Factors Associated with the Occurrence of Hearing Loss after Pneumococcal Meningitis

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Background. On the basis of a nationwide registration during a 5-year period (1999–2003), the frequency and severity of hearing loss was investigated retrospectively in 343 consecutive Danish patients who survived pneumococcal meningitis, to identify important risk factors (including the pneumococcal serotype) for development of hearing loss.

Methods. Results of blood and cerebrospinal fluid (CSF) biochemistry, bacterial serotyping, follow-up audiological examinations, and medical records were collected, and disease-related risk factors for hearing loss were identified. The mean pure-tone hearing threshold levels were compared with normative data.

Results. Of 240 patients examined by use of audiometry, 129 (54%) had a hearing deficit, and 50 (39%) of these 129 patients were not suspected of hearing loss at discharge from hospital. Of the 240 patients, 16 (7%) had profound unilateral hearing loss, and another 16 (7%) had bilateral profound hearing loss. Significant risk factors for hearing loss were advanced age, the presence of comorbidity, severity of meningitis, a low CSF glucose level, a high CSF protein level, and a certain pneumococcal serotype (P < .05). By applying multivariate logistic regression analysis, we found that advanced age, female sex, and a certain serotype were significant risk factors, because fewer patients with serotype 6B had hearing loss than did patients with serotype 12F (P = .03), which was the most commonly occurring serotype.

Conclusion. Hearing loss is common after pneumococcal meningitis, and audiology should be performed on all those who survive pneumococcal meningitis. Important risk factors for hearing loss are advanced age, female sex, severity of meningitis, and bacterial serotype.

Streptococcus pneumoniae remains the most common cause of bacterial meningitis and is associated with a high risk of an unfavorable outcome, with hearing loss as the most common complication [1]. Studies on the incidence and severity of hearing loss in adults are scarce. Most investigations have dealt with children, were rather small in size, and were often part of larger series on meningitis of various etiologies. The reported incidence of hearing impairment as sequel of pneumococcal meningitis ranges from 7% to 36% of survivors [2–5]. It has been suggested that the higher figure may be closer to the actual incidence, considering the difficulties in detecting hearing loss, even severe cases, in retrospective studies. Moreover, little is known about risk factors for hearing loss.

The incidence and serotype pattern of pneumococcal meningitis vary by geographic location [6–8], and case-fatality rates differ according to occurring serotype [9, 10]. However, to our knowledge, the correlation between serotype and postmeningitis hearing loss has not been addressed previously and may be of interest in relation to future treatment and vaccination strategies. This study represents a nationwide investigation of the frequency and severity of postmeningitis hearing loss in consecutive Danish patients with pneumococcal meningitis during a 5-year period (1999–2003).
RESULTS

Identification of patients with meningitis. A total of 506 consecutive episodes of pneumococcal meningitis involving 502 patients were identified during the period from January 1999 through December 2003. One patient had had 3 episodes of pneumococcal meningitis, and 2 patients had had 2 episodes. Each episode for these 3 patients was due to a different serotype. Of the 502 included patients, 107 (21%) died of the primary disease. Of the remaining 395 patients, 305 (77%) had medical records and discharge card information on hearing.

From the end of the inclusion period in 2003 to the end of data collection in 2009, 39 of the 395 primary survivors had died of other causes, 7 had emigrated or were residents of countries other than Denmark, and 6 were unable to be assessed by use of an audiometry because of health-related issues. Of the remaining 343 patients, 171 (50%) had an audiometry performed in relation to the primary disease, and 69 (20%) had an audiometry performed in relation to this study (see below). Thus, audiometric data were available for 240 (70%) of 343 possible cases. The median time between onset of disease and audiometric testing was 12 months (25th–75th percentiles: 3–60 months; range, 0–106 months). Four patients had audiometry performed within the first week after hospital admis-
Hearing Loss from Pneumococcal Meningitis

Figure 1. Mean pure-tone thresholds after pneumococcal meningitis in Denmark from 1999 to 2003 and the reference values individually matched for better and worse ear, age, and sex (normative data). A, Data obtained from the better ear (n = 240), compared with matched references. B, Data obtained from the worse ear (n = 240), compared with matched references. C, Data obtained from both ears (n = 480), compared with matched references (panels A and B combined). Data represent patients with no, mild, severe, or profound hearing loss (HL). The bars indicate the 95% confidence interval. The numbers in parentheses indicate sample size of ears tested at the individual frequencies. A mean HL distributed evenly across the frequency spectrum is apparent.

Figure 2. Age distribution, survival, and hearing outcome for meningitis due to Streptococcus pneumoniae in Denmark from 1999 to 2003 (N = 505). The hearing loss was determined by audiometric testing. Adult patients had a higher mortality and a higher occurrence of hearing loss, compared with pediatric patients (P < .001).
Fifty patients were evaluated as having no hearing loss at hospital discharge; however, an abnormal audiometric test result was demonstrated subsequently. In addition, audiometric testing could not confirm the suspicion of hearing loss for 8 adult patients. Six of these 8 patients had an ear focus and were discharged after a median of 12 days (range, 10–27 day), so the initial hearing loss could potentially be of conductive causes and may have improved before audiometric testing. The sensitivity, specificity, and positive and negative predictive values of medical records regarding hearing loss were respectively 51%, 91%, 87%, and 62% for all patients (38%, 100%, 100%, and 81% for children and 54%, 77%, 85%, and 42% for adults). Therefore, all hearing data are from audiometric testing only.

**Occurrence and severity of hearing loss.** A significantly higher proportion of patients with posthospitalization audiometric data had hearing loss, compared with patients examined after receiving the mailed request in relation to this study (102/171 [60%] vs 27/69 [39%]; \( P = .004 \)). Of the 240 patients tested by use of audiometry, 105 (44%) had hearing loss in the better ear. Of these patients, 81 (77%) were classified as having mild hearing loss, 8 (8%) were classified as having severe hearing loss, and 16 (15%) were classified as having profound hearing loss. Of the 123 patients (51%) with hearing loss in the worse ear, 69 (56%) were classified as having mild hearing loss, 22 (18%) were classified as having severe hearing loss, and 32 (26%) were classified as having profound hearing loss. Of the 240 patients tested by use of audiometry, 109 (54%) were found to have at least unilateral mild hearing loss, whereas there were 56 patients (23%) who had severe to profound hearing loss in at least 1 ear, 32 patients (13%) who had profound hearing loss unilaterally or bilaterally, and 16 patients (7%) who had profound hearing loss bilaterally.

The mean pure-tone thresholds for the better ear, the worse ear, and both ears are shown in Figure 1. Patients with mild to profound hearing loss were found to have an average hearing loss (ΔPTA) of 27.5 dB (95% confidence interval [CI], 22.4–

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**Table 1. Risk Factors for Hearing Loss after *Streptococcus pneumoniae* Meningitis in Denmark from 1999 to 2003**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Patients with no hearing loss (n = 111)</th>
<th>Patients with hearing loss (n = 127)</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Female sex</td>
<td>63/111 (57)</td>
<td>59/127 (47)</td>
<td>0.66 (0.40–1.10)</td>
<td>0.46 (0.23–0.93)</td>
</tr>
<tr>
<td>Age &gt;2 years</td>
<td>52/111 (47)</td>
<td>100/127 (79)</td>
<td>4.20 (2.39–7.40)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Predisposing condition</td>
<td>7/97 (7)</td>
<td>9/102 (9)</td>
<td>1.24 (0.44–3.48)</td>
<td>.03</td>
</tr>
<tr>
<td>Ear focus</td>
<td>43/103 (42)</td>
<td>57/117 (49)</td>
<td>1.33 (0.78–2.26)</td>
<td>.30</td>
</tr>
<tr>
<td>Lung focus</td>
<td>16/103 (16)</td>
<td>19/118 (16)</td>
<td>1.04 (0.51–2.16)</td>
<td>.91</td>
</tr>
<tr>
<td>Presence of comorbidity</td>
<td>12/97 (12)</td>
<td>24/102 (24)</td>
<td>2.18 (1.02–4.65)</td>
<td>.04</td>
</tr>
<tr>
<td>Fever</td>
<td>92/106 (96)</td>
<td>92/104 (98)</td>
<td>1.66 (0.27–10.2)</td>
<td>.58</td>
</tr>
<tr>
<td>Back rigidity</td>
<td>50/81 (62)</td>
<td>60/92 (65)</td>
<td>1.16 (0.63–2.16)</td>
<td>.63</td>
</tr>
<tr>
<td>Decreased consciousness</td>
<td>60/89 (90)</td>
<td>107/114 (94)</td>
<td>1.72 (0.61–4.81)</td>
<td>.30</td>
</tr>
<tr>
<td>Convulsion</td>
<td>23/97 (24)</td>
<td>31/110 (28)</td>
<td>1.26 (0.68–2.36)</td>
<td>.47</td>
</tr>
<tr>
<td>Receipt of mechanical ventilation</td>
<td>26/98 (27)</td>
<td>59/115 (51)</td>
<td>2.92 (1.64–5.20)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Receipt of steroid therapy</td>
<td>24/96 (25)</td>
<td>19/105 (18)</td>
<td>0.65 (0.33–1.29)</td>
<td>.22</td>
</tr>
<tr>
<td>CSF WBC count, cells/μL</td>
<td>1608 (533–3517)</td>
<td>1979 (530–5383)</td>
<td>1.23 (0.89–1.70)</td>
<td>.20</td>
</tr>
<tr>
<td>Proportion of patients</td>
<td>94/111</td>
<td>104/127</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>CSF protein level, g/L</td>
<td>1.9 (1.0–3.2)</td>
<td>3.1 (1.9–5.0)</td>
<td>1.28 (1.12–1.47)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Proportion of patients</td>
<td>85/111</td>
<td>96/127</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>CSF glucose level, mmol/L</td>
<td>1.6 (0.4–3.2)</td>
<td>0.7 (0.3–2.0)</td>
<td>0.73 (0.60–0.90)</td>
<td>.003</td>
</tr>
<tr>
<td>Proportion of patients</td>
<td>83/111</td>
<td>91/127</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>CSF/blood glucose ratio</td>
<td>0.22 (0.05–0.50)</td>
<td>0.10 (0.04–0.26)</td>
<td>0.11 (0.02–0.63)</td>
<td>.01</td>
</tr>
<tr>
<td>Proportion of patients</td>
<td>56/111</td>
<td>60/127</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Blood WBC count, 10⁶ cells/L</td>
<td>21.5 (13.9–26.7)</td>
<td>18.9 (11.5–26.3)</td>
<td>0.99 (0.96–1.02)</td>
<td>.41</td>
</tr>
<tr>
<td>Proportion of patients</td>
<td>94/111</td>
<td>104/127</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Serum sodium level, mmol/L</td>
<td>133 (130–136)</td>
<td>136 (133–139)</td>
<td>1.16 (1.07–1.27)</td>
<td>.001</td>
</tr>
<tr>
<td>Proportion of patients</td>
<td>56/111</td>
<td>63/127</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

**NOTE.** Data are proportion (%) of patients or median values (interquartile range), unless otherwise indicated. Hearing loss was determined by use of audiometry. CI, confidence interval; CSF, cerebrospinal fluid; OR, odds ratio; WBC, white blood cell.

* Two patients were excluded from the analysis because they had >1 episode of meningitis.

* Calculated per additional units for continuous data, except for CSF WBC count, which was log₁₀ cells/μL.

* Underlying disease was defined as previous splenectomy, presence of immunodeficiency, cancer, diabetes mellitus, alcoholism, and/or chronic obstructive lung disease/asthma, or the use of immunosuppressive drugs.
Figure 3. Serotype distribution, survival, and hearing outcome for meningitis due to *Streptococcus pneumoniae* in Denmark from 1999 to 2003 (*N* = 505). The hearing loss was determined by audiometric testing. The occurrence of hearing loss was related to bacterial serotype, with serotype 6B associated with a lower incidence of hearing loss, compared with serotype 12F, which was the most frequently occurring serotype (*P* < .05). The unlabeled bar at the top indicates cases with no data on serotype.

33.5 dB) in the better ear, 38.6 dB (95% CI, 33.0–44.3 dB) in the worse ear, and 33.5 dB (95% CI, 29.6–37.4 dB) when calculated for both ears.

**Risk factors for hearing loss.** Data on patient age in relation to survival and hearing outcome are presented in Figure 2. The occurrence of pneumococcal meningitis was highest for patients younger than 3 years of age (23% [115/506] of all episodes) and increased with older age among adults. Patients with hearing were statistically significantly older than were patients without hearing loss (median age, 53 years [range, 25–65 years] vs 2 years [range, 0–50 years]; *P* < .001). Overall, adult patients had a statistically significantly higher rate of hearing loss than did children less than 18 years of age (99/144 [69%] vs 29/94 [31%]; *P* < .001). This overall difference in the occurrence of hearing loss between age groups was due to a difference in mild hearing loss only (43% [66/144] vs 6% [6/94]; *P* < .001) and not in
severe hearing loss (10% [18/144] vs 6% [6/94]; P = .19) or profound hearing loss (10% [15/144] vs 18% [17/94]; P = .12).

Patients with an underlying disease had a statistically significantly higher frequency of hearing loss, compared with patients without hearing loss (67% [24/36] vs 45% [78/163]; P = .04), whereas predisposing conditions or a potential primary focus of infection was of no importance for a development of hearing loss (P > .05).

Clinical features (such as fever, back rigidity, decreased consciousness, and convulsion) were not statistically significantly associated with the occurrence of hearing loss (P > .05). In contrast, the severity of meningitis, as reflected by the need for assisted ventilation (P < .05), presence of comorbidity (OR, 0.20 [95% CI, 0.05–0.92; P = .003]), female sex (OR, 0.12 [95% CI, 0.03–0.46; P = .002]), and 0.09 [95% CI, 0.02–0.97; P = .01], respectively), female sex (ORs, 0.12 [95% CI, 0.03–0.46; P = .002] and 0.09 [95% CI, 0.02–0.97; P = .01], respectively), and need for assisted ventilation (ORs, 0.15 [95% CI, 0.04–0.64; P = .01] and 0.14 [95% CI, 0.22–0.92; P = .04], respectively), and for 13-valent (61% [62/101] vs 47% [65/137]; P = .04) but not for 23-valent pneumococcal vaccine (59% [29/49] vs 52% [98/189]; P > .05).

Despite the fact that there was no significant difference in mortality between vaccine serotypes and nonvaccine serotypes (P > .05; data not shown), hearing loss was significantly more frequent for meningitis due to nonvaccine serotypes, compared with vaccine serotypes for 7-valent (61% [97/158] vs 38% [30/80]; P = .001) and 13-valent (61% [62/101] vs 47% [65/137]; P = .04) but not for 23-valent pneumococcal vaccine (59% [29/49] vs 52% [98/189]; P > .05).

**DISCUSSION**

The present, nationwide study of 502 consecutive episodes of pneumococcal meningitis in Denmark over a 5-year period (1999–2003) showed that, among 240 survivors who were tested by use of audiometry, the overall rate of hearing loss was 54% (69% of adults and 31% of children): 23% had severe hearing loss in at least 1 ear, and 13% had profound hearing loss unilaterally or bilaterally. To our knowledge, this is the largest audiometric study of hearing loss after pneumococcal meningitis. The incidence of hearing loss among adult survivors was more than twice as high as reported in previous studies (15%–26%) [3, 12, 13], whereas previous studies in children showed variable hearing loss frequencies (7%–
36%) [2, 4, 14, 15]. This discrepancy may be explained by differences in methods of hearing evaluation between studies, because audiometric testing was only performed for patients clinically suspected of hearing loss in most previous studies, whereas we intended to test all patients. Indeed, we found that 38% of patients, who were not suspected of hearing loss at clinical bedside evaluation before hospital discharge, had hearing loss when tested by audiometry. Thus, our results indicate that a rough, clinical bedside evaluation of hearing loss by a nonspecialized physician may be of limited value, and we suggest that postmeningitis audiometric testing should be performed in all cases.

The risk factors for hearing loss identified in the unadjusted univariate analysis were advanced age, presence of comorbidity, severity of meningitis (eg, the need for assisted ventilation or signs of septic shock), a low CSF glucose level, and a high CSF protein level, which confirm previous findings [4, 14]. Also, a low serum level of sodium was associated with a higher risk of hearing loss, whereas no association was found between hearing loss and WBC count in CSF and blood. In the multivariate analysis, age and sex were of significant importance.

Although controversial, corticosteroids have been recommended as adjunctive therapy for bacterial meningitis to reduce the risk of developing hearing loss [16]. In Denmark, some pediatric departments use corticosteroids routinely as adjunctive therapy, whereas corticosteroids for treatment of adults were recommended in 2003 [17]. Before 2003, corticosteroids were used only for adult patients with severe brain edema. Thus, hearing loss was significantly higher in adult patients treated with corticosteroids but was slightly lower in pediatric patients.

Our study showed that pneumococcal serotype was associated with hearing loss after meningitis, because cases of meningitis due to serotype 6B and serotype 14 were associated with a lower risk of hearing loss, compared with serotype 12F. This was also found when we adjusted for other significant risk factors in multivariate analysis. An association between serotypes and mortality has previously been demonstrated [9, 10], which could result in an important selection bias for the identification of risk factors for the development of hearing loss; for example, risk for development of hearing loss could be underestimated in serotypes with a high mortality, because severity of the disease is associated with both mortality and hearing loss. However, serotypes 6B, 14, and 12F were associated with similar mortality rates in this study, as in previous studies [10]. Moreover, when we studied the relationship between serotypes and an unfavorable outcome (combination of hearing loss and mortality), no significant association was found (data not shown). Furthermore, serotypes not included in the 7-valent and the 13-valent resulted in higher risk for hearing loss than did vaccine serotypes, which is in conflict with a previous study of 86 children [18]. Thus, the pneumococcal serotype may be an important risk factor for the development of hearing loss.

Our study has some advantages over previous studies concerning this subject matter. Because meningitis is a notifiable disease with a centralized, national registration, we most likely identified all episodes during the period. Serotyping was performed in 93% of episodes. Thus, the study represents a large collection of unselected, consecutive cases. The large sample size allowed multivariate analysis, to identify risk factors for the development of hearing loss. Moreover, we compared postmeningitic hearing to normative data from an otologically unscreened population sample [11]. This method is likely to be more sensitive than previous study designs, considering the difficulties in detecting hearing loss in retrospective case series lacking predisease reference values.

Nevertheless, our study has some potential limitations. First, children younger than at least 5 years of age cannot participate in standard pure-tone audiometry. Thus, the detection and categorization of hearing loss is definitely more uncertain in the younger pediatric age group. Therefore, the incidence of hearing loss in these patients is probably underestimated, which may have introduced a bias in relation to the occurring, age-related difference. Second, audiometric data could not be retrieved for a proportion of our cohort (30%), which may have resulted in a selection bias. Patients not responding to our letter requesting an audiometry by their local oto-rhino-laryngologist may be assumed not to have considerable hearing problems, which may have led to an overestimation of the occurrence of hearing loss overall. Finally, although most patients with hearing loss after meningitis have a permanent loss of hearing, improvement does occur in rare cases [19, 20]. In our study, 4 patients had audiometry performed within the first week after hospital admission, whereas the vast majority of audiometric assessments (87%) were performed 2 months or more after admission.

Hearing loss is common after pneumococcal meningitis, and audiometry should be performed on all patients. Important risk factors for hearing loss are advanced age, female sex, severity of meningitis, and the presence of a certain bacterial serotype.

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Potential conflicts of interest. All authors: no conflicts.

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