Bacterial meningitis in adults
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CHAPTER 3

GROUP A STREPTOCOCCAL MENINGITIS IN ADULTS: REPORT OF 41 CASES AND A REVIEW OF THE LITERATURE

Diederik van de Beek, Jan de Gans, Lodewijk Spanjaard, Shlomo Sela, Marinus Vermeulen, Jacob Dankert

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ABSTRACT
Chart review of 41 adult patients with group A streptococcal (GAS) meningitis in The Netherlands revealed that this is a community-acquired disease and occurs mainly in patients with predisposing factors: of the 41 patients in this case series, 24 (60 percent) of 40 evaluable patients had otitis or sinusitis. Fever and neck stiffness were the most common clinical manifestations of disease, but, in addition, high rates of seizures (12 [32 percent] of 38 patients), focal neurologic findings (13 [36 percent] of 36 patients), and hyponatremia (20 [58 percent] of 35 patients) were found. In contrast with data from the literature that describes 27 adult cases, we found that GAS meningitis is a fulminant disease with a mortality rate of 27 percent (10 of 37 patients), and that neurologic sequelae occur in 44 percent (12 of 27) of surviving patients.

INTRODUCTION
Meningitis due to group A streptococci (GAS) occurs in approximately 2 percent of all patients with systemic infection due to GAS and accounts for 0.2 to 1 percent of all cases of meningitis.\textsuperscript{1-4} In reviews, meningitis due to GAS in adults has been described as a disease with relatively low mortality and morbidity rates.\textsuperscript{5,6} This is in contrast to GAS meningitis in children, which has been described as a fulminant type of meningitis.\textsuperscript{5-11} We studied the incidence and clinical features of GAS meningitis in a 14-year nationwide surveillance study in The Netherlands. In addition, we reviewed all adult cases of GAS meningitis described in the literature.

METHODS
Patients with meningitis were identified by use of the database of The Netherlands Reference Laboratory for Bacterial Meningitis (Amsterdam), which receives cerebrospinal fluid and blood specimens or isolates from approximately 85 percent of all patients with bacterial meningitis in The Netherlands (population, 15.8 million).\textsuperscript{12,13} During a period of 14 years (January 1987 through October 2000), 11,327 patients were identified who had culture-proven bacterial meningitis, of whom 7518 were children, and 3809 were adults. GAS had been isolated from cerebrospinal fluid in 25 (0.3 percent) of the 7518 children and in 44 (1.2 percent) of the 3809 adults; these cases together constitute 0.6 percent of the total number of cases of bacterial meningitis. Physicians were requested to fill in a case record form if they had patients aged at least 16 years old with GAS meningitis. Forty-one case record forms were returned; 3 additional patient charts were lost.

GAS were identified with use of the Streptex assay (Murex; Biotech Ltd); after identification, isolates were stored at -70°C in glycerol-based medium on glass beads. For susceptibility testing, 1 or 2 beads were removed from stock cultures, cultured on blood agar plates, and incubated for 18-24 h at 35°C in air with 5 percent CO₂. Susceptibility to penicillin G, clindamycin, erythromycin, tetracycline, ceftriaxone, and vancomycin was tested by use of the Etest (AB Biodisk). Both inoculation and susceptibility testing were performed according to the guidelines of the National Committee for Clinical Laboratory Standards.\textsuperscript{14}

Using the MEDLINE database (for the years from 1966 to the present) and EMBASE (for
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the years from 1974 to the present), we searched the medical literature for reports of adult patients with GAS meningitis. We used the search terms "Streptococcus pyogenes," "group A streptococcus," "group A β hemolytic," "GAS," "meningitis," and variants of those terms. Articles referenced in review articles on GAS meningitis were also checked. We found reports on 27 cases of GAS meningitis in adults.5,6,10,15-20 For statistical analysis of the data, we used the X² and the Mann-Whitney U tests; P<0.05 was considered significant.

RESULTS

Case series
The annual incidence of GAS meningitis in The Netherlands was calculated to be 0.04 cases per 100,000 population. GAS meningitis in children occurred at an annual rate of 0.06 cases per 100,000 population, and GAS meningitis in adults occurred at an annual rate of 0.03 cases per 100,000 population. The annual incidence did not increase during the period studied.

A demographic profile of the patients in this case series is given in Table 1. Of 41 patients, 20 were male and 21 were female; their median age was 52 years (range, 20-91 years). Forty patients had community-acquired meningitis. Of the 41 patients, 23 (78 percent) had predisposing factors, such as superficial mucosal infection of the respiratory tract. The most common causative conditions were acute otitis media (in 18 [43 percent] of 40 patients), chronic otitis media (in 4 [10 percent] of 40), sinusitis (in 3 [8 percent] of 40), and recent head trauma (in 2 [5 percent] of 40).

Table 1. Demographic and clinical characteristics of 68 adult patients with meningitis due to group A streptococci.∗

<table>
<thead>
<tr>
<th>Demographic or clinical characteristic</th>
<th>Patients in the case series (N=41)</th>
<th>Patients described in the literature (N=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, no. male/no. female</td>
<td>20/21</td>
<td>17/10</td>
</tr>
<tr>
<td>Age, median years (range)</td>
<td>52 (20-91)†</td>
<td>44 (17-81)</td>
</tr>
<tr>
<td>Class of infection, no. of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community acquired</td>
<td>40</td>
<td>23</td>
</tr>
<tr>
<td>Hospital acquired</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Predisposing factors present‡</td>
<td>32/41 (78)</td>
<td>26/27 (96)</td>
</tr>
<tr>
<td>Otitis or sinusitis</td>
<td>24/40 (60)</td>
<td>6/27 (22)</td>
</tr>
<tr>
<td>Immunocompromise</td>
<td>1/41 (2)</td>
<td>NA</td>
</tr>
</tbody>
</table>

∗Data are no. of patients with characteristic/no. evaluated (%), unless indicated otherwise. NA denotes not available.
†P<0.05.
‡Otitis, sinusitis, pneumonia, recent head injury, recent neurosurgery, presence of a neurosurgical device, altered immune status, alcoholism, or cerebrospinal fluid leak.

Clinical data for the study patients are listed in Table 2. Fever and neck stiffness were the most common clinical findings among the 41 patients with GAS meningitis. Of 37 patients, 4 (11 percent) were comatose at the time of admission to the hospital (defined as having a Glasgow Coma Scale score of <8). Focal neurologic deficits (defined as aphasia, cranial nerve palsy, monoparesis, or hemiparesis) were present in 13 (36 percent) of 36 patients; seizures occurred in 12 (32 percent) of 38 patients. Cranial computed tomography (CT) was performed in 32.
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Table 2. Clinical characteristics of 41 adult patients with meningitis due to group A streptococci in a case series.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value (N=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>28/41 (68)</td>
</tr>
<tr>
<td>Fever</td>
<td>32/36 (89)</td>
</tr>
<tr>
<td>Neck stiffness</td>
<td>31/41 (76)</td>
</tr>
<tr>
<td>Coma</td>
<td>4/37 (11)</td>
</tr>
<tr>
<td>Focal neurological deficits</td>
<td>13/36 (36)</td>
</tr>
<tr>
<td>Seizures</td>
<td>12/38 (32)</td>
</tr>
<tr>
<td>Died</td>
<td>10/37 (27)</td>
</tr>
<tr>
<td>Neurologic sequelae†</td>
<td>12/28 (43)</td>
</tr>
<tr>
<td>Duration of admission, median days (range)†</td>
<td>22 (14-123)</td>
</tr>
</tbody>
</table>

*Data are no. of patients with characteristic/no. evaluated (%), unless indicated otherwise.
†Data for patients who survived.

(78 percent) of 41 patients and revealed brain abscesses in 2 patients (6 percent). Thirteen (33 percent) of 40 patients had cardiorespiratory failure.

Examination of cerebrospinal fluid specimens showed some degree of leukocytosis in all patients. The erythrocyte sedimentation rate was elevated (>10 mm/h) in 39 patients (Table 3). In 89 percent of patients, the ratio of cerebrospinal fluid to blood glucose levels was <0.5. Gram staining of cerebrospinal fluid specimens revealed Gram-positive cocci in 10 (49 percent) of 41 patients. For 61 percent of patients, blood cultures were positive for GAS. During hospitalization, 20 (57 percent) of 35 patients developed hyponatremia; 13 patients had mild hyponatremia (defined as a plasma sodium level of 130-135 mmol/L) and 8 had severe hyponatremia (defined as a plasma sodium level of <130 mmol/L).

We tested the antimicrobial susceptibilities of 39 GAS isolates recovered from cerebrospinal fluid; 2 isolates were not viable after storage at -70°C in the reference laboratory. All isolates were susceptible to penicillin G, clindamycin, erythromycin, ceftriaxone, and vancomycin. Five isolates (13 percent) were resistant to tetracycline (defined as having a MIC of ≥1 mg/L). MIC<sub>50</sub> and MIC<sub>90</sub> of cerebrospinal fluid isolates for tetracycline were 0.064 and 10 mg/L, respectively.

Administration of antibiotic therapy was noted on 36 case record forms. Initial treatment consisted of penicillin or amoxicillin for 13 patients (36 percent). For 8 patients (25 percent), the regimen given initially consisted of multiple antibiotics and was changed to penicillin therapy within 3 days. Outcome was recorded for 37 (90 percent) of 41 patients. Ten patients (27 percent) died, and neurologic sequelae were present in 12 patients (44 percent). Death was related neither to the causative condition nor to any clinical parameter. However, for female patients, death was significantly associated with age (P<0.001). All 9 female patients who were <50 years of age survived. The case fatality rate for female patients aged ≥50 years was 45 percent (5 of 11 patients; P<0.05). Three female patients aged ≥50 years died of fulminant septic shock. Findings of CT scanning of the brain, which was performed for all 3 patients during the time of clinical deterioration, were not abnormal. The other 2 female patients died of sudden respiratory failure, which was caused, in at least 1 of these 2 patients, by cerebral herniation. In male patients, no association with age was found.

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Table 3. Laboratory findings for 68 adult patients with meningitis due to group A streptococci.*

<table>
<thead>
<tr>
<th>Finding</th>
<th>Patients in the case series (N=41)</th>
<th>Patients described in the literature (N=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At presentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR, median mm/h</td>
<td>66</td>
<td>NA</td>
</tr>
<tr>
<td>Blood leukocyte count, median cells ( \times 10^3 )/L</td>
<td>17,000</td>
<td>NA</td>
</tr>
<tr>
<td>CSF leukocyte count, median cells/mm³</td>
<td>1100</td>
<td>1600</td>
</tr>
<tr>
<td>CSF total protein level, median g/L</td>
<td>3.2</td>
<td>5.15</td>
</tr>
<tr>
<td>Ratio of CSF to blood glucose levels, median</td>
<td>0.28</td>
<td>NA</td>
</tr>
<tr>
<td>Hyponatremia during hospitalization†</td>
<td>21/36 (58)</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Data are no. of patients with characteristic/no. evaluated (%), unless indicated otherwise. CSF denotes cerebrospinal fluid. ESR denotes erythrocyte sedimentation rate. NA denotes not available.

†Hyponatremia was defined as a plasma sodium level of <135 mmol/L.

Literature review

A demographic profile of the 27 patients with GAS meningitis who are described in the literature is given in Table 1. Predisposing factors were present in all but 1 patient: 6 patients had symptoms of otitis or sinusitis, 6 had pharyngitis, and 4 had a skull fracture or skull defect. Data on the clinical characteristics of the patients were not stated. Data on the cerebrospinal fluid leukocyte count were available for 25 patients; the median was 1600 cells/mm³ (Table 3); in 2 patients, the cerebrospinal fluid leukocyte count was normal. The cerebrospinal fluid protein level was stated for 12 cases; all values were >4.5 g/L. Gram staining of cerebrospinal fluid specimens revealed gram-positive cocci in 15 (75 percent) of 20 specimens. Blood cultures were positive for GAS for 7 (58 percent) of 15 patients. Antibiotic treatment was given to 26 (96 percent) of 27 patients; 10 (38 percent) received monotherapy with penicillin or amoxicillin. Four patients (15 percent) died, and 2 patients (8 percent) were described as having only minor sequelae (neuritis optica and slight hearing loss).

DISCUSSION

The annual incidence of GAS meningitis in adults in The Netherlands was 0.03 cases per 100,000 population and remained constant during the period studied. This is in contrast with the dramatic increase in the number of cases of GAS invasive disease in other Western countries during this period. However, surveillance of invasive GAS infections in The Netherlands was started in 1990; therefore, an increase in the antecedent period cannot be excluded but is unlikely, because surveillance of bacterial meningitis, including GAS meningitis, had been started in The Netherlands much earlier, in 1976. Moreover, in the period 1990-2000, no clear trend towards increase or decrease in the number of blood cultures positive for GAS was noted, as assessed in a sentinel laboratory surveillance system with approximately 30 percent national coverage (JFP Schellekens, personal communication). The nationwide surveillance of invasive GAS infection during the period 1993-1995 revealed a relatively low incidence of 1.2 cases per 100,000 population per year. Meningitis due to GAS accounted for approximately 2 percent of all cases of GAS invasive diseases. This frequency was also found in a surveillance study performed in Atlanta, Georgia. In a study that included 323 patients with GAS invasive disease in Canada, however, no cases of meningitis were found.
In our patients, GAS meningitis was often preceded by otitis or sinusitis. This finding has been described previously in the literature.\textsuperscript{6,19,24,25,27} Infections of the upper respiratory tract occur frequently, although GAS meningitis is rare. Therefore, hematogenous spread of GAS from the upper-respiratory mucosa to the CNS is seen mainly in patients with predisposing factors and is perhaps due to an altered balance in the host microbe population. The mechanism underlying immunity and susceptibility to GAS invasive disease are not well understood.

An interesting new finding in our patients is the high rate of hyponatremia (58 percent of patients) found in adults with GAS meningitis. Although hyponatremia has not been described in adults with GAS meningitis, the frequency of neuroendocrinologic complications in children has been reported to be high.\textsuperscript{5} High rates of hyponatremia are known from case series of tuberculous meningitis and are known to occur in meningitis caused by \textit{Staphylococcus aureus}.\textsuperscript{34-36} Whether this hyponatremia is caused by cerebral salt wasting or inappropriate secretion of antidiuretic hormone remains to be elucidated.\textsuperscript{37}

No resistance of GAS to penicillin has been reported,\textsuperscript{38} but resistance of GAS to macrolide antibiotics and tetracycline does occur.\textsuperscript{18,39,41} In our study, all GAS isolates were susceptible to erythromycin, and isolates recovered from 13 percent of patients were resistant to tetracycline. The rate of GAS resistance to tetracycline varies geographically, from 4 percent of isolates in the United States to 42 percent in Iran, and resistance is reported with increasing frequency.\textsuperscript{40} Because GAS remains susceptible to β-lactam antibiotics, penicillin is the first-choice antibiotic for treatment of GAS meningitis.\textsuperscript{30}

Our case series showed that GAS meningitis in adults is a disease with a high mortality rate. Although this finding is in contrast with previous reports of GAS meningitis in adults, it is concordant with the fulminant clinical course described in GAS meningitis in children.\textsuperscript{5,7} The current study indicates that, although the incidence of meningitis due to GAS continues to be low, physicians must be aware that GAS meningitis in adults is a disease with a fulminant course and with relevant neurologic sequelae.

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