Hearing Loss at School Age in Survivors of Bacterial Meningitis: Assessment, Incidence, and Prediction

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ABSTRACT. Objectives. To establish the incidence of sensorineural hearing loss in children who survived non–Haemophilus influenzae type B (Hib) bacterial meningitis, to highlight the actual percentage whose hearing was evaluated, and to develop a prediction rule to identify those who are at risk of hearing loss.

Methods. In 1999, we compiled a cohort of 628 school-aged children who were born between January 1986 and December 1994 and had survived non-Hib bacterial meningitis between January 1990 and December 1995. Presence of sensorineural hearing loss (>25 dB) was determined, based on information from questionnaires and medical records. Potential risk factors for hearing loss were obtained from medical records; independent predictors were identified using multivariate logistic regression analysis, leading to the formulation of a prediction rule.

Results. The incidence of hearing loss was 7%. The hearing of 68% of the children was evaluated as part of their routine follow-up after bacterial meningitis, resulting in the detection of 75% of the cases of hearing loss. The remaining 25% were detected after this follow-up had ended. Using a prediction rule based on 5 factors—duration of symptoms before admission >2 days, absence of petechiae, cerebrospinal fluid glucose level ≤0.6 mmol/L, Streptococcus pneumoniae, and ataxia—62% of the postmeningitic children were selected as being at risk. All cases of hearing loss were in this at-risk group.

Conclusions. Hearing loss can be predicted satisfactorily. When the hearing of children who are predicted to be at risk is tested as part of their routine follow-up, no children with hearing loss need be missed. Pediatrics 2003;112:1049–1053; bacterial meningitis, cohort study, hearing assessment, hearing impairment, prediction.

ABBREVIATIONS. Hib, Haemophilus influenzae type B; CSF, cerebrospinal fluid; AUC, area under the curve.

Sensory neural hearing loss is the most common severe consequence of childhood bacterial meningitis, affecting approximately 9% of the children.1–8 Furthermore, bacterial meningitis is the leading cause of severe hearing loss acquired in childhood.4,6 As a result of vaccination, Haemophilus influenzae type B (Hib) meningitis has virtually disappeared from most Western countries,7,8 but it is not yet known to what extent this has influenced the incidence of hearing loss. Early identification and rehabilitation of hearing loss is essential for the acquisition of normal speech and language, as well as for the child’s educational and social development.9 Early identification of hearing loss is also important because ossification of the cochlea after meningitis may complicate cochlear implantation.10,11 Hearing evaluation, therefore, is recommended as part of the routine follow-up after bacterial meningitis.1,5,12,13 However, as up to 25% of the children do not undergo a formal hearing test after bacterial meningitis,12,13 identification of those who are at risk of hearing loss may help to ensure that they are evaluated. Previously proposed risk factors for hearing loss1,5,12,14,15 have not resulted in satisfactory prediction. The purposes of the present study were to 1) establish the incidence of sensorineural hearing loss in children who survived non-Hib bacterial meningitis, 2) report on the actual percentage whose hearing was evaluated after bacterial meningitis, and 3) develop a prediction rule to identify those who are at risk of hearing loss.

METHODS

Postmeningitic Cohort

Files of the Netherlands Reference Laboratory for Bacterial Meningitis were searched in 1999 for data on eligible patients. This laboratory collects bacterial isolates and data (eg, pathogen, name, date of birth, hospital of admission) from approximately 80% of all bacterial meningitis cases in the Netherlands. The diagnosis of bacterial meningitis was based on the presence of bacteria being demonstrated in the cerebrospinal fluid (CSF). The inclusion criteria were date of birth between January 1986 and December 1994 and recovery from meningitis caused by Neisseria meningitidis, Streptococcus pneumoniae, Streptococcus agalactiae, Escherichia coli, or Listeria monocytogenes between January 1990 and December 1995. The exclusion criteria were meningitis caused by Hib or other less common pathogens, “complex onset” of meningitis (defined as meningitis secondary to immunodeficiency states, central nervous system surgery, cranial trauma, or CSF shunt infections, or relapsing meningitis), cognitive or behavioral problems before meningitis, and diseases developed after meningitis (eg, cancer), which could have caused cognitive or behavioral problems. These last 2 exclusion criteria were applied because this cohort was compiled

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as part of a study on academic and/or behavioral problems after bacterial meningitis.\textsuperscript{16}

Inclusion criteria were met by 1605 patients, treated in 110 different hospitals. A pediatrician from every hospital involved sent the parents a standard letter requesting their participation. Participating parents were sent questionnaires on long-term outcome and on exclusion criteria.\textsuperscript{16} Subsequently, medical records of the children were studied to obtain detailed data on admission and follow-up. During this process, 860 (54\%) children were lost for various reasons: pediatricians' refusal (n = 205, 10 pediatricians), death (n = 40), addresses missing from medical records (n = 60), no response to letter requesting participation (n = 445), parents' refusal to participate (n = 49), questionnaires not returned (n = 16), filling in of questionnaires incomplete (n = 11), no permission from parents to study medical records (n = 14), and data on bacterial meningitis incomplete in medical records (n = 20). Moreover, 117 (7\%) children were excluded because of meningitis caused by Hib or other rare pathogens (n = 4), no meningitis (n = 1), meningitis "with complex onset" (n = 84), cognitive or behavioral problems before meningitis (n = 23), and diseases after meningitis that could have caused cognitive or behavioral problems (n = 5). Hence, this report concerns 628 children (57\% boys). Mean age at infection was 2.4 years (range: 0–9.5), and mean age in June 2002 was 11.7 years (range: 7.5–16.3).

**Hearing Loss and Hearing Evaluation**

Hearing loss was defined as a perceptive loss of >25 dB\textsuperscript{4}; the diagnosis was based on information from questionnaires and medical records. Also gathered from the medical records was information on timing and type of hearing evaluation. This information could not be found in 50 medical records, and so the report on this issue concerns a total of 578 children.

**Risk Factors for Hearing Loss**

By reviewing medical records, information was collected on all potential risk factors for hearing loss after bacterial meningitis. To reduce the number of factors to be evaluated, we selected only those reported in previous studies on sensorineural hearing loss after (non-Hib) childhood bacterial meningitis.\textsuperscript{1,5,12,14,15} (Appendix 1).\textsuperscript{17}

The study was approved by the medical ethics committee of the University Medical Center Utrecht. Written informed consent was obtained from the parents or guardians of all children and from the children themselves if they were at least 12 years of age.

**Data Analysis**

A 2-sample t test was used for continuous data, and a \( \chi^2 \) test was used for nominal data. Statistical significance was considered when two-tailed \( P \) values were \( \leq 0.05 \). Associations between hearing loss and potential risk factors were examined using univariate logistic regression analysis. Predictors univariately associated with outcome (\( P < .10 \)) were included in a multivariate logistic regression model. Continuous predictors were dichotomized. The model was reduced by excluding predictors from the model with \( P > .10 \), and the goodness of fit was estimated.\textsuperscript{18} The prognostic ability of the model, ie, to discriminate between patients with and without hearing loss, was estimated by measuring the area under the receiver operating characteristic curve (AUC).\textsuperscript{19} As multivariate regression analysis requires data to be complete for all patients,\textsuperscript{20} multiple imputation techniques were used to fill in missing variables. Per variable, no >20\% of the data were missing.\textsuperscript{21} Imputation was repeated 5 times to take into account uncertainties in imputed data.\textsuperscript{21} From each of the imputed data sets, a prediction model was estimated. Averaging the regression coefficients and standard errors of these logistic models resulted in a single prediction model.\textsuperscript{21} Furthermore, random bootstrapping techniques were used to calculate a shrinkage factor to adjust for overfitting (ie, too optimistic estimates of the regression coefficients) and to validate the model.\textsuperscript{20} The final model was transformed into a clinical prediction rule. Regression coefficients were divided by the smallest coefficient, multiplied by 10, and rounded off to the nearest integer. By assigning points for each variable and adding the results, a score was obtained for each patient. Patients were classified according to their score. For simplifying the interpretation of the model, a nomogram was prepared and a cutoff point chosen. The data were analyzed using SPSS 9.0 and S-plus, with help of the libraries Hmisc and Design of Harrell\textsuperscript{22} and mice of Van Buuren and Oudshoorn.\textsuperscript{23}

**RESULTS**

**Hearing Loss**

Forty-three (7\%) postmeningitic children had hearing loss. This was unilateral in 20 (3\%) and bilateral in 23 (4\%). In most children, hearing loss was severe (71–90 dB; \( n = 11 \)) or profound (>90 dB; \( n = 21 \)). Five children with profound loss received cochlear implants.

**Hearing Evaluation**

The hearing of 68\% (395 of 578) of the children had been evaluated as part of the routine follow-up after meningitis. They either underwent a formal hearing assessment (46\%)—auditory brainstem response in 132, audiogram in 97, test at an audiological center or by an otorhinolaryngologist in 38 children—or their hearing was screened using distraction methods (22\%) at the child health clinic. Hearing loss was diagnosed in 32 of these children (75\% of the children with hearing loss); with only 2 exceptions, hearing loss was detected within 6 months after bacterial meningitis. The hearing of 80 (78\%) of the 103 children with pneumococcal meningitis and of 287 (58\%) of the 495 children with meningococcal meningitis were tested as part of the routine follow-up after meningitis. The hearing of 5\% (26 of 578) of the children was evaluated because of complaints that emerged after the outpatient clinic follow-up had ended. Hearing loss was diagnosed in 11 cases (25\% of the children with hearing loss); 8 of these losses were >55 dB, and all but 1 were detected late (>6 months after bacterial meningitis). Of these 11 children, 3 had survived pneumococcal meningitis and 8 had survived meningococcal meningitis.

**Risk Factors**

Table 1 presents the associations between potential predictors and hearing loss. In the multivariate analysis, duration of symptoms before admission >2 days, absence of petechiae, CSF glucose level \( \leq 0.6 \) mmol/L, \( S \) pneumoniae, and ataxia emerged as independent predictors (Table 2). A prediction rule was constructed by assigning points for each variable. A total score was computed for each patient, ranging from 0 to 100. The AUC of the score was 0.85 (95\% confidence interval: 0.80–0.90). Figure 1 shows the nomogram of the rule, and Table 3 shows the numbers of subjects across categories of the score. With a cutoff of 0, all children with hearing loss were identified correctly. This cutoff point suggests that a patient is at risk when 1 of the predictors is present. With this cutoff, 62\% of the children were selected as being at risk, ie, 60\% of the children without hearing loss were falsely predicted as having hearing loss (false positives; Table 3). Alternatively, with a cutoff of 25 or more, 95\% of the patients with hearing loss were identified correctly. Of the 2 (5\%) children who were false negatives, 1 had mild and 1 severe loss. With this cutoff point, 49\% of the children were selected as at risk, ie, 46\% false positives (Table 3).
DISCUSSION

The incidence of sensorineural hearing loss in children who survived non-Hib bacterial meningitis is 7%. Approximately one third of the Dutch postmeningitic children do undergo a hearing evaluation as part of their routine follow-up after bacterial meningitis, resulting in late detection of one quarter of the cases of hearing loss. Using a rule based on 5 easily obtainable predictors, 62% of the postmeningitic children were identified as being at risk of hearing loss. Had these children received audiological follow-up, none of the children with hearing loss would have been missed.

To appreciate the true value of these results and place them in a proper context, a few points should be borne in mind. Of the 1605 children selected from the reference laboratory for bacterial meningitis, 628 were included. Most children were excluded because parents or pediatricians refused to participate or because parents could not be contacted. Selection bias could have occurred. However, sex, age, and causative pathogens of the 628 participants and the 1605
originally selected children were very similar, suggesting that our cohort is representative of the pediatric non-Hib bacterial meningitis population. Second, children with previous cognitive or behavioral problems, children with diseases that could have led to cognitive or behavioral problems, and children with "complex onset" of meningitis were excluded. The prediction rule may not be applicable to these excluded groups. Third, the hearing of 27% of the children was not tested. It is possible that some of these children had small, unobserved losses and that we have underestimated the incidence of hearing loss. Fourth, we collected risk factors retrospectively from routinely documented medical information. As a consequence, not all data were available for each patient. We dealt with this problem by using multiple imputation techniques. Finally, using bootstrapping techniques, we demonstrated that the prediction rule is robust. Although the regression coefficients shrank after bootstrapping, the AUC did not change. The actual performance of this scoring rule, however, does need to be confirmed in a new group of postmeningitic children before it can be implemented in clinical practice.

All risk factors found in our study have previously been reported. However, until now, hearing loss had not been predicted satisfactorily and comprehensive prediction rules had not been provided. With our prediction rule, all patients with hearing loss could be predicted with a cutoff of 0. We chose this cutoff point because we find it unacceptable to miss any case of hearing loss. Whereas the number of children who require hearing assessment (62%) will be slightly fewer than in current practice (68%), no cases of hearing loss will be missed (compared with 25% currently). With regard to the factor S pneumoniae in the prediction rule, it is important to realize that vaccines against common serotypes of S pneumoniae are currently available. Vaccination campaigns using these vaccines may alter the incidence of hearing loss and thus the prediction rule.

The hearing of 22% of the children was screened at a child health clinic (in the Netherlands, the hearing of every child is screened using distraction methods at a child health clinic at the age of 9 months). Although these children were not formally tested, their hearing was screened and losses were detected within 6 months. Recently, however, a program for neonatal hearing screening shortly after birth has been implemented in the Netherlands. Consequently, hearing screening using distraction methods at the age of 9 months will disappear. Thus, more postmeningitic children will have to undergo a formal hearing assessment.

It is currently not clear which testing strategy is most effective; should children at risk be tested with
an audiogram or auditory brainstem response, or should they be screened with oto-acoustic emissions and should only children who fail this screening be tested with an audiogram or auditory brainstem response? Another difficult issue concerns the timing of testing. Fluctuating hearing loss and deterioration of hearing in time have been reported. Hence, it may be insufficient to assess hearing just once (straight after discharge from hospital). Additional research into these issues is necessary.

CONCLUSIONS

Hearing loss is an important severe consequence of non-Hib bacterial meningitis, affecting 7% of the postmeningitic children. Using a prediction rule based on 5 easily obtainable patient characteristics, children who are at risk of hearing loss can be identified. The inclusion of hearing evaluation in the routine follow-up of these children after bacterial meningitis may prevent missed diagnoses of hearing loss. Additional research is required to validate the prediction rule further.


<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Significantly Associated With Hearing Loss</th>
<th>Not Significantly Associated With Hearing Loss</th>
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</thead>
<tbody>
<tr>
<td>Age at infection (y)</td>
<td>12†</td>
<td>1†, 5</td>
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<tr>
<td>Male sex</td>
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<td>1</td>
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<tr>
<td>Duration of symptoms before admission</td>
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<td>1†, 5</td>
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<td>Decreased consciousness</td>
<td>5, 15</td>
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<tr>
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<td></td>
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<tr>
<td>Meningeal irritation</td>
<td>5</td>
<td></td>
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<tr>
<td>Severity of illness correlates</td>
<td>15†</td>
<td></td>
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<tr>
<td>(eg, shock)</td>
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</tr>
<tr>
<td>Concomitant middle ear infection</td>
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<td></td>
</tr>
<tr>
<td>CSF leukocyte count</td>
<td>1, 5, 12</td>
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<tr>
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<td>1, 5, 12</td>
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<tr>
<td>CSF protein level</td>
<td>1, 5, 12</td>
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<td>Causative pathogen</td>
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<td>Serum leukocyte count</td>
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<td>Dexamethasone</td>
<td>1, 5, 14†</td>
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<tr>
<td>Mechanical ventilation</td>
<td>15†</td>
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<tr>
<td>Duration of hospitalization</td>
<td>1, 12†</td>
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<td>Hydrocephalus</td>
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<tr>
<td>Subdural effusion</td>
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</table>

Numbers refer to studies in the reference list.

* Review of risk factors for hearing loss reported in 20 studies between 1978 and 1991. Indicated is whether this review reported that overall a significant association between the risk factor and hearing loss, no significant association, or both were found in the reports studied.

† Meta-analysis of studies on effect of dexamethasone published until 1996. This meta-analysis reported no overall protective effect of dexamethasone in non-Hib bacterial meningitis but a protective effect in pneumococcal meningitis when administered with or before parental antibiotics.

ACKNOWLEDGMENTS

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