third-generation cephalosporins-aminoglycosides, 1 case as treated by by adding ciprofloxacin and 3 cases were treated by adding glycopeptide antibiotics to the clinical therapeutic regimes. We reported 3 cases complicated with hydrocephalus. The mortality rate was 25%.

Conclusion:

Bacterial meningitis is a medical emergency, and immediate diagnostic steps must be taken to establish the specific cause so that appropriate antimicrobial therapy can be initiated. Even with optimal therapy, morbidity and mortality may occur. Neurologic sequelae are common among survivors.

Keywords: Antibiotics, Bacterial meningitis, Cerebrospinal fluid, Lumbar puncture, Neonatal, Nosocomial.

1. INTRODUCTION

Neonatal bacterial meningitis is a severe rare infection. The prevalence varies in the world between 0.22 and 6.1 per 1000 live births [1]. It is particularly dreadful as it occurs in individuals with developing brains which also possess

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immature immune systems that places them at risk for the development of bacterial and viral infections. It differs from meningitis in older children and adults in many ways which make it difficult to diagnose and there is no specific sign. Neonatal meningitis still poses diagnostic and therapeutic challenges because of their unspecific and confusing semiology [2].

Bacterial meningitis in newborns causes high mortality and morbidity rates in Africa. *Escherichia coli*, *Streptococci* group D, *Listeria* are known frequent neonatal pathogens. Over the past few years, the evolution of microbial epidemiology has been marked by an increase of Gram-negative bacilli infections in newborns [3].

Nosocomial infections involving the central nervous system, skin and soft tissue, and bone have emerged as highly problematic. Nosocomial meningitis with multidrug resistance is rarely reported. We report some cases of neonatal meningitis in an African country which were caused by unusual pathogens.

The objectives of this study are to identify the clinical and bacteriological epidemiology and the outcome of neonatal bacterial meningitis in a newborn population in Marrakech.

2. MATERIALS AND METHODS

This study is a retrospective analysis of cases of neonatal bacterial meningitis which occurred in the Neonatal Intensive Care Unit (NICU) of Mohamed VI University Hospital of Marrakech, Morocco, between January and December 2016.

Demographic characteristics of the patients that were captured include: Birth weight, gestational age, gender, and mode of delivery. Information regarding maternal risk factors included the presence of fever on admission, premature rupture of membranes, and abnormal amniotic fluid traits.

Inclusion criteria were newborns who were hospitalized for a diagnosis of bacterial meningitis that was either positive for the presence of bacteria in cerebrospinal fluid or with more than 32 cells/mm^3 [4], predominance of neutrophils, the protein level greater than 1.5 g/l in premature; 1.7 g/l in term infants and glycorrhachia less than 44% in comparison with the plasma glucose.

3. RESULTS

Bacterial meningitis was diagnosed in 20 newborns, among the 794 neonates admitted during the study period, with a hospital prevalence of 0.49 per 1000. The sex-ratio was 1.5 males to females.

The mean age of patients was 9.45 days, 16 neonates had vaginal deliveries. The average birth weight was 2826.7g, there were 5 neonates with low birth weight (< 2500 g), with 4 premature (20%) deliveries.

Maternal fever was observed in 3 cases (15%), genital tract infection in 8 cases (40%), maternal urinary tract infection was observed in 5 cases (25%), presence of stained amniotic fluid was seen in 7 cases (35%) and prolonged rupture of membranes was observed in 6 cases (30%).

The clinical presentation was not specific for most cases. The main signs at admission were hyperthermia (43.2%), refusal to nurse (20.4%), seizures (18.2%) and respiratory distress (13.6%).

Bacteriological confirmation of meningitis was obtained in 14 cases (70%) by a positive culture of cerebrospinal fluid. The bacteria identified are represented in Table **1**.

Table 1. Bacteria isolated from CSF in neonates with meningitis.

-	Bacteria	Number of Cases
Community-acquired infection	*Streptococcus Pneumoniae*	4
	Coagulase-negative Staphylococcus	3
	Enterococcus	2
	Escherichia coli	1
	Neisseriae meningitis	1
	Klebsiella pneumoniae	1
Nosocomial infection	*Acinectobater Baumannii*	2

Blood culture was performed in all cases; it was sterile in 7 cases, *Coagulase negative Staphylococci* (CoNS) in 35% of cases, *E. coli*, *Neisseria meningitidis*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Enterococcus* and

Streptococci pneumoniae were represented respectively in 5% of cases. The antibiotic susceptibilities of the isolates were the same: either in the spinal fluid or in the blood culture (Table **2**).

The association of ceftriaxon-gentamicinwas used as first-line treatment in all cases, further adapted according to antibiogram results. Colistin was used in neonatal meningitis caused by *Acinetobacter baumannii*. Imipenem and amikacin in meningitis caused by *Klebsiella pneumonia*e, ciprofloxacin was associated during the first 5 days. Glycopeptide antibiotic was used in 3 cases: one case caused by *Enterococcus* and 2 cases caused by Coagulase *Negative-Staphylococci*.

The average duration of hospital stay was 28.6 ± 14.3 days (range: 1 to 93 days). Hydrocephalus and ventriculitis were reported in 3 cases.

The mortality rate was 25%; and the causes of death were due to septic shock (2 cases) and cardiopulmonary arrest due to neurovegetative disorders; such as apneas, respiratory distress and decompensation of the cardiorespiratory autonomic system (3 cases).

Table 2. The isolate's antibiotic resistance (R: Resistant; S: Sensitive ,; I: Inermediary).

Antibiotics	*Klebsiella pneumoniae*	*Enterococcus*	*Coagulase-negative Staphylococci*	*Acinetobacter baumani*	*E.coli*	*Pneumococcus*	*Neisseria meningitidis*
Amoxicilline	R	S	R	R	R	S	S
Ticarcilline	R			R	R		
Ticarcilline-clavulanate				R			
Piperacilline	R			R	R		
Amoxicilline-Clavulanate	R		R	R	R		S
Cefalotine	R			R	R		S
Cefoxitine	S		R	R	S		
Cefixime	R				S		S
Ceftazidime	R			R			
Cefotaxime	R	R	R	R	S	S	S
Imipeneme	S	S		S	S		S
Ertapenem	S				S		
Meropeneme	S			S	S		
Piperacilline- Tazobactam	R			R	R		
Aztreonam	R						
Nalidixic Acid	R						S
Ciprofloxacine	R	S		S	S		S
Tobramycine	R		R	S	S		
Gentamicine	R	S	R	S	S		
Amikacine	S			R	S		
Trimethoprime-Sulfamethoxazole	R	R	R	R	S		
Cefepime	R			S	S		
Peni G		I	R			S	
Teicoplanine		S	R			S	
Vancomycine		S	S			S	
Erythromycine		R	S			R	S
Lincomycine		R	S			R	
Rifampicine		S	S				
Fosfomycine		S	R				
Levofloxacine		S					
Oxacilline			R			S	
Pristinamycine			S				
Acide fusidique			R				
Kanamycine			R				
Linezolide			S				
Tetracycline			R				
Levofloxacine			R				

(Table 2) contd.....

Antibiotics	*Klebsiella pneumoniae*	*Enterococcus*	*Coagulase-negative Staphylococci*	*Acinetobacter baumani*	*E.coli*	*Pneumococcus*	*Neisseria meningitidis*
Tigecycline				R	S		
Colistine				S	S		
Aztreonam					S		
Norfloxacine						R	

4. DISCUSSION

Neonates are at higher risk of meningitis because of the immaturity of humoral and cellular immunity, and the absence of specific clinical signs makes the diagnosis of meningitis more difficult in neonates than in older children.

The incidence of neonatal meningitis varies between 0.25 and 0.32 per 1000 live births, in developed countries [5]. In contrast, very high isolation rate of neonatal bacterial meningitis was reported from Kenya which was 17.9% [6].

Signs of bacterial meningitis are often subtle in neonates; thus, the diagnosis of meningitis must be made by Cerebrospinal Fluid (CSF) examination. Currently, a positive CSF culture remains the golden standard for the diagnosis of neonatal bacterial meningitis in clinical practice.However, it may become negative within hours of antibiotic administration. Additionally, CSF culture has been shown to be of poor sensitivity for the diagnosis of bacterial meningitis. Therefore, clinicians must also rely on CSF glucose levels, White Blood Cell (WBC) count and protein levels to diagnose meningitis [7].

In this study; microbiology cultures were negative in 7 cases and the clinical diagnosis was made by review of the patient's history and clinical impressions obtained throughout the study including CSF glucose and protein levels.

While several mechanisms in the development of neonatal meningitis have been described, primary bloodstream infection with secondary hematogenous distribution to the central nervous system is most common. The late onset of symptoms and type of isolated bacteria may indicate a nosocomial origin.

Klebsiella pneumoniae meningitis, a cause of neonatal meningitis, has been reported in many studies as the most frequent etiologic agent responsible for the disease: 31% in Saudi Arabia [8], and 35.5% in Ahvaz [9]. The development of fulminant *K. pneumoniae* disease may have had community-acquired origins, suggesting bacteremia with hematogenous spread to the meninges. However, asymptomatic maternal urinary tract infection during pregnancy and nosocomial bacterial colonization during the neonate's hospital stay remain noteworthy measures to improve antenatal, intrapartum and delivery care, and greater measures during NICU hospitalization events are necessary to lower the overall risk of nosocomial infections [10], such as the case multidrug resistant K. *pneumoniae* diagnosed in the first day of life in this study.

Empirical Carbapenems and/or Aminoglycoside coverage in neonates with *K. pneumoniae* sepsis and meningitis, especially in areas with a high rate of Extended Spectrum Beta-lactamases (ESBL) producing bacteria may be warranted [11].

Coagulase Negative Staphylococci (CoNS) are known as common causes of central nervous system infections in patients with intraventricular catheters or shunts, and is inhabitant of the skin and mucous membranes; although a small proportion of neonates acquire CoNS by vertical transmission. The role of CoNS in meningitis is controversial. When cases of neonatal CoNS meningitis are described in the absence of foreign material, however, it is hard to know whether or not they represent CSF contaminants [12]. In these cases, we revealed abnormalities in CFS and signs of bacterial meningitis. All patients had hypotonia, anterior bulging fontanelle and convulsions.

Furthermore, *Acinetobacterbaumannii* are known for their multiple antibiotic resistance,are nosocomial infections whose treatment is a real therapeutic challenge, given the lack of efficient antibiotics and the lack of consensus concerning this clinical situation. Intrathecal or intravenous colistin seems to be a solution to this problem [13].

Streptococcus pneumoniae remains the most frequent cause of bacterial meningitis in children in the USA, and is caused by many distinct serotypes of pneumococci. Meningitis caused by *S. pneumoniae* is usually seen in older infants (less than 2 years of age), with its occurrence in newbornsararity [14].

Meningitis caused by serogroups A, B and C of *Neisseria meningitidis* have been described in newborns, the serogroup B remains predominant irrespective of age [15].

Enterococcal meningitis infections,though seen in neonates, are a rarity in healthy pediatric population. Patients

with head injuries, neurosurgery and enteric infections are predisposed for the above infections. It is an unusual agent for meningitis in a healthy child [16].

Neonatal bacterial meningitis is associated with significant mortality rates and devastating neurological sequelae, including hearing loss, seizures, motor function disorders, mental retardation and behavioral problems [17]. The mortality rate was 25%, similar to that observed in developed countries: The mortality rate varies based on the treatment, with survival rates of 17-29% and with complications rates of 15-68% [18].

CONCLUSION

This study emphasizes the severity of neonatal bacterial meningitis, especially in nosocomial patients, with a high rate of mortality; an early diagnosis and effective antibiotic therapy are needed to improve the prognosis.

The emergence of a nosocomially-acquired multidrug resistance pattern among Gram-negative bacilli was a trend observed in this study. These findings support the need for greater surveillance as well as continued monitoring of antibiotic resistance trends among bacterial pathogens. Lastly, the findings from this study also emphasize the need for better prenatal support care within the Marrakech geographical area.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

All research procedures followed were in accordance with the ethical standards of the committee "The Morrocan Code of Ethics" responsible for human experimentation (institutional and national).

CONSENT FOR PUBLICATION

A written informed consent was obtained from the parents.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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