

SALMONELLA TYPHIMURIUM MENINGITIS IN CHILDHOOD*

*Mehmet Ceyhan MD**, Erol Kınık MD***, M. Kâzım Çağlar MD*****

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Meningitis caused by organisms of the salmonella group is a relatively uncommon condition but it is important because of the very high mortality rate^{1,2}. The first case of salmonella meningitis, reported by Ghon³ in 1907, was due to *Salmonella paratyphi B*. Most cases of salmonella meningitis in the literature are due to *Salmonella enteritidis*, but some cases caused by other serotypes of the salmonella group have also been reported^{1,4}. Articles presenting salmonella meningitis generally report only a few cases, whereas larger numbers of cases are needed in order to be able to determine the epidemiological, clinical and laboratory features and the prognosis of this disease. In this presentation, 47 pediatric patients seen at Hacettepe Children's Hospital are evaluated from the epidemiological, clinical and laboratory points of view and the causes of the high fatality rate are discussed.

Material and Methods

Forty-seven pediatric patients admitted to Hacettepe Children's Hospital from 1977 through 1983, whose cerebrospinal fluid culture yielded *Salmonella typhimurium*, were included in the study group. The medical records of the patients were examined for clinical and laboratory findings and treatment. Particular attention was given to body weight, temperature and any complications. In addition to routine blood and cerebrospinal fluid (CSF) tests, the results of bacteriological cultures were also recorded.

Findings

At the time of admission, the patients ranged in age from two hours to 16 months; 28 (59.6%) were boys and 19 (40.4%) were girls. Thirty (63.9%) patients were below the third percentile for weight (Table I). The time between admission and diagnosis of meningitis was eight hours to 31 days, with a mean time of 11.5 ± 7.2 (SD) days. The time between the diagnosis of meningitis and death varied from 6 hours to 29 days (mean time: 5.9 ± 4.7 days).

* From the Hacettepe University Institute of Child Health, Ankara.

** Resident In Pediatrics, Hacettepe University Institute of Child Health.

*** Professor of Pediatrics, Hacettepe University Institute of Child Health.

**** Pediatrician, Ankara.

TABLE I
Weights of the Patients by Percentiles

<u>Percentiles</u>	<u>Number of patients</u>
<3	30 (63.9%)
3 – 10	7 (14.9%)
10 – 25	3 (6.4%)
25 – 50	4 (8.5%)
50 – 75	1 (2.1%)
75 – 90	1 (2.1%)
90 – 97	–
> 97	1 (2.1%)

No other salmonella species was isolated in CSF cultures during the period investigated. All the patients were diagnosed as having *Salmonella typhimurium* meningitis before death.

The body temperature measured in the axillary region was above 38 °C on at least one occasion in 45 (95.7%) of the 47 patients.

The severe manifestations and complications most commonly encountered were seizure, disseminated intravascular coagulation and subdural empyema (Table II).

TABLE II
The Severe Manifestations and Complications in 47 Cases with *Salmonella Typhimurium* Meningitis

<u>Severe manifestations and complications</u>	<u>Number of patients</u>
Seizure	16 (34.0%)
Disseminated intravascular coagulation*	9 (19.1%)
Subdural empyema	6 (12.8%)
Subdural fluid collection (other than empyema)	2 (4.2%)
Sclerema	2 (4.2%)
Pyopneumothorax	2 (4.2%)
Myocarditis	2 (4.2%)
Subarachnoid hemorrhage	2 (4.2%)
Hemiplegia	1 (2.1%)
Necrotizing enterocolitis	1 (2.1%)

* When prothrombin time and partial thromboplastin time were longer than five minutes and there were no thrombocytes in the peripheral blood films, the condition was diagnosed as disseminated intravascular coagulation (DIC).

TABLE III
Cerebrospinal Fluid Findings of the Patients with
Salmonella Typhimurium Meningitis

Cell count/mm ³		Protein (mg/dl)	Glucose (mg/dl)	Blood glucose [*] (mg/dl)
Polymorphonuclear leucocytes	Lymphocytes			
1302 ± 644**	57 ± 49	407.4 ± 128.9	22.9 ± 44.3	78.4 ± 21.9

* Obtained at the same time as CSF glucose

** Standard deviation

TABLE IV
Treatment Applied to Patients with
Salmonella Typhimurium Meningitis

Drugs	Number of patients
Ampicillin (iv)* + Aminoglycoside** (iv)	26 (55.3%)
Ampicillin (iv) + Chloramphenicol (iv)	3 (6.5%)
Ampicillin (iv) + Aminoglycoside (iv)	
+ Aminoglycoside (it)	8 (17.0%)
Ampicillin (iv) + Aminoglycoside (iv)	
+ TMSM*** (im)	2 (4.2%)
Ampicillin (iv) + Aminoglycoside (iv)	
+ Chloramphenicol (iv)	3 (6.5%)
Ampicillin (iv) + TMSM (im)	1 (2.1%)
Aminoglycoside (iv) + TMSM (im)	2 (4.2%)
Chloramphenicol (iv) + TMSM (im)	
+ Aminoglycoside (it)	1 (2.1%)
Ampicillin (iv) + Aminoglycoside (iv)	
+ Chloramphenicol (iv) + Aminoglycoside (it)	1 (2.1%)

* The route of administration :

iv : Intravenous

it : Intrathecal

im: Intramuscular

** In 42 patients who received intravenous aminoglycosides, gentamicin was used in 27, kanamycin in five, streptomycin in seven and neomycin in three. The intrathecal aminoglycoside used in ten cases was gentamicin.

*** TMSM: trimethoprim-sulfamethoxazole.

Whereas one severe manifestation was seen in each of 26 patients, two in seven patients, three in three patients, and four in one patient, no complication at all was seen in the remaining ten.

The white blood cell counts in the first five days of diagnosis were between 700 and 52.000/mm³, with a mean count of $17.657 \pm 12.285/\text{mm}^3$. There was PMNL (polymorphonuclear leucocyte) predominance in all the patients. CSF of all patients showed marked pleocytosis with a predominance of PMNL, increased levels of protein and decreased glucose (Table III).

The CSF culture which grew *Salmonella typhimurium* was obtained on the first day of hospitalization in 19 (40.4%) patients. Diarrhea was present in 42 (89.4%) cases. Feces cultures of 16 of these 42 patients (38.1%) were positive for *Salmonella typhimurium*. One of the six subdural fluid cultures obtained from the patients with subdural empyema and 57% of 47 blood cultures grew *Salmonella typhimurium*.

The drugs used for treatment are given in Table. IV.

Discussion

Meningitis caused by salmonellae of various types accounts for 1.4% of all bacterial meningitides⁵. *Salmonella* meningitis, especially that caused by *Salmonella typhimurium*, is quite rare in the developed countries^{1,5}, whereas in the developing countries and especially in childhood salmonella meningitis is mostly due to this type⁶. It has been shown that the frequency of salmonella meningitis is high among newborns in Turkey⁷. The largest series of salmonella meningitis to be presented was that by Watson¹ in 1958. This author reviewed the cases in the literature, and out of a total of 151 cases 13 were found to have been caused by *Salmonella typhimurium*. The incidence of salmonella microorganisms in acute bacterial meningitis was found to be 10.2% in a study in our hospital during the epidemic seasons⁶.

In general, salmonellae reach the meninges through the gastrointestinal tract and the blood⁸⁻¹¹. But it is hard to cultivate the microorganisms in feces and blood cultures on every occasion. The small percentage of positive cultures in our series may be due to the relatively short staying time of the bacteria in these materials and the difficulty of cultivating salmonella microorganisms.

Since *Salmonella typhimurium* is commonly spread indirectly by contaminated food, water, hands of personnel and instruments, hospital-borne epidemics are frequent^{12,13}. Although there are hospital infection series in the literature, the presence of *Salmonella typhimurium* in the CSF cultures obtained on the first day of admission shows the frequency of this microorganism in our community. *Salmonella* meningitis mainly affects newborns and infants^{1,2,5}. The reason for the increased incidence of salmonella meningitis in infants, and particularly in

neonates, is not known. The need for fewer microorganisms to establish infective disease in infants than in adults^{14,15}, birth trauma⁵, increased permeability of the blood-brain barrier¹⁶, decreased opsonization of gram-negative bacilli and immaturity of certain immune mechanisms¹⁷ are suggested to explain the high frequency of *Salmonella typhimurium* meningitis. A marked susceptibility of boys to the disease is also apparent in our series, as in other infections of the newborn period. The higher incidence in boys has also been reported for other types of salmonella infections¹⁸⁻²¹.

Salmonella meningitis has frequently been reported in children with malnutrition¹⁷, and 63.9% of our patients were below the third percentile, which supports the earlier studies.

There was a marked elevation in the number of white blood cells with a predominance of PMNL in the blood and cerebrospinal fluid. Although most of the patients were very young and malnourished, the presence of hyperthermia in a high proportion is interesting since hyperthermia is not a constant finding in salmonella meningitis in the literature⁸.

Although many antibiotics have been used for the treatment of salmonella meningitis, the results have not been encouraging¹⁴.

The death rate from this disease is very high and particularly so in infants as compared with older children and adults. Watson¹ reported the mortality rate as 100 percent in his series reviewed from the literature. Very few patients have recovered from this disorder²¹. The rapidly progressive clinical course of the patients in our series was remarkable, with less than a week elapsing between the diagnosis of meningitis and death.

Chloramphenicol and ampicillin were the drugs of choice⁵. It was reported that both these antibiotics achieve effective levels in the CSF and are bactericidal against most salmonella organisms². Other antibiotics used in the treatment of salmonella meningitis include trimethoprim-sulfamethoxazole, cephalosporin, chlortetracycline, aminoglycosides and intrathecal ampicillin^{2,5,21}. Combination chemotherapy composed of 2-4 antibiotics, even intrathecally in some cases, was unsuccessful in our patients, in whom the mortality rate was 100%. The most important cause of this high mortality is an F₁me plasmid coded for ampicillin, chloramphenicol, streptomycin, sulphonamide, tetracycline, gentamicin and trimethoprim resistance in *Salmonella typhimurium* in Turkey and other countries in the Middle East and South East Asia^{6,22,23}. Therefore, we suggest that these antibiotics are not effective in the treatment of *Salmonella typhimurium* meningitis, and combination chemotherapy composed of new antimicrobial drugs such as polymyxin-B, amikacin, tobramycin and sisomicin should be tried.

The incidence of sequelae of *Salmonella typhimurium* meningitis is uncertain, since there is no report including sufficient numbers of cases in the literature. The

rate of the severe manifestations in our 47 cases was high, and only ten of our cases were free of such complications.

In conclusion, meningitis caused by *Salmonella typhimurium* is highly dangerous and generally fatal, especially in the Middle East and South East Asia as pointed out in the literature. Generally it is resistant to the antimicrobial agents used at the present time. Therefore, it is necessary to use new antibiotics in combination.

Summary

Clinical and laboratory findings and prognosis of forty-seven children aged two hours to 16 months with *Salmonella typhimurium* meningitis are presented. Nineteen of the cerebrospinal fluid cultures were positive for *Salmonella typhimurium* on the first day of hospitalization. Although there was diarrhea in 42 patients, only 16 feces cultures were positive for *Salmonella typhimurium*. Malnutrition was frequent in our patients, but all had the cerebrospinal fluid findings expected in acute bacterial meningitis. Even with combination chemotherapy composed of 2-4 antibiotics, and with intrathecal administration of drugs in some cases, we were unable to prevent death. The life span after the diagnosis of meningitis was six hours to 29 days, with a mean time of 5.9 ± 4.7 days. The 100% mortality was probably an outcome of the resistance of this microorganism to various antibacterial drugs, which is most likely related to a plasmid of the microorganism. We believe that a new antibiotic regimen composed of new drugs such as polymyxin-B, amikacin, tobramycin or sisomicin should be tried.

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