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Prediction of academic and behavioural limitations in school-age survivors of bacterial meningitis

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Aim: To develop a prediction rule to identify postmeningitic children at high risk of academic and behavioural limitations. *Methods:* 182 children (mean age 10 y; range 5–14) were selected from a cohort of 674 school-age survivors of bacterial meningitis. These children had neither meningitis with "complex onset", nor prior cognitive or behavioural problems, nor severe disease sequelae. On average, 7 y after the meningitis, they were evaluated using an "Academic Achievement Test", and their parents filled in the "Child Behaviour Checklist". By reviewing the medical records, potential risk factors for academic and/or behavioural limitations were collected. Independent predictors were identified using multivariate logistic regression analysis, leading to the formulation of a prediction rule. *Results:* The cumulative incidence of academic and/or behavioural limitations among children who survived bacterial meningitis without severe disease sequelae was 32%. The prediction rule was based on nine independent risk factors: gender, birthweight, educational level of the father, *S. pneumoniae,* cerebrospinal fluid leukocyte count, delay between admission and start of antibiotics, dexamethasone use, seizures treated with anticonvulsive therapy, and prolonged fever. When 10 was taken as a cut-off point for the risk score computed using this rule, 76% of the children with limitations could be identified, while 38% of the children in the cohort were selected as at risk for these limitations.

Conclusion: With a prediction rule based on nine risk factors, postmeningitic children at high risk of developing academic and/or behavioural limitations could be identified. Additional research is required to further validate this prediction rule. In the future, a careful follow-up of high risk children may enhance early detection and treatment of these limitations.

Key words: *Bacterial meningitis, cohort study, nested case-control study, prediction, sequelae*

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Bacterial meningitis is a severe infectious disease affecting approximately 15 children per 100 000 per year in The Netherlands (1). In about 15% of the children who survive bacterial meningitis, severe sequelae such as sensorineural hearing loss, motor problems, seizures and mental retardation occur (2–8). More subtle adverse outcomes such as cognitive, academic and behavioural problems are present in over 20% (4–7, 9–13). These problems often remain undetected until the children start school, several years after they have been cured of their meningitis. As a result, more of these children require special education and end up repeating the year (5, 11). Early detection of academic and behavioural problems may enable prompt and adequate treatment and thus prevent worsening.

Several risk factors for severe and more subtle sequelae after bacterial meningitis have been proposed, including male gender, young age at illness, acute-phase neurological complications and S. *pneumoniae* as the infective pathogen (2, 6, 7, 9, 11, 13–15). However, academic and/or behavioural problems were not specifically addressed and none of the reports provided comprehensive prediction rules, which could be used in practice to detect children at high risk. This study was conducted to determine risk factors for academic and/or behavioural limitations after surviving bacterial meningitis. (Following the concepts of the recently published *International Classification of Functioning, Disability, and Health* (ICF) (16) for the description of the human functioning and disability, the studied academic and behavioural problems are denoted and classified as activity limitations.) With these risk factors, a prediction rule was devised to identify the children at risk of developing these limitations.

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Patients and methods

Study population

In 1999, we compiled a cohort of 674 Dutch school-age children who had recovered from non-*Haemophilus influenzae* (Hib) bacterial meningitis 5 to 10 y earlier without severe sequelae. The inclusion process of these children has been described in our report on parental perception of educational and behavioural problems (17). Briefly, the inclusion criteria were: birth date 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 cerebrospinal fluid (CSF) shunt infections or relapsing meningitis), mental retardation, bilateral deafness, cognitive or behavioural problems prior to meningitis and diseases developed after meningitis (such as cancer) which could by themselves or their treatment have led to cognitive and/or behavioural problems.

We studied the files of The Netherlands Reference Laboratory for Bacterial Meningitis for data on eligible patients. This laboratory collects data (e.g. causative pathogen, name, gender, date of birth, date of infection and hospital of admission) from approximately 80% of all bacterial meningitis cases in The Netherlands. The diagnosis of bacterial meningitis was based on the isolation of bacteria in the CSF. We detected 1605 patients who met the inclusion criteria. The children had been treated in 110 different hospitals. We asked a paediatrician from every hospital involved to send the parents of the postmeningitic child a standard letter requesting their participation in our study. The parents who agreed to participate were sent two questionnaires on academic and behavioural problems (School Achievement Rating Scale (SAR) and Functional Status II (R) (FS-II)) (17) and one questionnaire to check on exclusion criteria. During this process, 826 (51%) children were lost because of various reasons: paediatricians' refusal ($n = 205$ [12.8%]; 10 [9%] paediatricians); death ($n = 40$ [2.5%]); addresses missing from the medical records ($n = 60$ [3.7%]); no response from the parents to the letter requesting participation ($n = 445$ [27.7%]); parents' refusal ($n = 49$ [3.1%]); questionnaires not returned ($n = 16$ [1.0%]); filling in of questionnaires incomplete ($n = 11$ [0.7%]). Furthermore, 105 (7%) children were excluded because of: meningitis "with complex onset" ($n = 73$ [4.5%]); mental retardation after meningitis ($n = 5$ [0.3%]); bilateral deafness after meningitis ($n = 6$ [0.4%]); cognitive or behavioural problems prior to meningitis ($n = 16$ [1.0%]); diseases after meningitis which could have led to cognitive and/or behavioural limitations ($n = 5$ [0.3%]). Hence, the final cohort consisted of 674 children (57% boys) with a mean age at infection of 2.4 (range 0–9.5) y. Bacterial meningitis was caused by *N. meningitidis* in 526 (78.0%), *S. pneumoniae* in 109 (16.2%), *S. agalactiae* in 23 (3.4%), *E. coli* in 12 (1.8%) and *L. monocytogenes* in 4 (0.6%) of the children. Gender, age and causative pathogens of the 674 participants and the 1605 originally selected children were very similar (17).

Sampling of children for assessment

Because it would have demanded an excessive amount of time and resources to examine 674 children, we selected two equal groups of children from the cohort on the basis of the data gathered by SAR and FS-II with respect to complaints about school achievement and behaviour, following a two-step sampling procedure (Fig. 1):

1. Classification of the cohort into two groups, according to parental complaints. Children with the worst 10th percentile of scores on the SAR, those going to a special-needs school and those with the worst 10th percentile of scores on the FS-II were classified as children whose parents complained about academic achievement and/or behaviour; 134 (20%) children met these criteria. The remaining 540 (80%) children were classified as children whose parents had no complaints (Fig. 1).

2. Random sampling from both groups. One hundred of the 134 children whose parents had complaints, and 101 of the 540 children whose parents had no complaints, were sampled randomly (nested case-control approach, Fig. 1). Of these children, the academic achievement and behaviour were assessed, and the medical records were reviewed for a final and thorough check of the exclusion criteria and to obtain data on the risk factors. Five children were lost from the study because data on the bacterial meningitis were missing from the medical records and 14 children had to be excluded because of: Hib meningitis ($n = 2$); meningitis caused by other rare pathogens ($n = 2$); meningitis with "complex onset" ($n = 7$); cognitive problems prior to meningitis ($n = 3$). Hence, the final study population consisted of 182 children; 89 whose parents had complaints and 93 whose parents had no complaints (figure). The children were assessed at a mean age of 9.7 (range 5.3–14.2) y, on average 7.4 (range 4.0–10.4) y after meningitis.

Assessment methods

Academic Achievement Test (AAT). Written arithmetic (copying and solving computational problems), reading aloud and reproducing stories, writing to dictation, and copying sentences were assessed using tasks taken from standard educational packages (18). The tasks were selected according to the child's actual educational

level, and simpler levels were presented if necessary. Two independent experts, a senior neuropsychologist (AJ-S) and an educationalist, scored per task whether the child performed according to group (or form) level (score 0), below group level (score 1), whether extraneous elements (perseveration or other manifestations of diminished control) (19) were present (score 2), and whether the performance was both below group level and contained extraneous elements (score 3). The experts did not know whether the task performances were from a child whose parents had complaints or from one whose parents had not, and they were also unaware of the child's neuropsychological profile. They knew the age and gender of the child. Performances below group level and/or containing extraneous elements in at least two of the four AAT tasks were considered to indicate academic limitations.

Child Behaviour Checklist (CBCL). This 138-item parent-questionnaire makes an inventory of behavioural problems (20, 21). On the basis of an impressive body of research on the CBCL (22), we used the Total Problem Scale. A Total Problem Score that exceeded the mean of the Dutch norm group of healthy children by two standard deviations or more (21) was considered to indicate behavioural limitations.

Risk factors

By reviewing the medical records, information on all potential risk factors for academic and/or behavioural limitations after bacterial meningitis were collected. Detailed information was gathered on patient history and physical examination at admission to the hospital, laboratory results obtained during hospitalization, and details of treatment and clinical course during hospitalization. Because it was difficult to decide retrospectively whether a child had had convulsive activity, seizures were defined as convulsive activity for which a doctor had given anticonvulsive therapy. Insufficient data were available on whether dexamethasone therapy was started prior to or after antibiotics. Because the continuous variable dexamethasone use was not normally distributed, this variable was dichotomized in use for 2 d or less and use for more than 2 d. Socioeconomic status was assessed and defined as the highest level of education attained by the mother and the father. The following classification was made: lower educational level (administrative and technical schooling), middle educational level (secondary schooling) and higher educational level (university or equivalent education). Also, ethnicity was recorded; "non-Dutch ethnicity" was defined as speaking a language other than Dutch at home.

This study was approved by the medical ethical committee of the University Medical Centre Utrecht. Written informed consent was obtained from the parents or guardians of all children and from the children themselves if they were 12 y or older.

Data analysis

The association between the presence or absence of academic and/or behavioural limitations and each potential risk factor was examined using univariate logistic regression analysis. When continuous variables were not normally distributed, they were dichotomized (except in the case of CSF leukocyte count, which performed best untransformed). Predictors that were univariately associated with the outcome ($p < 0.20$)

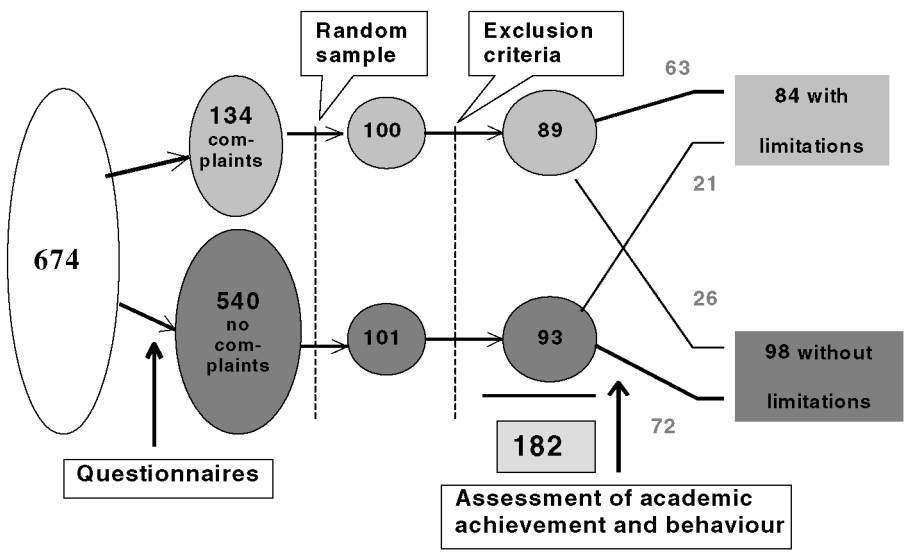

Fig. 1. The nested case-control approach.

were included in a multivariate logistic regression model to determine their independent value in the prediction of outcome. The model was reduced by excluding predictors from the model with a *p*-value of >0.10. The goodness of fit of this model was estimated using the Hosmer and Lemeshow test (23). The prognostic ability to discriminate between patients with and without academic and/or behavioural limitations was estimated using the area under the receiver operating characteristic curve (AUC) (24).

Because data for multivariate regression analysis have to be complete for all patients, multiple imputation techniques were used to fill in missing variables (25). If more than 30% of the data for a particular variable were missing, this variable was excluded from the analysis. Imputation was repeated five times to take account of uncertainties in imputed data (26). 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 (26).

Random bootstrapping techniques were used to calculate a shrinkage factor to adjust for over-fitting (i.e. overly optimistic estimates of the regression coefficients of the prediction model) and to validate the model (25). The final model was then transformed into a clinical prediction rule. The regression coefficient of each variable in the model was divided by the smallest one and rounded off to the nearest integer. The intercept of the model was left out, because the intercept does not estimate the absolute baseline risk of academic and/or behavioural limitations as a consequence of our nested case-control design. By assigning points for each variable and adding the results, a score was obtained for each individual patient. Furthermore, to estimate the true absolute incidence of these limitations in the total cohort, all subjects were given a weight, which was the inverse of the sampling fraction (134/100 for children in the group with complaints and 540/101 for children in the group with no complaints; Fig. 1). To simplify the interpretation of the model, a nomogram was made and a cut-off point was chosen. Patients were classified according to their risk score, and the absolute numbers of limitations were determined among categories of risk score. The data were analysed using SPSS 9.0 and S-plus.

Results

Academic and/or behavioural limitations were present in 84 children: 44 (52%) children were diagnosed with academic, 20 (24%) children with behavioural, and 20 (24%) with both academic and behavioural limitations. Ninety-eight children showed no signs of academic and/or behavioural limitations on evaluation (Fig. 1). The children with and without these limitations did not differ significantly with regard to age at assessment (Table 1).

Table 1 shows the important univariate associations between academic and/or behavioural limitations and various demographic, patient and illness-related characteristics. In presenting history and physical examination, there were no significant differences between the children with and without limitations regarding age at infection, body temperature, decreased consciousness, meningeal irritation and severity of illness correlates (e.g. sepsis, shock and admission to intensive care unit). Nor did the blood leukocyte count, blood neutrophil

Table 1. Demographic, patient and illness characteristics of post-meningitic children with and without academic and/or behavioural limitations.

Characteristics	Limitations ($n = 84$)	No limitations ($n = 98$)	*p*-value
Demographics			
Age at assessment (y)[a]	9.6 (1.9)	9.8 (2.2)	0.7
Ethnicity[b]	4 (9)	13 (13)	0.05
Educational level, mother[c]			0.003
Lower education	38 (46)	21 (21)	0.003
Middle education	32 (38)	51 (52)	0.6
Higher education	13 (16)	26 (27)	RC
Educational level, father[c]			0.01
Lower education	31 (38)	26 (26)	0.004
Middle education	41 (51)	43 (44)	0.002
Higher education	9 (11)	29 (30)	RC
Male gender	62 (74)	56 (57)	0.02
Birthweight (g)[a]	3367 (581)	3505 (446)	0.08
Patient history and physical examination			
Symptoms prior to admission >2 d	24 (29)	17 (17)	0.07
Focal neurological signs on admission[d]	11 (13)	5 (5)	0.06
Laboratory tests			
CSF protein (g/l)[a]	1.4 (1.3)	1.9 (1.6)	0.05
CSF leukocyte count (/μl)[a]	6100 (9039)	10573 (13765)	0.01
Causative pathogen			0.4
S. pneumoniae	14 (17)	12 (12)	0.2
N. meningitidis	67 (80)	79 (81)	0.3
Other	3 (3)	7 (7)	RC
Therapy and clinical course			
Seizures treated with anticonvulsive therapy	7 (8)	15 (15)	0.2
Duration fever during admission (d)[a]	4.3 (4.5)	3.1 (2.6)	0.04
Delay >6 h between admission and start of antibiotics	13 (16)	3 (3)	0.003
Dexamethasone			0.09
≤ 2 d	7 (8)	5 (5)	0.6
>2 d	12 (14)	27 (28)	0.04
No	65 (78)	66 (67)	RC

Values represent numbers (percentages), unless stated otherwise.

[a] Mean (standard deviation).

[b] Non-Dutch ethnicity is defined as speaking a language other than Dutch at home.

[c] Lower education: lower administrative or technical education; middle education: secondary education; higher education: university education.

[d] Focal neurological signs are defined as cranial nerve deficits, increased or decreased reflexes of arms or legs, increased or decreased tonus of arms or legs, and ataxia.

CSF: cerebrospinal fluid; RC: reference category.

count and CSF glucose concentration differ significantly. Also, the duration of meningeal signs and the duration of disturbed consciousness during admission were not associated with outcome.

After stepwise multivariate analysis of the univariately associated variables, the independent predictors for academic and/or behavioural limitations were: male gender, birthweight of 3000 g or less, educational level of the father (or educational level of the main caregiver in a single parent family), *S. pneumoniae* as causative pathogen, CSF leukocyte count, delay of more than 6 h between admission and start of antibiotics, dexamethasone use, seizures treated with anticonvulsive therapy and prolonged fever (Table 2). The AUC of this model was 0.83 (95% CI: 0.77–0.89). Table 2 presents the regression coefficients of these independent predictors after bootstrapping. The AUC of the model after bootstrapping was 0.78. Based on these regression coefficients, a prediction rule was constructed by assigning points for each variable present (see Table 2). A total score was computed for each individual patient. In our population, the score ranged from 0 to 23 and the AUC of the score was 0.81 (95% CI: 0.75–0.87).

To estimate the absolute incidence of academic and/or behavioural limitations across categories of the score in the total cohort, all subjects were given a weight, which was the inverse of the sampling fraction. In this way, a new data set was created resembling the entire study population. The cumulative incidence of these limitations among children who survived bacterial meningitis without severe disease sequelae was 32% (196 out of 616 patients [Table 3], 95% CI: 25–39%). Fig. 2 shows the nomogram of the rule and Table 3 the numbers of subjects across selected categories of the score. If 10 was taken as a cut-off point for the risk score from this prediction rule, 76% of the patients with limitations could be predicted. With this cut-off, 38% of the children in the cohort were selected as possibly having limitations, i.e. 21% of the children without limitations were falsely predicted as children with limitations (false positives).

A non-Dutch ethnicity was a strong risk factor for academic and/or behavioural limitations. However, because our inclusion procedure was based on questionnaires filled in by parents, we selected patients with parents who were able to read and write Dutch. It is therefore possible that we did not select a representative sample of the non-Dutch population. For this reason, we did not include this factor in our multivariate model. When we excluded the children with a non-Dutch ethnicity from the multivariate analysis, the factors in the model and their regression coefficients did not change materially.

Table 2. Independent predictors of academic and/or behavioural limitations after bacterial meningitis.

Variable	Odds ratio (95% CI)	Regression coefficient[a]	Contribution to score
Male gender	4.0 (1.8–9.1)	1.0	3
Birthweight ≤3000 g	3.2 (1.3–8.0)	0.8	2
Educational level, father[b]			
Lower education	10.8 (3.1–37.6)	1.7	5
Middle education	7.0 (2.2–22.3)	1.4	4
Higher education	RC		
S. *pneumoniae*	4.2 (1.2–14.9)	1.0	3
CSF leukocyte count (/μl)/10000[a]	0.62 (0.41–0.95)	−0.3	−1
Delay >6 h between admission and start of antibiotics	3.8 (0.7–19.6)	0.9	3
Dexamethasone			
≤2 d	2.0 (0.4–10.4)	0.5	1
>2 d	0.35 (0.1–0.9)	−0.7	−2
No	RC		
Seizures treated with anticonvulsive therapy	0.1 (0.03–0.7)	−1.4	−4
Prolonged fever (>9 d)	27.2 (2.2–336.8)	2.3	7

Score = 3 + 3 × male gender + 2 × birth weight ≤3000 g + 5 × lower educational level father + 4 × middle educational level father + 3 × *S. pneumoniae*–1 × CSF leukocyte count (/μl)/10000 + 3 × delay between admission and start of antibiotics + 1 × dexamethasone ≤2 d × − 2 × dexamethasone >2 d − 4 × seizures treated with anticonvulsive therapy + 7 × prolonged fever.

[a] After bootstrapping.

[b] Lower education = lower administrative or technical education, middle education = secondary education, higher education = university education.

[c] CSF leukocyte count (/μl)/10000 = total CSF leukocyte count per μl divided by 10000.

CSF: cerebrospinal fluid; 95% CI: 95% confidence interval.

Table 3. Number of patients (percentages) in the original cohort with and without academic and/or behavioural limitations across categories of the risk score.

Risk score	Patients in the cohort (*n* = 616)	Patients with limitations (*n* = 196)	Patients without limitations (*n* = 420)
<5	87 (14)	0	87 (21)
≥5 and <10	293 (48)	47 (24)	246 (58)
≥10 and <14	199 (32)	112 (57)	87 (21)
≥14	37 (6)	37 (19)	0

Discussion

One-third of the children who survived bacterial meningitis without severe disease sequelae had academic and/or behavioural limitations when assessed, on average, 7 y after their illness. It was possible to predict which children were at risk of developing these limitations with a rule based on nine easily obtainable patient characteristics. With 10 as a cut-off point for the risk score computed using this rule, 76% of the children with limitations could be identified, while 38% of the children in the total cohort were selected as children at risk of developing these limitations.

To appreciate the results of this study, some aspects

need to be discussed. First of all, the selection of patients in this study should be considered because this could affect the generalizability of the prediction rule. The postmeningitic cohort was assembled retrospectively and, of the 1605 children selected from The Netherlands Reference Laboratory for Bacterial Meningitis, 674 were included. Most children were excluded because parents or paediatricians refused to participate (254/1605) or because parents could not be contacted (445/1605). In this process, selection bias may have occurred. However, gender, age and causative pathogens of the 674 participants and the 1605 originally selected children were very similar (17). Sociodemographic data were unavailable. We excluded children with meningitis caused by Hib or other less common pathogens and children with "complex onset" of meningitis. Also, we excluded children with prior cognitive or behavioural problems, children with diseases which could have led to cognitive or behavioural problems, and children with mental retardation and bilateral deafness. These latter three groups of children were excluded because we wanted to study the academic and behavioural limitations in the segment of children who survived bacterial meningitis without severe sequelae. Epilepsy and minor neurological problems were not considered severe sequelae and thus children with these sequelae were not excluded. The prediction rule may not be applicable to the above three groups of excluded children. Moreover, among the children who were excluded because of "complex onset" of meningitis were seven children who developed bacterial meningitis during their time of hospitalization due to premature birth (gestational age <35 wk) or low birthweight (<2200 g); we considered them to be immune-compromised. However, since these children form an important proportion of the neonatal bacterial meningitis cases, we repeated the multivariate analysis after including them. This did not alter the prediction rule (data not shown). Thus, our results pertain to a population of prior healthy children who recovered from non-Hib bacterial meningitis without severe sequelae. Secondly, our nested case-control design enabled us to study a relatively large number of patients with academic and/or behavioural limitations and thus a large number of risk factors. With this design, it was also possible to extrapolate the numbers of patients with limitations in the case-control study to absolute numbers of limitations in the cohort. It is important to realize that this incidence figure is an extrapolation and that it is necessary to confirm it in a study in which all children are assessed. Thirdly, it is important to realize that the children were classified as having "limitations" based on the "Academic Achievement Test" and the "Child Behaviour Checklist". We defined "academic limitations" and "behavioural limitations" by arbitrary but in practice widely used cut-off points. Comparison with other studies is difficult because the definition of "limitations" differs between studies. Fourthly, the risk

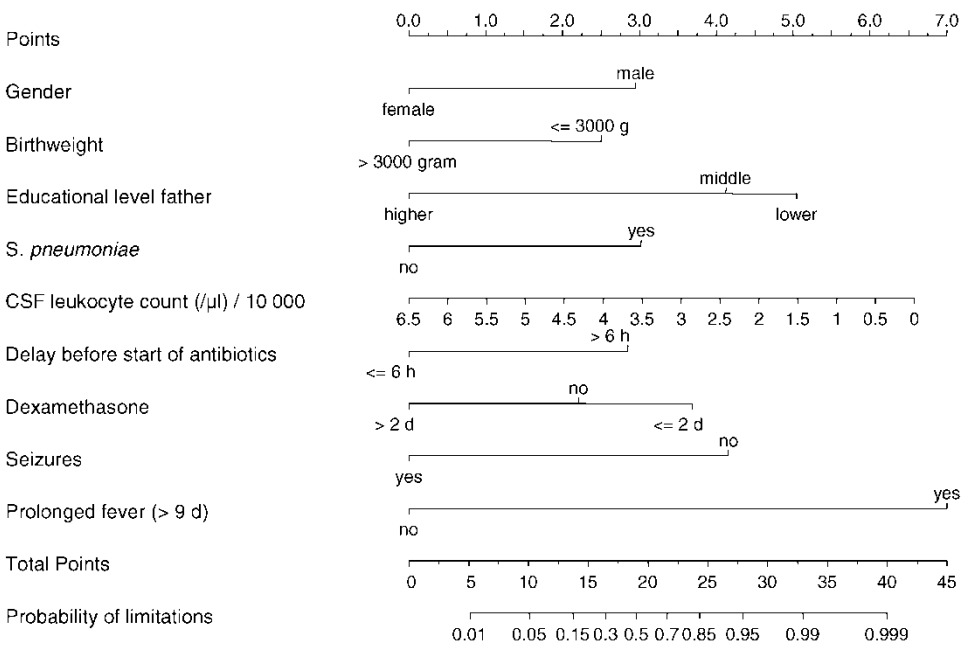

Fig. 2. This nomogram can be used to determine the predicted probability of academic and/or behavioural limitations given the set of predictor variables. The number of points per predictor variable can be read from the top line. By adding these together, an estimate of the probability of these limitations can be obtained using the "Total Points" line. For example, a child with *S. pneumoniae* meningitis (3 points), a delay of more than 6 h between admission and start of antibiotics (3 points) and prolonged fever (7 points) has a score of 13, corresponding to an estimated probability of academic and/or behavioural limitations of about 0.15.

factors in this study have been collected retrospectively from routinely documented medical information in hospital charts. Although prospective collection of information on risk factors might have been more accurate, retrospective collection was very efficient in this long-term follow-up study. The quality of the data collected in this way reflects the level of quality normally available in practice. As a consequence of the retrospective data collection, not all data were available for each patient. We have dealt with this problem by using multiple imputation techniques on predictors with less than 30% of missing data. With this technique, it is possible to overcome selection bias due to missing data and to increase the efficiency of the analysis because data are available for all patients. Finally, using bootstrapping techniques, we demonstrated that the prediction rule is robust. Although the regression coefficients were shrunk after bootstrapping, the AUC did not change. Still, the actual performance of this scoring rule should be confirmed in a new group of children with bacterial meningitis before implementation of the model in clinical practice.

Our study showed that academic and/or behavioural limitations after bacterial meningitis were more common than previously thought. We found a cumulative incidence of 32%, where others have reported incidences of approximately 20% (4–7, 9–13). Our incidence figure is especially striking in view of the fact that most researchers have studied severe and more subtle adverse outcomes simultaneously (2, 4–7, 9–13). In contrast to these studies, we excluded the children with severe adverse outcomes, such as mental retardation and complete deafness, and still found this high incidence. As mentioned above, these differences in incidence figures may partly be explained by differences in the definition of limitations and by the nested case-control design. However, the studied "limitations" were well defined and the definition was rather conservative, which indicate—in our opinion—real problems. Furthermore, although the incidence figure was extrapolated from the nested case-control study, it is consistent with previous published data from our cohort study, in which we reported that parents perceive educational, behavioural and general health problems in more than 30% of postmeningitic children (17). Another explanation for the differences in incidences may be that the other studies (4–7, 9–13) did not specifically address academic and/or behavioural problems and, because of that, found lower incidences.

Most of the risk factors found in our study have been reported previously (2, 6, 7, 9, 11, 13–15). However, these authors all studied death or severe sequelae simultaneously with academic and/or behavioural limitations as outcome, and none of these studies provided a prediction rule to detect children at high risk for these limitations (2, 6, 7, 9, 11, 13–15). Furthermore, most studies included children with Hib meningitis (2, 6, 9, 11, 13, 15). In contrast with our findings, acute-phase neurological complications have been reported as major factors associated with adverse outcome (2, 6, 7, 11). For example, seizures occurring before or during hospitalization have been reported as good predictors of mortality and morbidity (6, 7, 15). Our results did not support these findings; we showed an inverse relationship between seizures and the studied limitations. A possible explanation for this finding may be that seizures are particularly associated with severe sequelae and death. The effect of adjunctive dexamethasone therapy on academic and/or behavioural limitations has not been studied before. Dexamethasone treatment has a protective effect on hearing loss in pneumococcal meningitis when administered before the start of the antibiotic therapy (27). We found that children treated with dexamethasone for more than 2 d had a lower risk, and that children treated for 2 d or less had a higher risk of limitations.

We arbitrarily proposed using a cut-off point of 10 for the risk score above, at which postmeningitic children are at risk for academic and/or behavioural limitations. We considered 21% false-positive predictions to be acceptable, simply because we assumed that the consequences of such misclassification (i.e. longer outpatient clinic follow-up) would not be harmful. Further research is needed to determine the consequences of this in terms of effects for children and parents and in terms of costs. Also, further research is needed to determine which kind of follow-up should be offered to these children, for example a yearly follow-up at the outpatient clinic (aimed at the child's development and at complaints of the parents about their child's behaviour, development or school achievement) until the child has proven to be functioning well at elementary school. Possibly, this should be combined with a comprehensive assessment by a neuropsychologist before the start of elementary school.

In conclusion, one-third of the postmeningitic children, who survived without severe sequelae, developed academic and/or behavioural limitations. These limitations could be predicted using a rule based on the factors male gender, birthweight 3000 g or less, educational level of the father, *S. pneumoniae* as causative pathogen, CSF leukocyte count, delay of more than 6 h between admission and start of antibiotics, dexamethasone use, seizures treated with anticonvulsive therapy and prolonged fever. With 10 as a cut-off point for the risk score computed using this rule, 76% of the children with limitations could be identified, while 38% of the children in the total cohort were selected as children at risk of developing these limitations. Additional research is required to further validate this prediction rule. In the future, it may be possible to identify children at high risk of developing these limitations after bacterial meningitis. Follow-up of this selected group of postmeningitic children may lead to early detection and adequate treatment of these limitations.

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