Hemophilus meningitis

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HEMOPHILUS MENINGITIS

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College of Medicine, University of Nebraska

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Omaha, Nebraska
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HEMOPHILUS MENINGITIS

Introduction

Hemophilus meningitis is a disease which is frequently fatal or crippling when occurring in young children. In the United States H. influenzae is the most common cause of bacterial meningitis in the two to thirty-six month age group. Although the prognosis of these patients has improved greatly with the advent of modern antibiotics, rapid diagnosis and treatment are necessary to prevent death or severe sequelae.

This paper is an attempt to review all the cases of this disease which occurred in the Omaha area during the ten-year period from 1953 through 1962. A review of the recent literature on the subject is included for completeness and for purposes of comparison. It was hoped to determine the characteristic signs and symptoms, the methods of diagnosis and their reliability, the methods of treatment, and the mortality and sequelae of this disease.

History and Epidemiologic Review

Hemophilus influenzae was first isolated by Pfeiffer in 1892 from patients suffering from epidemic influenza. Until 1918, it was believed to be the cause of this disease. It is now known to cause secondary pulmonary
infections during viral-caused influenza epidemics, rather than to cause influenza.

Man is the only known natural host for H. influenza. Nonencapsulated, nonvirulent strains can be isolated from the nasopharynges of many normal persons and occasionally virulent organisms are found in apparently normal persons. Presumably, transmission is by droplet infection, although one cannot exclude the possibility that certain nonvirulent strains can acquire capsules and attain virulence following virus infections such as a common cold.

Virulent strains of H. influenzae have polysaccharide capsules which protect the organism from phagocytosis. Strains have been classified into six immunologic types: a, b, c, d, e, and f. Only type b is a consistent cause of meningitis, although occasional cases due to type a or type f have been reported. Diagnostic antiserums may be prepared for each type, the antigens being specific polysaccharides.

Virulent encapsulated strains are frequently found in chronic infections of the nasal sinuses and the pharynx following viral colds and are frequently the cause of severe infections of the sinuses, middle ear, pharynx, bronchi, and lungs. Eighty-five per cent of
the cases of Hemophilus meningitis occur in children between the ages of two months and three years. Meningitis in adults usually follows chronic infections of the sinuses, middle ear, or mastoid cells.

Review of Recent Literature

According to a recent study\textsuperscript{15} of 252 cases of meningitis seen at Children's Memorial Hospital in Omaha, Nebraska, during the period 1948-1960, the incidence differs considerably with the etiologic organism:

- Hemophilus influenzae \(34\%\) (86 cases)
- Neisseria meningitidis \(18\%\) (44 cases)
- Diplococcus pneumoniae \(11\%\) (28 cases)
- Miscellaneous bacteria \(5\%\) (14 cases)
- Undetermined \(32\%\) (80 cases)

Not only was Hemophilus found to be the most frequent cause of meningitis in this study, but it was also found to result in a higher mortality \((20\%)\) than the average mortality resulting from all types of meningitis \((14\%)\). In addition, a higher incidence of sequelae, such as hydrocephalus, epilepsy, and mental deterioration, was noted with Hemophilus.

A similar review by Kneebone\textsuperscript{12} of 237 cases at Adelaide Children's Hospital also named \textit{H. influenzae} as the most common cause of bacterial meningitis in
children. He reported that the peak incidence of Hemophilus meningitis occurs during the second year of life, while other bacterial meningitides are more common in patients under one year of age.

Dennis also names H. influenzae as the most common etiologic agent in the one month to three year age group, but lists E. coli as the most common cause of meningitis in the newborn and meningococcus as the most common cause in children over three. This author states that the overall mortality due to bacterial meningitis in children is approximately 25%. The reasons for this high mortality rate are as follows: 1) failure to make an early diagnosis clinically; 2) inadequate identification of the etiologic agent; 3) improper selection and use of therapeutic agents; and 4) development of resistant organisms.

The clinical picture of meningitis is not classical in young children. Kneebone lists a tetrad of symptoms frequently found in patients of this age group: vomiting, irritability, difficulty in feeding, and undue drowsiness. According to Merselis et al., the clinical manifestations of Hemophilus meningitis are not specific enough to differentiate it from other forms of acute bacterial meningitis. The onset may be sudden or insidious and frequently follows a brief prodromal period.
of upper respiratory infection. Fever and leukocytosis are nearly always present. Other frequent findings include headache, disorientation, restlessness, stupor, signs of meningeal irritation, and varied neurological symptoms. Kneebone\textsuperscript{12} found that convulsions are more common with Hemophilus meningitis than with other types and that the sugar level of cerebrospinal fluid is lower.

The strikingly high incidence of Hemophilus meningitis in the one to thirty-six month age group is apparently related to the bactericidal activity of blood against this organism. Fothergill and Wright\textsuperscript{5} in 1933 pointed out that this activity is relatively high at birth, decreases abruptly during the first two months of life, and remains low until approximately age three. After age three complement and specific anti-body titers begin to increase as a result of contact with these organisms in the respiratory tract. Considerable variation was found in the anti-body titer of children from three to ten years of age, with approximately one-third of this age group having no bactericidal activity at all. The titer was high in the blood of all patients over ten. Because of this rise in anti-body titer with age, the prognosis in adults was good compared to other types of meningitis. Hemophilus meningitis in children, however,
was nearly always fatal prior to the advent of chemotherapy.

Although the mortality of this type of meningitis has decreased from over 90% to 10-15%, sequelae may be severe. The cause of such sequelae is still uncertain. Smith and Landing, in a study of 34 fatal cases, found three to have a thick subarachnoid exudate and another to have subdural effusions and membranes. It was felt that interference with venous drainage resulting in brain damage may have been present in these four cases. Five other cases revealed focal encephalomalacia caused by venous thrombosis. Arterial thrombosis, although found in several cases, was thought to be responsible for brain damage in only one.

Rorke and Pitts state that all pyogenic organisms produce essentially the same pathologic lesions, but that the different bacteria do tend to give rise to individually distinctive changes. Influenzal meningitis usually appears as a thick fibrinopurulent exudate with loculated pockets of pus in the basilar cisterns and in the sulci over the cortex, especially if the infection has been prolonged. This organism also has a tendency to produce arteritis and phlebitis which may lead to secondary softening, hemorrhage or abscess.
Complications of bacterial meningitis usually involve the nervous system. The neurones most likely to be damaged are those of the highest order, causing such findings as hemiplegia, aphasia, and mental retardation. One direct result is the loss of neurones with glial proliferation. This may give rise to a focus for post meningitic seizures.

Cranial nerves, involved where they must traverse areas with accumulated exudate, may be damaged enough to cause deafness, facial palsy, or ocular paralysis.

Hydrocephalus is an occasional sequel. The usual cause is obstruction to flow and resorption of cerebrospinal fluid, with the common sites of obstruction being the foramina of Luschka and Magendie and the basal cisterns.

Subdural effusion, thought to be a result of transudation from damaged or inflamed vessels of the dura, has been reported by Rorke and Pitts as occurring in up to 50% of patients with Hemophilus meningitis. These authors state that one should consider this complication when 1) the fever persists for more than 72 hours, in spite of adequate treatment; 2) the spinal fluid persistently shows a positive culture; 3) the patient has recurrent focal or generalized seizures; and 4) the
patient develops focal neurologic signs. The usual method of dealing with this complication is by performing subdural taps every one or two days until the collection disappears. If the effusion persists after two weeks, trephination should be carried out. If membranes have formed around the effusion, they should be removed at a subsequent craniotomy.

Prior to the advent of specific therapy, Hemophilus meningitis was fatal in 90-100% of cases, with frequent sequelae in the few who did survive. Ross et al.\(^\text{21}\) state that the introduction of rabbit antiserum in 1939, coupled with sulfa, provided the most effective therapy until the advent of streptomycin in 1945. At the present time most authorities agree that chloramphenicol in combination with a sulfonamide is the treatment of choice,\(^\text{1,12,13,16,21,22,26}\) although some feel that chloramphenicol alone is adequate.\(^\text{19,21}\)

Chemoprophylaxis is suggested by Kline\(^\text{11}\) for those children of the age group two to thirty-six months who have been intimately exposed. Among the cases he reports are two pairs of siblings who contracted Hemophilus meningitis, the second member of each pair becoming ill three to five days after his sibling. This author states that in his review of the literature he
found a lack of unanimity concerning administration of chemoprophylaxis to young children exposed to Hemophilus meningitis. Although disease in intimate contact is fairly uncommon, he feels that prophylaxis is indicated for infants from two to thirty-six months of age who are intimately exposed.

Material

The data for this paper was obtained by reviewing the medical records of all the hospitals located in Omaha, Nebraska. Cases were found in the following:

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bishop Clarkson Memorial Hospital</td>
<td>1</td>
</tr>
<tr>
<td>Children's Memorial Hospital</td>
<td>69</td>
</tr>
<tr>
<td>Immanuel Hospital</td>
<td>2</td>
</tr>
<tr>
<td>Nebraska Methodist Hospital</td>
<td>2</td>
</tr>
<tr>
<td>Saint Catherines Hospital</td>
<td>3</td>
</tr>
<tr>
<td>Saint Josephs Hospital</td>
<td>2</td>
</tr>
<tr>
<td>University of Nebraska Hospital</td>
<td>9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>88</strong></td>
</tr>
</tbody>
</table>

Eighty-eight cases of meningitis due to Hemophilus influenzae are included in the study, covering the ten-year period 1953 through 1962. It is probable that not all of the cases occurring during this time period were discovered, as some problems were encountered in locating the files.

Results

The findings which were recorded and tabulated are presented below.
Age: In agreement with most articles reviewed, the great majority of the patients were between the ages of two and thirty-six months. The age distribution is shown in Graph A and Table I.

Graph A
Age Distribution

Table I
Age Distribution

<table>
<thead>
<tr>
<th>Age Distribution</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under two months</td>
<td>4½% (4 cases)</td>
</tr>
<tr>
<td>2-12 months</td>
<td>40% (35 cases)</td>
</tr>
<tr>
<td>13-36 months</td>
<td>41% (36 cases)</td>
</tr>
<tr>
<td>Over 36 months</td>
<td>14½% (13 cases)</td>
</tr>
</tbody>
</table>

Only two adults are included, one age 16 and one age 66. The 66 year old patient presented with a
history of "flu" three weeks prior to admission and a cold five days prior to admission. Findings on admission included fever, nausea, vomiting, dizziness, weakness, marked nuchal rigidity, and positive Brudzinski and Kernig's signs. The 16 year old patient had a much shorter history. Her only initial symptoms were tiredness and malaise. This progressed to a severe headache the following night, and to vomiting and nuchal rigidity by the next morning. Both patients improved rapidly after initiation of specific therapy and were discharged following apparently complete recovery, the younger after seven days and the elder after twelve days.

Signs and symptoms: The most constant symptom was fever, usually quite high. The recorded admission temperatures are presented in Graph B and Table II.

Graph B
Temperature on Admission

(11)
Table II
Recorded Temperature on Admission

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Percentage</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 100°</td>
<td>7%</td>
<td>6 cases</td>
</tr>
<tr>
<td>100°</td>
<td>4½%</td>
<td>4 cases</td>
</tr>
<tr>
<td>101°</td>
<td>12½%</td>
<td>11 cases</td>
</tr>
<tr>
<td>102°</td>
<td>20½%</td>
<td>18 cases</td>
</tr>
<tr>
<td>103°</td>
<td>24%</td>
<td>21 cases</td>
</tr>
<tr>
<td>104°</td>
<td>21½%</td>
<td>19 cases</td>
</tr>
<tr>
<td>105°</td>
<td>4½%</td>
<td>4 cases</td>
</tr>
<tr>
<td>Greater than 105°</td>
<td>3½%</td>
<td>3 cases</td>
</tr>
<tr>
<td>Not recorded</td>
<td>2%</td>
<td>2 cases</td>
</tr>
</tbody>
</table>

The labile temperature of patients of this age group is illustrated by the fact that in several of the cases which recorded a relatively low temperature on admission, a much higher reading had been previously obtained by the parents and was recorded in the history.

Other signs and symptoms and the frequency with which they appeared in the different age groups can best be illustrated by Table III.
Table III
Frequency of Signs and Symptoms

<table>
<thead>
<tr>
<th>Age</th>
<th>Number of cases</th>
<th>Nuchal rigidity</th>
<th>Lethargy</th>
<th>Vomiting</th>
<th>Irritability</th>
<th>+ Kernig</th>
<th>Convolusions</th>
<th>Sem: coma or coma.</th>
<th>Bulging fontanelle</th>
<th>+ Brudzinski</th>
<th>Headache</th>
<th>Petechiae</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 mo</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2-12</td>
<td>35</td>
<td>23</td>
<td>17</td>
<td>15</td>
<td>10</td>
<td>6</td>
<td>12</td>
<td>5</td>
<td>13</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>13-24</td>
<td>27</td>
<td>23</td>
<td>20</td>
<td>12</td>
<td>7</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>7</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>25-36</td>
<td>9</td>
<td>8</td>
<td>4</td>
<td>5</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3-10 yr</td>
<td>11</td>
<td>10</td>
<td>2</td>
<td>7</td>
<td>0</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>&gt;10 yr</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Totals</td>
<td>88</td>
<td>67</td>
<td>44</td>
<td>42</td>
<td>22</td>
<td>22</td>
<td>18</td>
<td>14</td>
<td>14</td>
<td>13</td>
<td>8</td>
<td>2</td>
</tr>
</tbody>
</table>

Nuchal rigidity, while notably absent in some cases, was present in over 75%. Kerning and Brudzinski signs were frequently not recorded, but did seem to be much more frequently recorded as positive in patients over one year of age.

Convulsions, opisthotonus, semi-coma or coma, purpuric spots, and flaccid paralysis were findings which were limited mainly to the more severely ill patients.

An upper respiratory infection was recorded as preceding the onset of meningitis in 43 of the 88 cases. In some instances this was only one or two days prior, while in others the respiratory infection occurred up

(13)
to three weeks or more prior. Three cases followed a bout of "flu," and one occurred following head trauma.

Cerebrospinal fluid findings: The findings of cerebrospinal fluid smear and culture are seen in Table IV.

<table>
<thead>
<tr>
<th>Smear and Culture</th>
<th>Percentage</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture and smear positive</td>
<td>65%</td>
<td>57 cases</td>
</tr>
<tr>
<td>Culture positive, smear negative</td>
<td>12½%</td>
<td>11 cases</td>
</tr>
<tr>
<td>Culture negative, smear positive</td>
<td>10%</td>
<td>9 cases</td>
</tr>
<tr>
<td>Culture and smear negative</td>
<td>1%</td>
<td>1 case</td>
</tr>
<tr>
<td>Smear read erroneously</td>
<td>4½%</td>
<td>4 cases</td>
</tr>
<tr>
<td>Smear not reported</td>
<td>3½%</td>
<td>3 cases</td>
</tr>
<tr>
<td>Culture not reported</td>
<td>1%</td>
<td>1 case</td>
</tr>
<tr>
<td>Neither smear nor culture reported</td>
<td>2½%</td>
<td>2 cases</td>
</tr>
</tbody>
</table>

In 57 cases both culture and smear were positive for Hemophilus. In 11 cases the culture was positive but the smear negative, while in nine the reverse was true. Both culture and smear were negative in one case, and neither was reported in two (all of these were cultured at autopsy). The smear was read as gram-positive diplococci in four cases, the correct diagnosis being made on the basis of the culture. In three cases
the smear was not reported in the record, and in one no mention was made of the culture.

Other cerebrospinal fluid findings are tabulated in Tables V, VI, VII, and VIII.

Table V
Cells Per Cubic Millimeter

<table>
<thead>
<tr>
<th>Range</th>
<th>Percent (%)</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 50</td>
<td>2½%</td>
<td>2</td>
</tr>
<tr>
<td>50-500</td>
<td>8%</td>
<td>7</td>
</tr>
<tr>
<td>501-1,000</td>
<td>13%</td>
<td>11</td>
</tr>
<tr>
<td>1,001-2,000</td>
<td>9½%</td>
<td>8</td>
</tr>
<tr>
<td>2,001-5,000</td>
<td>21½%</td>
<td>18</td>
</tr>
<tr>
<td>5,001-10,000</td>
<td>24%</td>
<td>20</td>
</tr>
<tr>
<td>Greater than 10,000</td>
<td>21½%</td>
<td>18</td>
</tr>
</tbody>
</table>

Table VI
Per Cent of White Cells which were Neutrophils

<table>
<thead>
<tr>
<th>Range</th>
<th>Percent (%)</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 50%</td>
<td>1½%</td>
<td>12</td>
</tr>
<tr>
<td>50-75%</td>
<td>13%</td>
<td>11</td>
</tr>
<tr>
<td>76-90%</td>
<td>29%</td>
<td>24</td>
</tr>
<tr>
<td>Greater than 90%</td>
<td>43½%</td>
<td>36</td>
</tr>
</tbody>
</table>

Table VII
Glucose

<table>
<thead>
<tr>
<th>Range</th>
<th>Percent (%)</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 25 mgm%</td>
<td>52%</td>
<td>38</td>
</tr>
<tr>
<td>25-50 mgm%</td>
<td>34%</td>
<td>25</td>
</tr>
<tr>
<td>Greater than 50 mgm%</td>
<td>14%</td>
<td>10</td>
</tr>
</tbody>
</table>

(15)
Table VIII

Protein

<table>
<thead>
<tr>
<th>Range</th>
<th>Percentage</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-45 mgm%</td>
<td>27%</td>
<td>20</td>
</tr>
<tr>
<td>46-100 mgm%</td>
<td>37%</td>
<td>27</td>
</tr>
<tr>
<td>Greater than 100 mgm%</td>
<td>36%</td>
<td>26</td>
</tr>
</tbody>
</table>

While trends may be illustrated in the above cerebrospinal fluid findings, the range in each of the categories was great. Table IX emphasizes this fact.

Table IX

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cells</td>
<td>32</td>
<td>86,000</td>
</tr>
<tr>
<td>Per cent neutrophils</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Glucose</td>
<td>2.5</td>
<td>115</td>
</tr>
<tr>
<td>Protein</td>
<td>10</td>
<td>650</td>
</tr>
</tbody>
</table>

Patient follow-up: Of the 88 patients, 58 apparently made a complete recovery, 16 died and 14 suffered sequelae ranging from very severe to mild.

Eight patients suffered severe sequelae, including hydrocephalus (4), convulsive states (1), mental retardation (1), retardation with deafness and blindness (1), and decerebrate rigidity (1). One suffered only deafness, which is listed below as a moderately severe sequel. The remaining five demonstrated mild sequelae, such as...
a residual internal squint (1), mild arching of the
back or slightly ataxic gait at the time of dismissal
(but improving) (2), and arrested hydrocephalus (asym­
tomatic at time of dismissal) (2).

Table X
Incidence and Severity of Sequelae

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>18% (16 cases)</td>
</tr>
<tr>
<td>Severe sequelae</td>
<td>9% (8 cases)</td>
</tr>
<tr>
<td>Moderately severe sequelae</td>
<td>1% (1 case)</td>
</tr>
<tr>
<td>Mild sequelae</td>
<td>6% (5 cases)</td>
</tr>
</tbody>
</table>

Findings at autopsy (post mortem examination was
performed on 14 cases) are presented in Table XI. These
diagnoses represent findings in addition to purulent
meningitis and are not necessarily causes of death.

Table XI
Autopsy Diagnoses

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>57% (8 cases)</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>21% (3 cases)</td>
</tr>
<tr>
<td>Adrenal failure</td>
<td>21% (3 cases)</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>21% (3 cases)</td>
</tr>
<tr>
<td>Splenitis</td>
<td>21% (3 cases)</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>14% (2 cases)</td>
</tr>
<tr>
<td>Empyema</td>
<td>14% (2 cases)</td>
</tr>
</tbody>
</table>

(17)
The final cause of death in four cases was listed as respiratory failure. In two of these four cases, cardiac failure was also diagnosed. One case terminated by intra-adrenal hemorrhage and adrenal failure. Massive gastrointestinal hemorrhage from a stress ulcer of the duodenum was the final event in another. No specific cause, other than meningitis, was given for the remainder of the fatal cases.

Discussion

The most common as well as the most severe type of meningitis among children from two months to three years of age is that caused by Hemophilus influenzae. The incidence is much lower in adults because of an immunity which apparently results from past contact.

Hemophilus meningitis is quite frequently preceded by an upper respiratory infection. This may occur from one day to more than three weeks before the onset of symptoms of meningitis.

Clinical manifestations of Hemophilus meningitis are not sufficiently specific to differentiate it from other forms of bacterial meningitis. The infant under six months of age who contracts bacterial meningitis may present a difficult diagnostic problem. If the anterior fontanelle is open and the baby is not dehy-
drated, increased intracranial pressure may be detected as the earliest sign. If this is not present, other signs which may suggest the diagnosis include alternating drowsiness and irritability, a high-pitched cry, a vacant stare, or an unexplained fever. Early diagnosis in a child six months of age or older is usually made less difficult by the presence of signs of meningeal irritation.

In a recent study by Hutchison and Kovacs of 41 cases of purulent meningitis in childhood, the signs and symptoms in order of frequency were listed as follows:

1. Fever
2. Vomiting
3. Preceding URI
4. Irritability
5. Listlessness
6. Semi-coma, coma
7. Stiff or sore neck
8. Headache
9. Convulsion
10. Nuchal rigidity
11. Kernig's sign
12. Opisthotonus
13. Full fontanelle
14. Petechial rash
15. Unilateral CNS signs
16. Brudzinski's sign
17. Unilateral CNS signs

The fundamental problem in childhood meningitis is delayed diagnosis. According to McLean it should be suspected in infants under 12 months of age who develop fever and do not do well. If suspected, a lumbar puncture should be done immediately and a gram stain made of the cerebrospinal fluid. The specimen should be centrifuged and the sediment examined microscopically as soon as possible. A culture should always be done.
as the diagnosis made be examination of a smear of the cerebrospinal fluid is occasionally in error. In addition, a cell count and protein and sugar determinations should be carried out.

If the etiologic agent cannot be identified promptly, Haggerty and Ziai suggest the use of multiple drugs aimed at the three most common organisms causing meningitis in children (Hemophilus influenzae, Neisseria meningitidis, and Diplococcus pneumoniae) in the following dosages:

- Chloramphenicol 100 mgm/kg/day
- Streptomycin 100 mgm/kg/day
- Sulfadiazine 100-200 mgm/kg/day
- Penicillin ½-1 million u every 2-3 hr

If Hemophilus is identified, chloramphenicol with a sulfonamide is the treatment of choice of several authors. McLean suggests the following dosages:

Chloramphenicol, 20 mg/lb bid for 3 days, then 20 mg/lb/day IM, for a minimum of 7 days. The patient should be afebrile and have no signs of active disease at least 2 days before the drug is discontinued. Chloramphenicol is a quite toxic drug, however, and should rarely be used for more than ten days.
This may be combined with sulfisoxazole (Gantrisin):

Gantrisin, 40mg/lb IV at once (up to 1 1/3gm), then 30 mg/lb upto 1 gram every 4 hours, or 6 gm/24 hours. This should be given IV at first, then orally.

One should bear in mind when examining a child with an upper respiratory infection that Hemophilus meningitis frequently presents in this fashion. The patient may be treated empirically and inadequately with penicillin and sent home, only to return a few days later with obvious meningeal irritation.

Kneebone\textsuperscript{12} reported a higher mortality rate in cases of Hemophilus meningitis which had been treated with an antibiotic prior to admission. Rantasalo and Kavhtio\textsuperscript{16} do not agree with this, however, stating that mortality decreased from 37\% to 11\% when an antibiotic had been given prior to hospitalization. In our own study several patients who were treated on an outpatient basis for an upper respiratory infection subsequently developed severe meningitis within a few days. Treatment of this nature seems to have the effect of causing both the parents and the physician to feel that the patient has been treated adequately. As a result, the patient's condition may become quite critical before
additional medical aid is sought. This supports the philosophy of not treating an upper respiratory infection with an antibiotic unless it is complicated by secondary bacterial invasion. If antibiotics are used, the patient should be followed closely to insure that no more serious condition is being masked.

Administration of an antibiotic prior to obtaining a sample of cerebrospinal fluid is associated with an increased frequency of negative cultures, according to the recent study completed by Methodist Hospital in Omaha. This study also revealed that in vitro antibiotic sensitivity testing is of little value when the organism is one of the common pathogens and the antibiotic therapy consists of multiple agents.

Because of the frequent complications and the high mortality rate associated with Hemophilus meningitis, it may be advisable to give appropriate chemoprophylaxis to all intimately exposed children from two to 36 months of age. The drugs and dosages suggested by Kline are as follows:

Chloramphenicol, 50 mg/kg/day.

Tetracycline, 30 mg/kg/day.

Either is given in three divided doses per day for five days.
Summary and Conclusions

1. Eighty-eight cases of Hemophilus meningitis from seven hospitals in Omaha, Nebraska, covering the ten-year period from 1953 through 1962 inclusive were reviewed.

2. The recent literature on the subject was surveyed and relevant items included.

3. Hemophilus meningitis is the most common organism causing meningitis in children who are from one or two months to two or three years of age.

4. The bactericidal activity of blood against H. influenzae is quite low from two months to three years of age.

5. An upper respiratory infection frequently precedes Hemophilus meningitis. Access to the bloodstream is usually gained from a primary infection in the respiratory tract.

6. High fever is a very common finding. The temperature is usually higher than with meningitis caused by a different organism.

7. Lethargy, vomiting, and irritability are common symptoms.

8. In four of the 88 cases a misdiagnosis of pneumococcal meningitis was made by examination of a
smeer of the cerebrospinal fluid.

9. The usual cerebrospinal fluid findings include increased protein, decreased sugar, and a cell count of greater than 1,000 cells per cubic millimeter. These values may vary widely, however.

10. The severity of this disease is indicated by the mortality rate (18%) and the incidence of severe sequelae (9%) of the cases studied.

11. The final cause of death was found to be respiratory failure in four of the 14 cases autopsied; pneumonia was diagnosed in eight.

12. Rapid treatment with chloramphenicol coupled with sulfisoxazole can enable complete recovery in many cases.

13. Failure to make the diagnosis coupled with antibiotic therapy for an upper respiratory infection may result in severe meningitis with sequelae or death.

14. If meningitis is suspected and the organism cannot be identified by examination of the cerebrospinal fluid, multiple drug therapy should be used.

15. Chemoprophylaxis for intimately exposed children is mentioned.
Bibliography


15. Nebraska Methodist Hospital study of pediatric meningitis cases at Children's Memorial Hospital, 1948-61, unpublished.


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