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# Clinical Study on Neonatal Meningitis

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A clinical study was made on 68 cases of neonatal meningitis occuring under the age of 1 month at the department of Pediatrics at Severance Hospital, Yonsei University College of Medicine from 1st Jan. 1965 to 31th Dec. 1981.

The sex ratio of male to female was 1.8:1 approximately. Neonatal predisposing factors significantly associated with neonatal meningitis were omphalitis(14 cases), skin infection (13 cases), birth injury(9 cases) and pneumonia(8 cases) etc. The most common maternal predisposing factor was difficult labor(13 cases). In 27 out of the 68 cultured CSF, the most common organisms were E. coli (29.6%), Staphylococcus coagulase(+) (22.2%) and Beta meholytic streptococcus (22.2%). Gram negative organisms were found in 12 cases (44.4%). The most common presenting symptoms were non-specific in nature – an elevated or subnormal body temperature, convulsion, poor feeding, irritability, jaundice and vomiting in that order of frequency. The presence of a poor Moro reflex, neck stiffness, unconsciousness or convulsion correlated with the high mortality rate significantly. Complications and sequelae included convulsion(11 cases), subdural effusion(8 cases), candida infection(8 cases), hydrocephalus(2 cases) and cerebral hemorrhage(2 cases) in that order of frequency. In the 68 cases, there were 29 mortalities or 42.6%.

**Key Word:** Neonatal Meningitis

Infections are a frequent and important cause of morbidity and mortality in the neonatal period. Neonatal meningitis especially is one of the most severe infections in the neonatal period.

There are several factors which contribute to the frequency and severity of neonatal infection and emphasize the importance of early diagnosis and appropriate therapy. First, a variety of organisms are etiologic agents. Second, the presenting clinical features in the neonate with infection may be subtle and may mimic the features of other common diseases during this period, as a result, the diagnosis of infection is often missed or delayed until the process has become widespread. Third, some routine laboratory tests available to aid in the diagnosis of infection appear to be imprecise or do not provide the rapid results needed. Fourth, the host resistance mechanisms present in the newborn infants, particularly the sick premature infants, may be immature and easily

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overcome by invading microorganisms. Infections, therefore, may fulminate and cause death within a few hours or days, despite appropriate and intensive antimicrobial therapy. Finally, many of the bacterial infections are caused by organisms relatively resistant to antibiotics, particularly the gram-negative enteric bacillic. These infections are difficult to treat and the dose of antibiotics that can safely be used is limited by toxic side effects. Thus early and precise diagnosis of neonatal meningitis and aggressive therapy is critically important.

## MATERIAL AND METHODS

The author has collected comprehensive clinical statistical data in 68 cases of neonatal meningitis concerning the etiological agents, predisposing factors, major clinical symptoms and signs, physical findings, other clinical symptoms in relation to prognosis, mortality rate and complications and sequelae from Jan. 1965 to Dec. 1981, a 17 year period at the department of Pediatrics, Yonsei University College of Medicine, Seoul, Korea.

All 68 cases were under one month of age. Three cases were delivered at Severance Hospital Prematurity was present in 2 pases and the other 66 cases were all fulltern neonates.

Neonatal meningitis was diagnosed on the basis of the criteria described by Groover et al, including positve bacterial cutlure, 200 or more cells in the CSF, 300mg/dl or more protein and less than 20mg/dl sugar in CSF, and postmortem evidence of purulent meningitis.

Blood agar, chocolate agar and thioglycollate medium was used for bacterial culture. Blood agar used tryptose, blood agar (Difco) and chocolate agar used GC medium base (Difco) as the base medium and 5% human bank blood was added to both media. Thioglycollate medium used fluid thioglycollate medium or modified thioglycollate medium. Inoculated blood agar and chocolate agar were cultured in a candle jar or the $CO_2$ incubator. Streak Staphylococcus on the inoculated blood agar plate promoted Hemophilus influenzae culture since 1974. Identification of isolated bacteria was done by the general method in the manual of clinical microbiology described by Blair et al.

## RESULTS

### 1) Incidence rate and mortality rate

The incidence of neonatal meningitis is that 44 cases were male and 24 cases were female with a male to female ratio of 1.8:1 and so males are more commonly affected by neonatal meningitis. During this 17 year period, the total number of admitted neonates were 3,326 among which were 68 cases of neonatal meningitis which represented 2.0% of the overall admitted neonates. With 29 deaths among 68 cases of neonatal meningitis, the mortality rate was 42.6% (Table 1).

During this period between 1965 and 1981, there was little change in the annual incidence rate of neonatal meningitis which comprised 2-4% of the overall admitted neonates (Fig. 1).

### 2) Onset by age and mortality rate

Cases of neonatal meningitis were most common among infants within the first week after birth with 28 cases or 41.2% and the mortality rate was also high among infants within the first week after birth with 13 cases or 46.4%. After one week of age, there was no difference in morbidity rate between the other age groups. There was little correlation between the age incidence and the mortality rate of neonatal meningitis although the 1-2 weeks of age group and a lower mortality rate than other age groups (Table 2).

Table 1. Incidence and mortality rate of neonatal meningitis (1965-1981)

| Sex | Total neonatal admissions | Number of cases (%) | Number of deaths (%) |
|---|---|---|---|
| Male | 1,941 | 44 (2.3) | 19 (43.2) |
| Female | 1,385 | 24 (1.7) | 10 (41.7) |
| Total | 3,326 | 68 (2.0) | 29 (42.6) |

Table 2. Onset by age and mortality rate of neonatal meningitis

| Onset | Number of cases (%) | Number of deaths |
|---|---|---|
| Under 1 week | 28 (41.2) | 13 |
| 1-2 weeks | 13 (19.1) | 2 |
| 2-3 weeks | 12 (17.6) | 6 |
| Over 3 weeks | 15 (22.1) | 8 |
| Total | 68 (100.0) | 29 (42.6%) |

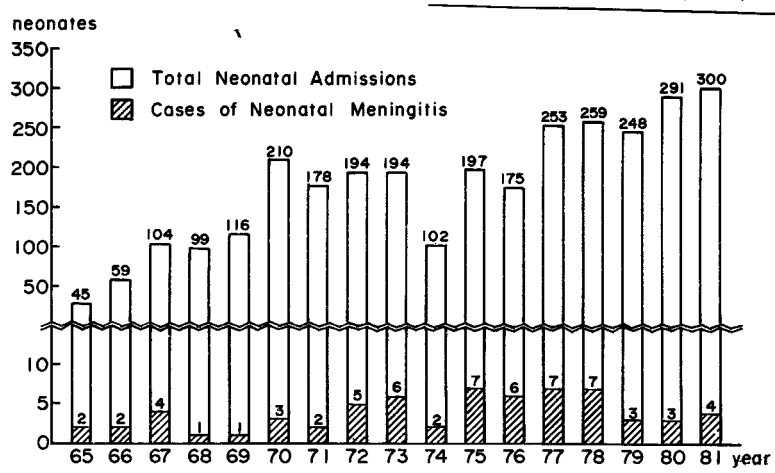


Fig. 1. Annual incidence of neonatal meningitis.

Table 3. Predisposion factors of neonatal meningitis in both infant and mother

| Infantile factors | No. of cases (%) | Maternal factors | No. of cases (%) |
|---|---|---|---|
| Omphalitis | 14 (20.6) | Prolonged or difficult labor | 13 (19.1) |
| Skin infection | 13 (19.1) | Early rupture of membrane | 4 ( 5.9) |
| Birth injury | 9 (13.2) | Precipitate labor | 3 ( 4.4) |
| Pneumonia | 8 (11.8) | Emergency C/S | 3 ( 4.4) |
| SAH* | 3 ( 4.4) | | |
| Prematurity | 2 ( 2.9) | | |
| Otitis | 1 ( 1.5) | | |
| Meningomyelocele | 1 ( 1.5) | | |

* Subarachnoidal hemorrhage

### 3) Predisposing factors

Among the predisposing factors of neonatal meningitis, direct infantile causes included omphalitis with 14 cases or 20.6%, skin infection with 13 cases or 19.1% and birth injury with 9 cases or 13.2% etc. Secondary maternal factors related to neonatal meningitis included pro-

**Table 4. Identified causative organisms of neonatal meningitis**

| Organism | CSF No. of cases (%) | Blood No. of cases (%) |
|---|---|---|
| E.-coli | 8 (29.6) | 7 (29.2) |
| Staphylococcus coagulase (+) | 6 (22.2) | 7 (29.2) |
| Beta-streptococcus | 6 (22.2) | 4 (16.7) |
| Proteus mirabilis | 2 ( 7.4) | 1 ( 4.2) |
| Enterococcus | 2 ( 7.4) | 1 ( 4.2) |
| Pseudomonas | 1 ( 3.7) | 1 ( 4.2) |
| Alpha-streptococcus | 1 ( 3.7) | |
| Hemophilus influenzae | 1 ( 3.7) | |
| Staphylococcus coagulase (−) | | 1 ( 4.2) |
| Serratia marcescence | | 2 ( 8.3) |
| Total | 27 (100.0) | 24 (100.0) |

**Table 5. Clinical symptoms of neonatal meningitis**

| Symptoms | No. of cases (%) |
|---|---|
| Temperature | 53 (77.9) |
| high temperature | 50 (73.5) |
| subnormal temperature | 3 ( 4.4) |
| Convulsion | 39 (57.4) |
| Poor feeding | 27 (39.7) |
| Irritability or listlessness | 23 (33.8) |
| Jaundice | 18 (26.5) |
| Lethargy | 17 (25.0) |
| Vomiting | 16 (23.5) |
| Diarrhea | 12 (17.6) |
| Respiratory difficulty (dyspnea, apnea, shortness of breath) | 11 (16.2) |
| Cyanosis | 9 (13.2) |
| Crying abnormality (high piched, feeble) | 6 (8.8) |
| Nystagmus | 3 ( 4.4) |

longed difficult labor with 13 cases or 19.1% and early rupture of membranes with 4 cases or 5.9% etc. (Table 3).

### 4) Causative organisms

Identified by CSF culture, E. coli with 8 cases or 29.6% were most common, Coagulase positive staphylococcus with 6 cases, Beta hemolytic streptococcus with 6 cases, Proteus mirabilis with 2 cases and Enterococcus with 2 cases in decreasing order of frequency. Other organisms such as Pseudomonas, Alpha hemolytic streptococcus and Hemophilus influenzae with one case each were also observed. Thus gram negative bacteria were implicated in 44.4% or 12 cases and gram positive bacteria were 55.6% or 15 cases.

In blood culture, E. coli with 7 cases and Coagulase positive staphylococcus with 7 cases were common organisms. Other observed organisms were Beta hemolytic streptococcus, Proteus mirabilis, Enterococcus, Pseudomonas, Coagulase negative staphyloccus and Serratia marcescens. In 11 cases the same organisms were identified in pus, blood and CSF culture (Table 4).

### 5) Clinical symptoms and signs

High or low body temperature was found in 53 cases or 77.9%, convulsions in 39 cases or 57.4%, poor feeding in 27 cases or 39.7%, irritability or listlessness in 23 cases or 33.8%, jaundice in 18 cases or 26.5% and lethargy in 17 cases or 25.0%. Vomiting, diarrhea, respiratory difficulty and cyanosis were also observed (Table 5).

Other clinical features of neonatal meningitis included poor Moro reflex in 40 cases or 58.9%, neck stiffness in 20 cases or 29.4%, impaired consciousness in 32 cases or 47.1%, presence of tense or bulging anterior fontanel in 29 cases or 40.6%, anisocoria in 3 cases or 4.4%, positive Kernig's sign in 18 cases or 26.5% and positive Brudzinski's sign in 10 cases or 14.7% (Table 6).

**Table 6. Mortality rate of neonatal meningitis in relation to clinical features.**

| Clinical features | | No. of cases (%) | No. of Deaths (%) |
|---|---|---|---|
| Moro reflex | Fair | 28 (41.2) | 3 (10.7) |
| | Poor | 40 (58.8) | 26 (65.0) |
| Neck stiffness | Present | 20 (29.4) | 10 (50.0) |
| | Absent | 48 (70.6) | 19 (39.6) |
| Impaired consciousness | Present | 32 (47.1) | 18 (56.3) |
| | Absent | 36 (52.9) | 11 (30.6) |
| Body temperature | High fever | 50 (73.5) | 21 (42.0) |
| | Normal | 15 (22.1) | 7 (46.7) |
| | Subnormal | 3 ( 4.4) | 1 (33.3) |
| Convulsion | Present | 40 (58.8) | 19 (47.5) |
| | Absent | 28 (41.2) | 10 (35.7) |
| Tense or bulging fontanel | Present | 29 (42.6) | 11 (37.9) |
| | Absent | 39 (57.4) | 18 (46.2) |
| Anisocoria | Present | 3 ( 4.4) | 3 (100.0) |
| | Absent | 65 (95.6) | 26 (40.0) |
| Kernig's sign | Present | 18 (26.5) | 12 (66.7) |
| | Absent | 50 (73.5) | 17 (34.0) |
| Brudzinski's sign | Present | 10 (14.7) | 5 (50.0) |
| | Absent | 58 (85.3) | 24 (41.4) |

**Table 7. Cerebrospinal fluid findings of neonatal meningitis**

| | Ranges | No. of cases (%) | No. of cases (%) |
|---|---|---|---|
| Protein (mg/dl) | 50 | 4 ( 7.2) | 3 (75.0) |
| | 50-100 | 11 (20.0) | 1 ( 9.1) |
| | 100-300 | 22 (40.0) | 4 (18.2) |
| | 300-700 | 9 (16.4) | 5 (55.6) |
| | 700 | 9 (16.4) | 8 (88.9) |
| | Total | 55 | 21 |
| Sugar (mg/dl) | 20 | 18 (32.7) | 4 (22.2) |
| | 20-40 | 14 (25.5) | 2 (14.3) |
| | 40-60 | 10 (18.2) | 4 (40.0) |
| | 60 | 13 (23.6) | 4 (30.8) |
| | Total | 55 | 14 |
| Cells ( /$mm^3$) | 20 | 4 ( 6.6) | 1 (25.0) |
| | 20-100 | 19 (31.1) | 8 (42.1) |
| | 100-500 | 18 (29.4) | 2 (11.1) |
| | 500-1000 | 4 ( 6.6) | 4 (100.0) |
| | 1000 | 16 (26.2) | 8 (50.0) |
| | Total | 61 | 23 |

### 6) Relationship between clinical features and prognosis

Among 68 patients, 29 patients died with a mortality rate of 42.6%. With a poor Moro reflex, the death rate was 65.0%, with the presence of neck stiffness, the death rate was 50.0%, with convulsions, the death rate was 47.5%, with anisocoria, the death rate was 100.0%, with the presence of Kernig's sign, the death rate was 66.7% and with Brudzinski's sign, the death rate was 50.0% (Table 6).

### 7) Cerebrospinal fluid findings

A protein level over 100mg/dl was found in 72.8%. Sugar level below 40mg/dl was found in 52.8%. Cell counts over 100/mm$^3$ were found in 62.3% with the majority of cells being monocytes. There was no close relationship between CSF findings and mortality rate (Table 7).

### 8) Complications and sequelae

There were various post-therapeutic complications and sequelae of the neonatal meningitis such as continued convulsions in 11 cases, subdural effusion in 8 cases, Candida infection in 8 cases, hydrocephalus in 2 cases and cerebral hemorrhage in 2 cases. Seven cases of subdural effusion were diagnosed by subdural tap 4-7 days after the onset of meningitis. There was no improvement of high fever, seizures or bulging anterior fontanel after initiation of the therapy. So the patients had transillumination with positive results and were confirmed by subdural effusion with subdural tapping. In 1 case of subdural effusion, pus discharged from the subdural tap done 2 hours after onset of neonatal meningitis and Beta hemolytic streptococcus was identified by culture from the CSF. Five cases out of eight having subdural effusion expired. Two cases developed hydrocephalus one month and three months after discharge. They complained of enlarged head size. On physical examination, continuing buling anterior fontalel and positive Macewen's reaction were observed. Hydrocephalus was confirmed by skull X-ray and C-T brain scan. They were treated with ventriculo-peritoneal shunt. One out of two cases of cerebral hemorrhage showed localized cerebral hemorrhage by autopsy. One case of sepsis devleoped high fever abruptly after improvement of the treated meningitis and Serratia marscence was identified by blood culture (Table 8).

**Table 8. Complications and sequelae of neonatal meningitis**

| | Number of cases (%) |
|---|---|
| Convulsion | 11 (16.2) |
| Subdural effusion | 8 (11.8) |
| Candida infection | 8 (11.8) |
| Poor muscle tone | 7 (10.3) |
| Thrombocytopenia | 5 ( 7.4) |
| Hydrocephalus | 2 ( 2.9) |
| Cerebral hemorrhage | 2 ( 2.9) |
| Decerebrate rigidity | 2 ( 2.9) |
| Sepsis | 1 ( 1.5) |
| Osteomyelitis | 1 ( 1.5) |
| Orbital cellulitis | 1 ( 1.5) |
| Phlebitis | 1 ( 1.5) |
| Pneumonia | 1 ( 1.5) |

### 9) Prognosis

With 24 deaths among 68 neonatal meningitis cases, the morality rate was 42.6% (Table 1). We were able to follow 19 cases among 44 survivors from 1 month to 3$^6/_{12}$ years. Among them, we observed three cases of cerebral palsy and two cases of hydrocephalus. Pleocytosis of the CSF was observed in one case upto two months after discharge.

## DISCUSSION

The morbidity and mortality of purulent

meningitis in pediatric patients has been sharply decreased due to improvement of treatment modalities with the development of antibotics. However, the prognosis of the neonatal meningitis is very poor and even if the baby survives the residual complications and sequelae rate remains high.

Fortunately, neonatal meningitis is not very common. According to Cruickshank, there was 4.1% meningitis in 800 autopsy cases of neonates. According to Groover and Overall, the incidence of neonatal meningitis is 0,4-0.46 percent 1,000 births. In the analysis of 409 cases of pediatric meningitis by Smith, the frequency was most common within the first month of life than for any other age group. The author experienced 2.0% meningitis among all hospitalized neonates during the same period.

According to Groover, McDonald, Overall and Ziai, the diagnostic criteria of neonatal meningits consist of isolation of the causative organism, pleocytosis, increased protein and decreased glucose level in the CSF, and finally confirmation by autopsy.

According to Groover and Ziai, most of the neonatal meningits occur within the one week after birth and premature infants develop meningitis earlier than fullterm infants. The author's findings are similar; 41.2% of the cases occured within the first week after birth which comprised almost half of the cases. However, there was no difference in incidence rate in the other age groups. This may be explained by the difference in predisposing factors experienced by the author compared to others. According to Feigin, Overall, Riley and Ziai, the main predisposing factors were prematurity and obstetric complications. However, we have found that omphalitis and skin infections caused by Staphylococcus and Beta hemolytic streptococcus were the main predisposing factors. This may be the cause of the delay in the age of incidence in general. Mortality rate is lowest in the 1-2 week aged group. This may be due to the relatively late onset of the disease than the high risk neonate group and relatively early treatment than any other age groups.

Berman, Watson and Ziai described that neonatal meningits during the first two weeks of life was mainly due to gram negative organisms and gram positive organisms were predominent after the first two weeks of life. This is similar to our findings. Neonatal meningits due to E. coli was seen mainly during the first two weeks and those due to Beta hemolytic steptococcus and Staphylococcus were seen mainly after the first two weeks of life.

Gotoff, Washburn and Wison reported that neonatal sepsis is more prevalent in the male and this is in line with the Haggerty and Ziai study which indicated male predominence in neonatal meningitis with 57 male cases compared with 27 female cases. Our experience is similar, with 44 male cases and 24 female cases, a male to female ratio of 1.8·1. The reason for male predominence in neonatal sepsis and meningitis remains unknown but there are two theories. Berman, Kaplan and Washburn state that factors regulating the synthesis of immunoglobulin reside in the X chromosome and so the male is more susceptible than female. Eichenwald and Wilson state that there is male predominence in congenital urinary tract anomalies which predisposes to urinary tract infection and secondarily to sepsis.

According to Overall, there are no seasonal or yearly variations in the incidence rate of neonatal meningitis. Our study revealed similar findings. We compiled data on the last seventeen years on a yearly basis. The incidence rate of neonatal meningitis is about 2-4% per year.

The cause of neonatal meningitis can be seen as combination of maternal, neonatal and microbiological factors. According to Berman and

Fulginiti, maternal infections, especially of uterus, cervix, vagina and the urinary tract are closely related to the neonatal infections. Berman, Fulginiti, Kaplan, Keitel and Overall described that this close relationship is suggested by isolation of the same organism in the maternal infection site and the neonatal CSF. According to Baker and Eickhoff, the neonatal infections due to E. coli and Beta hemolytic streptococcus frequently follow maternal infections of cervix and vagina particularly. According to Berman and Pryles, neonatal infection rate is also high in cases of maternal pyrexia without a specific infection site. Other maternal factors that increase the risk for neonatal meningitis are premature rupture of the membranes, placenta previa, abruptio placenta and fetal distress during delivery are described by McDonald, Overall, Pryles and Tyler. Overall's study indicated that complications during delivery were the main predisposing factors of neonatal meningitis. Haggarty and Ziai reported that 62.5% of the neonatal meningitis were due to complications during delivery. Groover reported that 56% of the neonatal meningitis were due to obstetric complications during delivery also. In our experience, 23 cases of neonatal meningitis were due to obstetric complications during delivery. Feigin reported that cephal hematoma was the most common external neonatal trauma following difficult delivery and cephal hematoma can be complicated by osteomyelitis and meningitis.

As stated previously, the risk of neonatal sepsis is high with prematurity. Groover reported that premature infants has 17 times the risk of neonatal meningitis compared with fullterm infants. Low birth weight infants have 4 times the risk.

Sepsis is a very common predisposing factor for neonatal meningitis. This is suggested by positive blood cultures in neonatal meningitis cases. Bulter and Gotoff reported that the blood culture was positive in more than 2/3 of the neonatal meningitis patients and about 1/3 of the neonatal sepsis cases were accompanied by meningitis. Our study found that 24 of 27 positive CSF cultures (89%) had a positive blood culture.

According to Berman, Overall and Ziai, skin infection, omphalitis, pneumonia, otitis media, urinary tract infection and gastrointestinal tract infection predispose to neonatal meningitis. There is a high risk of neonatal meningitis in meningomyelocele patients also.

Our study found that of the neonatal predisposing factors, omphalitis was the most common with 14 cases. Of these, 12 put of 14 cases were home delivered and in 7 cases the umbilical cord was cut with unsterilized scissors. This suggests that unsterile home delivery remains a big problem in Korea. Education about the antenatal care and sterile delivery conditions are urgently needed.

Other predisposing factors that we have found are skin infection, external trauma during delivery, pneumonia and otitis media. Most of the cases of external trauma during delivery were with difficult delivery and age of the incidence was lower in these cases.

Bellanti stated that the resistance to infection is lower in neonates compared to older children and the infection is lower in neonates compared to older children and the infection rate from microorganisms is high due to a deficiency in host immunity. According to Anderson, Felgin and Miller, neonates in general, lack phagocytic activity, including chemotaxis, opsonization and intracellular killing. According to Fireman, there is a deficiency in chemotaxis and the chemotactic activity in serum is deficient which is due to the lower level of $C_3$ and $C_5$. According to Dosset and McCracken, there is deficient opsonization in serum against

Serratia marcescens which is due to the inability of IgM antibody to pass through the placenta. According to Forman, in a low birth weight infant, there is deficient opsonization in serum against Serratia marcescens, E. coli, Proteus, Pseudomonas and Staphylococcus and also IgA antibody can't cross the placenta.

Welsh described that there are lower rates of gram negative sepsis, meningitis and infections in breast fed neonates. According to Hanson and Winberg, bacteria begin to colonize the body shortly after birth. E. coli is the first to colonize the intestinal tract. Hanson decribed that the reason such a strong pathogenic organism cannot infect neonates is due to the intrinsic colonization resistance against alkaline bacteria present in the intestinal tract and the protective immune activities of the intestinal mucosa. Breast milk, especially secretory IgA in the colostrum, has a local protective effect in the gastrointestinal tract. Breast milk also contains secretory IgA against the O & K antigen of E. coli. The secretory IgA and other factors in the breast milk play an important role in control of bacteria in the intestinal tract and help prevent neonatal meningitis and sepsis. In other words, during early neonatal period when local immunity is deficient, the breast milk plays the main protective function.

According to Feigin, inhalation therapy equipment, monitoring devices, venous or umbilical catheterization and contact with adults are causative factors of the neonatal meningitis. This is especially true in high risk infants because premature infants and sick neonates usually use the equipment.

The specific type or group of bacteria plays an important role in causing the neonatal meningitis. Baker reported that neonatal sepsis caused by Beta hemolytic group B streptococcus is related to subgroup I and II, whereas neonatal meningitis infection is related to subgroup III. Albritton et al, recently reported that neonatal meningitis due to Listeria monocytogenesis is mainly caused by type IV.

According to McCracken and Robbins, the neonatal meningitis caused by E. coli is mainly due to the E. coli possessing the KI capsular polysaccharide antigen. The morbidity, mortality and complication rates are higher in the E. coli possessing the KI capsular polysaccharide antigen compared to the E. coli that do not possess it. This is especially true when the concentration of the KI antigen is increased in the CSF. This suggests that there are some antigens which may aid in CNS invasion.

According to Feigin, the main causative organisms of neonatal meningitis are gram negative bacteria. Of the gram negative bacteria, E. coli is the most common causative organism. The second most common organism is the gram positive beta hemolytic group B streptococcus. Feigin and Shearer reported that Listeria monocytogenes and Flavobacterium meningosepticum infected meninges easily. According to Overall, mixed bacterial infection or bacteria and viruses can be observed in the neonatal meningitis.

According to Robbins, resuscitation or inhalation therapy of neonates predispose to infection by Serratia marcescens, Proteus and Pseudomonas, and the use of indwelling catheter predisposes to sepsis and meningitis due to Staphylococcus, Pseudomonas, Bacterioides and Citrobacter.

Our study found 27 cases or 39.7% of positive CSF culture. This is similar to. 43.2% of positive CSF bacterial culture recently reported by Lee of a study concerning the pediatric purulent meningitis in Korea. This finding is considerably lower than the 93% positive CSF bacterial culture reported by Groover, 90% reported by Fosson, 80% reported by Overall and 79% reported by McDonald. The possible explana-

tion for this discrepancy is the antibiotic abuse before hospitalization, antibiotic use for infections of the umbilical cord and skin which became infected during unsterile delivery and the technical errors of culture, including using inappropriate culture media.

In our study E. coli was the most common bacteria isolated and this is similar to other reports. The second most common bacteria found was Coagulase positive staphylococcus. This is in contrast to other reports which state that Beta hemolytic streptococcus is the second most common organism. The possible explanation for this difference is that we had more infections of the umbilicus and skin with Staphylococcus as predisposing factors.

Overall and Riley stated that clinical manifestation of neonatal meningitis are non-specific so that early diagnosis is difficult, and the younger and smaller the infant, the symptoms are more non-specific and more uncharacteristic. Generalized symptoms of irritability, respiratory difficulty, cyanosis, jaundice, poor feeding, vomiting and hyperthermia or hypothermia may occur. Fever may or may not occur.

Particularly in premature infants, hypothermia occur as frequently as hyperthermia. Also tachypnea, cyanosis, tachycardia and bradycardia may occur. Symptoms and physical findings show individual variation and the clinical course is very rapid so that death is possible within several hours.

Most of the deaths occured within the first week in our study. Localized neurologic findings, cranial nerve palsy, abnormal Moro reflex and an abnormal crying sound may be present. Abdominal distension, diarrhea, jaundice, hepatosplenomegaly, pallor, petechiae and purpura may occur. Meningeal irritation signs including nuchal rigitidty or increased intracranial pressure signs are very rare. According to Fulginiti and Groover, it is usually seen as a terminal stage of the disease and if it is seen in the early stage, the prognosis is very poor. Butler reported that the neurologic findings are not prominent. Nuchal rigidity was seen in less than 10% of the patients with neonatal meningitis and anterior fontanel bulging was seen in less than 40% of the patients.

Overall and Riley stated that the diagnosis of neonatal meningitis requires early the suspicion of meningitis and perform early blood culture and the CSF study. The cell counts in CSF may reach 10,000-12,000/$mm^3$ but it may be within normal limits. The CSF protein can be elevated or normal. The CSF glucose level in meningitis is usually one half of the blood glucose level. However, hypoglycemia is common in neonates so that a decrease in CSF glucose is not very helpful in diagnosis as compared to an adult or older child. Gram stain and culture of the CSF must be performed regardless of the color of the CSF. McCracken and Robbins reported that the use of group B meningococcal antisera for finding KI antigen of E. coli and antisera against a variety of group B streptococcal serotypes may be helpful in diagnosis. Berman reported that the limulus assay, used for detection of endotoxin in body fluids, is helpful in diagnosing gram negative meningitis although a causative organism cannot be identified. Berman, Feigin and Shackelford state that neonatal meningitis is frequently associated with sepsis so that two or more blood cultures are necessary and counter-immunoelectrophoresis and limulus lysate assay of blood and urine can be helpful in diagnosis.

Localized infection may progress to meningitis so that culture of body orifices or body fluids can be helpful in early diagnosis. Skin infection and abscess must be measured and cultured. Stool or urine culture in also helpful in locating a primary site of meningitis caused by intestinal bacteria. One of our cases which

had infection of the umbilicus and a skin abscess, grew Coagulase positive staphyloccus from cultures of both sites.

According to Overbach, a frozen section of the placenta or amnion in cases of neonatal meningitis accompanied by chorioamnionitis are helpful in diagnosis.

According to Scanlon, sepsis can be confirmed by 3 or more white cells seen with the light microscope examination of external ear canal tissue smear.

According to Bellanti, Feigin and Ziai, leukopenia indicates an infection. Bacterial infection increases band forms in particular. We had two cases of leukopenia and both expired. The rest of the cases had leukocytosis and on differential count, polymorphonuclear leukocytes and band forms were increased.

Hypoglycemia and hyponatremia may also be present. Hypoglycemia is more common in gram negative sepsis than in gram positive bacterial infection.

Eichenwald, Feigin, Kaplan and McCracken described that the treatment of neonatal meningitis should be started immediately if there is any suspicion of neonatal meningitis. Ampicillin and gentamicin or kanamycin should be used before confirming the diagnosis. McCracken reported that gentamicin instead of kanamycin is more commonly used because of the emergence recently of kanamycin resistant Enterobacter in 25-35% of the neonatal sepsis. Aminoglycosides can be injected into the subarachnoid space but there is no difference in the effectiveness when compared with the noninjected group.

If a specific organism is cultured, then appropriate antibiotics should be given based upon the sensitivity test. Use penicillin G for Beta hemolytic group B streptococcus, ampicillin for Listeria monocytogenes, Proteus and Enterobacter. Use carbenicillin and gentamicin for Pseudomonas and methicillin for Staphylococcus.

According to Eichenwald and McCracken, meningitis caused by gram negative bacteria should be treated for at least three weeks or treated for two more weeks after the CSF findings have normalized. In case of gram positive bacteria, it should be treated for at least 14 days. Repeat the CSF culture after the termination of the antibiotic therapy.

Feigin has described recently a new treatment method being used. Antibiotics injected into the ventricle of the brain. Chloramphenicol is used instead of aminoglycoside since it penetrates blood-brain barrier easily.

According to Bellanti and Groover, other supportive treatments are also important. Stop oral medications. Parenteral therapy of adequate fluids, electrolytes and glucose is recommended. Transfusion of fresh whole blood is helpful in recovery from anemia and shock, it increases chemotaxis and supplies phagocytic material. Temperature regulation is also important. Rectal temperature should be maintained at 37-38°C and the body suface temperature should be maintained at 36-37°C. Give oxygen for hypoxemia and phenobarbital and diphenylhydantoin for seizures.

Complications include subdural effusion, apnea (requiring assisted ventilation), thrombophlebitis, hydrocephalus and septic arthritis. According to Berman, hydrocephalus is an especially common complication in the neonate and this is due to the destruction of the arachnoid villi or meningeal fibrosis.

We had 8 cases of subdural effusion. Overall reported 3 cases of subdural effusion out of 25 meningitis patients. We had 2 cases of hydrocephalus. One of the cases developed hydrocephalus 3 months after cessation of treatment and was treated by ventriculo-peritoneal shunt.

In general, the prognosis of neonatal menin-

**Table 9. Mortality rate of neonatal meningitis.**

| Author | Year | Number of patients | Number of expired cases | Motrality rate |
|---|---|---|---|---|
| Smith | 1954 | 36 | 24 | 67% |
| Watson | 1957 | 45 | 29 | 64% |
| Ziai & Haggerty | 1958 | 83 | 62 | 75% |
| Groover et al | 1961 | 39 | 25 | 67% |
| Berman & Banker | 1966 | 29 | 20 | 70% |
| Fosson & Fine | 1968 | 21 | 16 | 76% |
| Chevrie & Aicardi | 1969 | 36 | 22 | 61% |
| Overall | 1970 | 25 | 15 | 60% |
| Mcdonald | 1971 | 82 | 41 | 50% |
| Lee | 1982 | 68 | 29 | 43% |

gitis is poor although several antibiotics are available. Now there are differences in the mortality rate as noted in other reports but most are in the range of 50-70% which is quite high (Table 9). In our study, the mortality rate was 43%.

According to Berman, Overall, Watson and Ziai, there is a 63-85% complication rate after survival from treated neonatal meningitis. These include quadriplegia, blindness, deafness, seizure, mental retardation and hydrocephalus. We had 3 cases of cerebral palsy and 2 cases of hydrocephalus out of 19 follow up cases. There was one case of pleocytosis in the CSF persisting more than 2 months after discharge.

Poor prognostic clinical symptoms and signs that are related to mortality rate include poor Moro reflex, nuchal rigidity, unconsciousness, seizure, anisocoria and positive Kernig's sign.

According to Overall, a poor Moro reflex, nuchal rigidity and unconsciousness are related to a high death rate; McDonald also reported that seizure indicated a poor prognosis and other poor prognostic factors are hypothermia, leukopenia, age of onset less than one week after birth and a positive blood culture. We had two cases of leukopenia and both expired. We found that hypothermia and when onset was less than one week after birth, did not influence the prognosis. Of the 24 cases of positive blood culture, only 8 cases expired, so that this also did not have much influence on the prognosis. McDonald reported that an increased CSF protein level indicates a poor prognosis and we had similar findings.

According to Berman, autopsy findings of neonatal meningitis are similar to the autopsy findings of meningitis in older children. But the differences include a lower lymphocyte count during the subacute stage of meningeal reaction, many bacteria in meningeal effusion after adequate antibiotic treatment and more frequent complications of hydrocephalus, encephalitis and cerebral tissue infarction.

We performed two autopsies. The first case was admitted because of a seizure episode and meningitis was confirmed by the CSF findings. This case expired during treatment. The autopsy findings included confirmation of meningitis by gross inspection and a localized cerebral hemorrhage was noted. The other case had necrosis in the basal ganalia and Proteus was isolated from the culture of the necrotic tissue.

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