Pneumococcal meningitis in the newborn period in a prevaccination era: a 10-year experience at a tertiary intensive care unit

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There are few data with respect to pneumococcal meningitis in neonates. Epidemiological aspects, clinical features and outcomes in newborn infants diagnosed with pneumococcal meningitis were evaluated in this study. Nineteen newborn infants in a neonatal intensive care unit diagnosed with culture-proven community-acquired bacterial meningitis between January 1999 and December 2008 were reviewed, and of them, eight patients were diagnosed as pneumococcal meningitis. Overall, among 10,186 hospitalized newborn infants, 132 community-acquired sepsis/meningitis cases (1.3%) were suspected, and blood cultures were performed in all, while cerebrospinal fluid (CSF) cultures could be performed in 124 cases. Rate of blood culture positivity was 45%. Nineteen (15.3%) of 124 were diagnosed as culture-proven community-acquired bacterial meningitis, which was confirmed by CSF growth. Eight (42.1%) of 19 had pneumococcal meningitis. In pneumococcal cases, abundant Gram-positive diplococci were seen on CSF smear and *Streptococcus pneumoniae* was isolated from CSF cultures. All isolates were susceptible to penicillin and third-generation cephalosporins. Irritability (n: 7), poor sucking (n: 7) and fever (n: 6) were the principal findings on the initial physical examination. Of all patients with pneumococcal meningitis, four were initially given cefotaxime plus amikacin treatment, and the remaining four were initially given cefotaxime plus ampicillin plus vancomycin. Antibiotic treatment in two patients was revised during their clinical course. Additionally, in three patients, vancomycin and ampicillin was discontinued on the third day when antibiogram of CSF cultures revealed penicillin sensitivity. Overall, mortality in pneumococcal meningitis was 50%. In the surviving patients, two had epilepsy, one sensorineural hearing loss, and two mental-motor retardation. Pneumococcal meningitis was the leading cause of community-acquired neonatal meningitis in our patients. Immunization against pneumococcal disease in developing countries would be beneficial for public health and for newborn infants.

Key words: meningitis, newborn infant, etiology, Streptococcus pneumoniae.

Bacterial meningitis of the newborn is a different entity from that in older children and adults. Despite the advances in newborn intensive care, mortality and neurological morbidity rates remain high[1,2]. Even though *Streptococcus pneumoniae* is the most commonly detected microorganism in pediatric bacterial meningitis, it is rare in newborn infants[1]. In neonatal sepsis, incidence of pneumococci varies between 1% to 11.5%[3,4].

Since few data are available with respect to pneumococcal meningitis in neonates, the objective of this study was to determine the epidemiological aspects, clinical features and

outcomes of newborn infants diagnosed with pneumococcal meningitis.

Material and Methods

Patients and Clinical Data

Medical records of the patients in the neonatal intensive care unit of Dr. Sami Ulus Maternity and Children's Hospital with culture-proven community-acquired bacterial meningitis (19 patients) between January 1999 and December 2008 were reviewed. Patients with meningitis were screened from the hospital's patient registry and tracking system. Nosocomial infection was the exclusion criterion. A hospital-acquired infection, also called nosocomial infection, is considered if an infection first appears between 48 hours and four days after a patient is admitted to a hospital or other health-care facility[5]. Therefore, patients that admitted to the hospital more than four days after discharge following delivery were accepted as having community-acquired sepsis/meningitis.

After the study had been approved by the local research ethics committee, clinical data, results of laboratory testing and radiological studies, administered medication, and outcome of the patients with pneumococcal meningitis were recorded from the patients' medical files.

Laboratory and Radiological Studies

Microorganisms isolated from cerebrospinal fluid (CSF) cultures were recorded. *CSF* was evaluated in all cases. *CSF* evaluation included total and differential cell count, biochemistry, and microscopic evaluation after Gram and India ink staining. Additionally, results of blood culture and acute-phase reactants were also assessed. In the patients whose CSF smear revealed Gram-positive diplococci and/or CSF cultures indicated growth of *S. pneumoniae,* results were confirmed by optichin susceptibility and solubility in deoxycholate. Blood and CSF cultures were considered concordant if both were positive with the same organism. CSF and blood cultures were considered discordant if the CSF was positive and the blood culture was negative or if the organism isolated from the CSF was different from that determined in the blood isolate. Antibiotic sensitivity tests of all culture-proven patients were also assessed. Antibiotic sensitivity tests were performed according to the suggestions of the National Committee for Clinical Laboratory Standards[6].

Radiological findings of the patients were also investigated. Cranial ultrasonography (USG) was performed in all patients by an experienced pediatric radiologist. Additionally, the patients suspected of having infarction were evaluated with computed tomography.

Statistical Analysis

Statistical analyses were performed using SPSS 16.0 for Windows. Data were expressed as mean (SD).

Results

a. Demographic features and clinical findings: During the study period, 132 community-acquired sepsis/meningitis cases (1.3%) were suspected among 10,186 hospitalized newborn infants, and blood cultures were performed in all, while CSF cultures could be performed in 124 cases. Blood culture positivity was 45%. Nineteen (15.3%) of 124 were diagnosed as culture-proven meningitis, which was confirmed by CSF growth. Eight (42.1%) of 19 had pneumococcal meningitis. The mean age of the 8 patients at admission was 15 ± 9.2 days (range: 5-29 days). Of them, 5 patients (62.5%) were female. Four patients (50%) were full-term and 4 (50%) were preterm infants. Gestational age and birthweight are shown in Table I. None had a history of premature rupture of membranes, or maternal fever or infection during gestation. It was noted that all cases were from low socioeconomic status families and 4 were from crowded families. The number of family members and principal complaints from the patient history are also shown in Table I.

Blood pressure values were within normal limits for all patients at admission, but the exitus patients (Cases 1-4) needed positive inotropic support during their clinical course. Irritability (n: 7), poor sucking (n: 7) and fever (n: 6) were the principal findings on the initial physical examination. Vital signs and clinical findings are summarized in Table I.

b. Laboratory findings: The CSF growth distribution in the 19 patients was as follows: *S. pneumoniae* in 8 cases, *Klebsiella pneumoniae* in

Table I. Demographic Features and Clinical Findings of the Newborn Infants with Pneumococcal Meningitis

Case no	Age at admission (d)	Gestational age (w)	Birthweight (g)	M/F	Number of family members	Principal complaints on history	Body temperature (°C)	Pulse rate (beats/min)	Respiratory rate (breaths/min)	Pathological findings on initial examination	Initial treatment	Clinical course	Outcome
1	20	Term	3400	F	13	Fever, vomiting, and hematemesis in last two days	38.7	140	48	Fever, poor sucking, tense fontanelle, superficial respiration, hyperactive tendon reflexes	Cefotaxime (17 days) plus amikacin (10 days)	After enterococcus sepsis developed on 17th day of the hospitalization, the treatment was supplanted with vancomycin	Exitus on 25th day of hospital stay
2	7	Term	3650	M	17	Fever in last two days	39.2	192	64	Fever, irritability, poor sucking, and convulsion	Cefotaxime plus amikacin	In spite of intensive care, the patient died on the 2nd day of hospitalization with intractable convulsions	Exitus on 2nd day of hospital stay
3	12	Preterm (37)	2900	F	8	Diarrhea and poor sucking in last three days	36.4	170	42	Irritability, poor sucking, tense fontanelle, convulsion	Cefotaxime plus amikacin (2 days)	The patient developed intractable convulsions on 2nd day. Amikacin was withdrawn and supplanted by vancomycin	Exitus on 10th day of hospital stay
4	5	Preterm (30)	1800	F	3	Fever, poor sucking in last two days	38.5	110	32	Fever, irritability, poor sucking	Cefotaxime plus amikacin	On the 2nd day, she had severe apnea attacks and need for mechanical ventilation	Exitus on5th day of hospital stay
5	9	Term	3800	F	4	Fever and poor sucking in last two days	38.9	170	44	Fever, irritability, poor sucking, and convulsion	Cefotaxime plus ampicillin plus vancomycin	Vancomycin was discontinued on the 3rd day when antibiogram of CSF culture revealed penicillin sensitivity. Dalteparin was used for dural sinus thrombosis	Discharged on 14th day of hospital stay with oral phenobarbital
6	29	Term	3050	F	4	Fever in last two days	38.8	110	48	Fever, irritability, tense fontanelle	Cefotaxime plus ampicillin plus vancomycin	Vancomycin was discontinued on the 3rd day when antibiogram of CSF culture revealed penicillin sensitivity	Discharged on 14th day of hospital stay
7	27	Preterm (35)	2300	M	6	Fever and poor sucking for one day	38	140	40	Fever, irritability, poor sucking, and convulsion	Cefotaxime plus ampicillin plus vancomycin	Vancomycin was discontinued on the 3rd day when antibiogram of CSF culture revealed penicillin sensitivity	Discharged on 14th day of hospital stay with oral phenobarbital
8	11	Preterm (36)	2530	M	3	Lethargy and poor sucking in last two days	36	166	48	Lethargy, irritability, and poor sucking	Cefotaxime plus ampicillin plus vancomycin	Ampicillin was discontinued on the 14th day, but vancomycin plus cefotaxime was continued till day 21 when treatment was completed	Discharged on 22nd day of hospital stay

3, *Enterobacter sakazakii* in 1, *Escherichia coli* in 3, coagulase-negative staphylococci in 2, Group B streptococcus in 1, and *Serratia marcescens* in 1 case.

Laboratory test results and radiologic findings of the patients with pneumococcal meningitis are given in Table II. Biochemical parameters including plasma glucose, electrolytes, blood urea nitrogen, creatinine, transaminases, and coagulation test results were within normal limits for all patients on admission. In all cases, abundant Gram-positive diplococci were seen on CSF smear and *S. pneumoniae* was isolated from CSF cultures. All these isolates were susceptible to penicillin and third-generation cephalosporins. Of these patients, 5 (62.5%) had positive blood culture.

c. Treatment and outcome: Of all patients, 4 (Cases 1-4) were initially given cefotaxime plus amikacin treatment. All these patients (Cases 1-4) additionally received supportive inotropic treatment, and Cases 2 and 3 also received phenobarbital for seizures. The first patient (Case 1) deteriorated for hours following the hospitalization. On the 2nd day, she developed severe apnea attacks and needed mechanical ventilation. She did not respond to treatment and died on the 25th day of hospitalization. The second patient (Case 2) who had intractable convulsions expired on the 2nd day of hospitalization. In the third patient (Case 3), intractable generalized tonic convulsions were observed during her clinical course. Cranial computerized tomography revealed advanced cerebral edema and multiple infarcts. On the 10th day of hospitalization, a cardiac arrest developed during a convulsive attack and she did not respond to resuscitation. The fourth patient (Case 4) had severe apnea attacks and needed mechanical ventilation on the 2nd day of admission. Despite appropriate antibiotic treatment and proper supportive therapy, she died on the 5th day of the hospital stay.

After CSF smear revealed abundant Gram-positive diplococci, cefotaxime plus ampicillin plus vancomycin were initiated for Cases 5-8. Additionally, Cases 5 and 7 received phenobarbital for seizures. In Cases 5-7, vancomycin and ampicillin were discontinued on the third day when antibiogram of CSF culture revealed penicillin sensitivity. All these patients (Cases 5-7) were discharged on the

Table II. Laboratory Test Results and Radiologic Findings of the Patients with Pneumococcal Meningitis

Case no	WBC (mm^3)	Hb (g/dl)	Plt ($/mm^3$)	CRP (mg/L)	CSF PMNL ($/mm^3$)	CSF protein (mg/dl)	CSF glucose (mg/dl)	CSF / serum glucose	CSF culture	Blood culture	Antibiogram	Radiological findings‡
1	7200	13.7	543000	220.3	130	80	8	0.08	*Streptococcus pneumoniae*	*Streptococcus pneumoniae*	Penicillin sensitive	Cerebral edema and multi-infarcts
2	1900	11.6	160000	148	Abundant	180	0	0.0	*Streptococcus pneumoniae*	*Streptococcus pneumoniae*	Penicillin sensitive	Normal
3	9200	11.7	630000	131.9	Abundant	378	15	0.06	*Streptococcus pneumoniae*	*Streptococcus pneumoniae*	Penicillin sensitive	Cerebral edema and multi-infarcts
4	2900	12.9	157000	86	800	242	0	0.0	*Streptococcus pneumoniae*	Negative	Penicillin sensitive	Normal
5	3300	15	323000	84.7	450	210	2	0.03	*Streptococcus pneumoniae*	Negative	Penicillin sensitive	Dural sinus thrombosis
6	18100	11.3	540000	111	Abundant	124	45	0.36	*Streptococcus pneumoniae*	*Streptococcus pneumoniae*	Penicillin sensitive	Normal
7	13200	10.4	649000	248	Abundant	156	34	0.46	*Streptococcus pneumoniae*	*Streptococcus pneumoniae*	Penicillin sensitive	Subdural effusion
8	14000	15.7	538000	104	Abundant	853	8	0.11	*Streptococcus pneumoniae*	Negative	Penicillin sensitive	Ventriculitis

WBC: White blood cell, Hb: Hemoglobin, Plt: Platelet, CSF: Cerebrospinal fluid, PMNL: Polymorphonuclear leukocyte.

14th day of treatment. In Case 8, there was evidence of ventriculitis on cranial USG. Ampicillin was discontinued on the 14th day, but vancomycin plus cefotaxime were continued till day 21 when treatment was completed.

Overall, mortality in pneumococcal meningitis was 50%. Prognoses in the surviving patients were poor: 2 had epilepsy (Cases 5 and 7), 1 sensorineural hearing loss (Case 6), and 2 mental-motor retardation (Cases 6 and 8).

Treatment, clinical course and outcome of the patients are summarized in Table I.

Discussion

The incidence of neonatal meningitis has been reported to be 0.02-0.72%, and epidemiological and etiological aspects of neonatal meningitis are similar to those of neonatal sepsis. Meningitis is accompanying in 25% of the cases with neonatal sepsis[2,7]. *S. pneumoniae* is the most prevalent agent in the etiology of childhood meningitis. However, it is a rare pathogen in the newborn period[1]. The incidence of invasive pneumococcal disease in Western Europe has been reported as 27 cases per 100,000 children under two years[8]. In a study by Giorgi Rossi[9], Streptococcus spp. was the primary cause of meningitis (17.2%) in the first three months of life. Accordingly, in our study, *S. pneumoniae* interestingly was the leading etiologic agent (42.1%) in newborns with community-acquired meningitis. Other isolated agents in our cases were *K. pneumoniae*, *E. coli*, coagulase-negative staphylococci, *E. sakazakii*, Group B streptococcus, and *S. marcescens*, similar to the agents acquired from the hospital setting. As seen in our study, lower socioeconomic status and overpopulated living conditions may have a role in both the incidence and prognosis of neonatal meningitis. All our patients were of lower socioeconomic background and four of them were from crowded families. In these situations, low hygienic conditions may be responsible for the colonization of newborn infants. A prevention intervention, like educating families regarding hygienic care and living with fewer people to control streptococcus infections in the first three months of life, would have a greater impact on reducing the number of meningitis cases.

The primary colonization site of the pneumococci is the nasopharynx. However, there is limited information on the frequency of nasopharyngeal colonization in newborns. Although the level of polymeric immunoglobulin binding receptor in neonates is unknown, a possible deficiency in this receptor level would make invasion difficult and the probability of pneumococcal infection would be unlikely. However, as seen in the present study with a 50% mortality rate and poor prognosis, once bacteremia develops, management of this infection is difficult in the newborn period[10,11].

Pneumococci may also reach the fetus or newborn infant via the transplacental route, secondary to maternal bacteremia, ascending infection from the maternal genital tract, and passage through a colonized birth canal[10]. There are rare reports of neonatal sepsis with this organism by vaginal transmission and endometritis[12,13]. In our study, despite the absence of maternal risk factors such as early membrane rupture, endometritis, and foul-smelling vaginal discharge, two patients had symptoms beginning on the 3rd and 5th days of life, which led to a clinical suspicion of vaginal transmission of the infection leading to early sepsis. Unfortunately, maternal vaginal swabs could not be performed in these cases.

If bacterial meningitis is suspected, an aggressive empirical antibiotic treatment, covering all the suspected and possible pathogens, should be started as early as possible. Combination of ampicillin with aminoglycosides or third-generation cephalosporins has been recommended[2]. Cefotaxime is the first-line drug for penicillin-resistant strains. In cephalosporin-resistant cases, vancomycin is recommended in the treatment of *S. pneumoniae*[14,15]. In our study, cefotaxime plus ampicillin plus vancomycin were the choices for initial treatment in four patients after abundant Gram-positive diplococci were seen on CSF smear, but the remaining four were initially given cefotaxime plus amikacin treatment. In two patients, the treatment was supplanted with vancomycin during their clinical course. In addition, in three patients, vancomycin and ampicillin were discontinued on the third day when antibiogram of CSF cultures revealed penicillin sensitivity. Although all growths in the culture antibiograms were sensitive to penicillin and

third-generation cephalosporins, all patients who were initially given cefotaxime plus amikacin died. However, it was observed that the patients initially given cefotaxime plus ampicillin plus vancomycin survived. Despite appropriate antibiotic treatment, the high mortality in our cases was striking. Therefore, it can be speculated that despite *in vitro* susceptibility of *S. pneumoniae* isolates to the penicillin and third-generation cephalosporins, vancomycin should be the drug choice for initial treatment in the clinical setting, if Gram-positive diplococci are seen on CSF smear.

The overall mortality of neonatal meningitis is 20-25%[16]. It has been reported as 24% in England[13] and 34% in African studies[17]. In one study, it was reported that approximately 50% of the hospitalized pneumococcal meningitis cases died in the newborn period[10]. Like the above-mentioned studies, similar rates of overall mortality in neonatal meningitis and specific mortality in pneumococcal meningitis were found in our study.

In a study conducted in Canada[18], seizures lasting longer than 72 hours, comatose state of the patient, need for inotropic drug administration, and leukopenia were found among the associated factors for poor prognosis in neonatal meningitis. In the present study, leukopenia was present in three patients and two of them needed inotropic drug administration. In the aforementioned study[18], it was also found that a ratio of CSF glucose to blood glucose of <0.5 constitutes a risk factor for poor prognosis. Accordingly, in the present study, all the patients had a ratio of CSF glucose to blood glucose of <0.5, and a poorer prognosis was seen, especially in those in whom the ratio of CSF glucose to blood glucose was near zero. Presence of these risk factors for poor prognosis is important in mortality and morbidity rates in spite of prompt and appropriate antibiotics and supportive treatment[18].

Late admission to the hospital will increase the antigenic load in the blood and lead to rapid development of inflammation. In addition, the number of microorganisms in the blood has also been reported as an important factor in determining the severity of pneumococcal infection[7]. In a study conducted in Canada[18], the patients with onset of symptoms <29 hours before admission to the hospital had better outcomes. In our study, all exitus patients had been admitted to the hospital 48 hours after the onset of their symptoms. Therefore, rapid diagnosis and prompt treatment can be life-saving.

S. pneumoniae is the most common cause of bacterial pneumonia, meningitis and sepsis in children worldwide. Immunization is one of the most beneficial and cost-effective disease prevention measures. Immunization of infants against *S. pneumoniae* at the age of two months will increase public immunity and thus indirectly decrease the probability of infecting a newborn infant from the community[19,20]. Poehling et al.[21] reported that after introduction of heptavalent pneumococcal conjugated vaccine (PCV7), the rates of invasive pneumococcal disease in young infants decreased significantly, providing evidence that vaccinating children aged 2 to 23 months has led to changes in pneumococcal carriage in infants too young to receive PCV7. In their study, rates of PCV7-serotype isolates decreased significantly from 7.3 to 2.4 per 100,000 live births, while rates of non-PCV7 serotypes remained stable. Since 2008, infants in Turkey are routinely vaccinated against pneumococcal disease with PCV7. The routine schedule is 2, 4, 6, and 12 to 15 months of age. Routine vaccination of healthy infants under two years could prevent an important number of pneumococcal infections and reduce related mortality and morbidity.

In conclusion, pneumococcal meningitis was surprisingly the leading cause of community-acquired neonatal meningitis in our patients. Immunization against pneumococcal disease in developing countries would be beneficial for public health and also for newborn infants.

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