Meningitis due to Salmonella in preterm neonates

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Meningitis due to Salmonella is a rare condition. Here we report seven cases with neonatal Salmonella meningitis diagnosed and treated in the Pediatric Neonatology Unit of Ondokuz Mayıs University Faculty of Medicine between January 1985-February 2001. Five cases were cured with appropriate treatment; in two of them no neurological sequelae were seen. Of the remaining three, reversible hydrocephalus occurred in two cases and subdural empyema was found in one. Two patients died on the 30th and 40th days of hospitalization: one of them had hydrocephalus and the other ventriculitis. In this report we point out the importance of neonatal meningitis due to Salmonella serotypes, though it rarely occurs.

Key words: Salmonella, meningitis, newborn.

Salmonella are motile, Gram-negative, non-encapsulated, nonsporulating rods of the Enterobacteriaceae family. Salmonella can localize in any organ or tissue. Salmonella serotypes (Salmonella typhimurium, Salmonella heidelberg, Salmonella enteritidis, Salmonella saint-paul, Salmonella newport and Salmonella panama) which cause neonatal meningitis are usually associated with bacteriemia[1,2]. Salmonella meningitis (SM) is a disease with high relapse and mortality rate. Antibiotic therapy should be given at least for four weeks in order to decrease the mortality rate. If the antibiotic therapy is discontinued before the third week of therapy, relapse is observed in 64% of cases[3,4]. In the survivors of neonatal meningitis with Gram-negative bacteria, complications such as hydrocephalus, convulsion, abscess formation and subdural empyema are frequently observed[5,6]. The aim of this study was to review cases with SM in our clinic together with the literature.

Material and Methods

This retrospective study was based on seven preterm infants with SM who were diagnosed in the Neonatology Unit of Ondokuz Mayıs University Faculty of Medicine between January 1985-February 2001. The diagnois of SM was established on the basis of positive cerebrospinal fluid (CSF) and/or blood culture results in addition to CSF findings, which were correlated to bacterial meningitis. Complete blood count, ALT, AST, total bilirubin, direct bilirubin, total protein and albumin levels were measured. Antibiotic susceptibilities were determined using Microbroth dilution method. Gruber-Widal agglutination test and cranial computerized tomography (CT) were performed in all patients.

Results

Four hundred and forty newborns with bacterial meningitis were hospitalized in our unit during the study period. Seven (4 female, 3 male) of them had SM (1.6%). All babies were preterm and birth weights ranged from 1,700 to 2,700 g. The mean age of the cases was 13.1 ± 3.1 days (6 to 27). There was no finding of infection in the parents, and cultures were negative for Salmonella.

All patients were born in different centers and transferred to our clinic because of meningitis, developed during hospitalization. Diarrhea (86%), convulsion (71%), fever (57%), vomiting (57%), respiratory distress (43%), jaundice (43%) and peripheral facial paralysis (14%) were observed in the patients. Meningitis was associated with acute gastroenteritis and sepsis in five patients (71%). Esophageal atresia was diagnosed in one patient with sepsis (Case 2) and myelomeningocele was found in another (Case 4).

Complete blood count revealed mean hemoglobin levels, and white blood cell and platelet counts as 11.2 ± 2.1 g/dl, 15.1 ± 4.3 X 10^9/L and 82.3 ± 21.6 x 10^9/L , respectively. On CSF examination, cell counts were within 380-9,200/ mm^3 and the mean CSF protein and glucose levels were 210 ± 36.4 mg/dl and 24.6 ± 5.1 mg/dl, respectively, before the initiation of therapy. All Salmonella serotypes were sensitive to cefotaxime, ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole (TMP/SMX) and ciprofloxacin according to the results of culture and susceptibility tests. In addition to the antibiotic therapy, intravenous immunoglobulin (IVIG) was given to four cases (Cases 3, 4, 6, 7). Five cases were cured (Cases 1, 3, 5-7). Two patients died on the 30th and 40th days of hospitalization, one with hydrocephalus (Case 2) and the other with ventriculitis (Case 4).

Gruber-Widal agglutination test was negative in all cases. CSF findings of the patients with SM showed improvement on the 14th day of the treatment except for two infants (Cases 2, 4). The clinical and laboratory characteristics of these infants are summarized in Tables I and II.

Discussion

Although the involvement of the central nervous system is a rare complication of Salmonella infections, it forms a serious problem in the newborn and early infancy periods[5,7]. Salmonella meningitis accounts for 0.8 to 6% of bacterial meningitis cases, and is usually seen during infancy period[8,9]. It affects neonatal babies and those under four months of age. In the newborn period, our cases with SM totalled 1.6% of all cases with meningitis in the same age range. Though the mortality rate in SM was 94% before antibiotic therapy, it decreased to 59-62% between 1960 and 1970. Recently, the mortality rate has been decreased to 37% in developed countries[9]. It was determined as 29% in our study.

Salmonella typhimurium is the most commonly encountered Salmonella in neonatal meningitis[10,11], but other serotypes can be isolated[2,5]. The most frequent serotype of Salmonella was also Salmonella typhimurium (4 of 7 cases) in our study.

West et al.[3] reported that acute neurological complications consisting of ventriculitis, subdural empyema and hydrocephalus were

Table I. Clinical Findings in Cases with Salmonella Meningitis

Case No.	Sex	GA	AD	BW	Treatment	TD	IVIG	Outcome	NS
1	F	33	8	2300	CF+AMP	30	–	Recovered	–
2	M	30	6	1700	CF+AMP	30	–	Died	HD
3	F	34	14	2600	CF+AMP, CIP	32	+	Recovered	Subdural empyema
4	M	32	11	2200	CF+AMP, CIP	40	+	Died	Ventriculitis
5	F	34	12	2300	CF+AMP, CIP	31	–	Recovered	HD
6	F	35	14	2700	CF+AMP, CIP	30	+	Recovered	HD
7	M	34	27	2600	CF+AMP, CIP	30	+	Recovered	–

F : Female.
M : Male.
GA : Gestational age (week).
AD : Age at diagnosis (day).
BW : Birth weight (g).
TD : Therapy duration (day).
IVIG : Intravenous immunoglobulin.
CF : Cefotaxime.
AMP : Ampicillin.
CIP : Ciprofloxacin.
NS : Neurological sequelae.
HD : Hydrocephalus.

Table II. Laboratory Findings of Cases with Salmonella Meningitis

Case no.	Hb	WBC	PLT	CSF findings: Cell count (mm^3)	CSF findings: Protein (mg/dl)	CSF findings: Glucose (mg/dl)	Gruber-Widal test	Culture	Salmonella serotypes	CT
1	11.1	14.2	57.6	380	200	26.4	Negative	Blood	S. typhimurium	N
2	10.8	8.2	76.4	9200	270	10.2	Negative	Blood+CSF	S. enteritidis	A
3	11.2	14.6	92.6	4000	160	24.4	Negative	Blood	S. typhimurium	A
4	9.2	19.2	61.3	3200	220	13.2	Negative	CSF	S. enteritidis	A
5	10.6	16.7	98.6	960	200	36.1	Negative	Blood+CSF	S. species	A
6	14.2	15.6	94.2	1400	190	28.4	Negative	CSF	S. typhimurium	A
7	11.3	17.2	95.4	670	230	33.5	Negative	Blood	S. typhimurium	N

Hb : Hemoglobin (g/dl).
WBC : White blood cell count (10^9/L).
PLT : Platelet count (10^9/L).
CSF : Cerebrospinal fluid findings.
CT : Computerized tomography.
N : Normal.
A : Abnormal.

found in 43% of the cases, and they observed relapses in 64%. Dunn et al.[12] erported 12 cases of subdural empyema, two of them associated with SM. Krcmery et al.[8] reported reversible hydrocephalus that responded to intraventricular punctures in two of the 12 cases with SM. Hansen et al.[13] reported two cases of SM; one died six days after admittance to the hospital and the other recovered without sequelae. In our study, five of the seven cases were cured and two of them had no neurological sequelae (Cases 1, 7). Reversible hydrocephalus that responded to treatment was seen in two cases (Cases 5, 6). One case had subdural empyema (Case 3). Two patients died on the 30th and 40th days of hospitalization, one with hydrocephalus (Case 2) and the other with ventriculitis (Case 4).

Over the last 20 years, Salmonella meningitis was often treated with ampicillin and chloramphenicol with high relapse and mortality rates. Third generation cephalosporins such as cephotaxime and ceftriaxone, with a good penetration to CSF, were found more effective. Children with septicemia, enteric fever, or metastatic sites of infection should be treated initially with systemically administered cephotaxime and ceftriaxone. Ciprofloxacin and TMP/SMX are alternative agents. It is known that ciprofloxacin is effective in the treatment of SM. After the negative effect of ciprofloxacin on the development of cartilage was demonstrated in animal models, the use of ciprofloxacin under the age of 18 was limited[8,14]. However, this effect has not been supported in clinical tirals. Krcmery et al.[8] reported that 10 of 12 cases of neonatal and infant nosocomial meningitis treated with ciprofloxacin were cured. In our study, ciprofloxacin was given to the patients (5 of 7 cases) who did not show any sign of clinical improvement on the 7th day of treatment, which included a third generation cephalosporin antibiotic; even the susceptibility tests revealed no resistance. Four of the five cases recovered (Cases 3, 5-7), but one died (Case 4) on ciprofloxacin therapy.

Intravenous immunoglobulin has been proposed recently for neonatal SM. Brandun et al.[15] determined that there were antibodies against the D antigen of Salmonella in certain IVIG production pools and declared that IVIG could be used in serious Salmonella infections. In a study which was performed by Gökalp et al.[16], IVIG was given to three preterm newborns with Salmonella typhimurium infection. One of them recovered without sequelae, another had hydrocephalus and the other had subdural empyema. In our study, four cases received IVIG; three of them recovered (Cases 3, 6, 7) and one of them died (Case 4). On the other hand, one of the three cases who did not receive IVIG died (Case 2), while the other two recovered. It seems there is no additional effect of IVIG on the clinical improvement of the cases with Salmonella meningitis in the neonatal period. Our results may confirm the idea of Harry[17] on IVIG use in the neonatal period.

We conclude that SM should be considered among the causes of bacterial meningitis in the newborn period. Immediate suitable treatment is essential to obtain satisfactory recovery.

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