Predicting the long-term outcome of bacterial meningitis in childhood

de Jonge, R.C.J.

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Chapter 7

Diagnostic value of the strengths and difficulties questionnaire and prevalence of behavioral functioning of childhood bacterial meningitis survivors

Rogier C.J. de Jonge
Evelyne M. de Kluiver
Caroline B. Terwee
Irene Koomen
Lodewijk Spanjaard
A. Marceline van Furth
ABSTRACT

Aim:
Bacterial meningitis (BM) is a serious infection of the central nervous system. Behavioral problems are reported in 9-46% of BM survivors. The Strengths and Difficulties Questionnaire (SDQ) is a short questionnaire to quickly measure child behavior. This study aimed to assess the diagnostic value of the SDQ to identify behavioral problems as compared to the Child Behavior Checklist (CBCL). Second aim was to determine the occurrence of behavioral problems with the SDQ in a cohort of Dutch school-age BM survivors.

Patients and methods:
A cohort was constructed from all Dutch non-Haemophilus influenzae type b (Hib) BM survivors, who were born between January 1993 and December 1995 and who suffered from BM between January 1997 and December 2001. In a nested cohort the correlation between SDQ total difficulties-score and the gold standard CBCL-Total score was determined, and level of agreement for the classifications “normal”, “borderline” and “abnormal” behavior was calculated. Sensitivity, specificity, positive and negative predictive value (PPV and NPV) of the SDQ were assessed. Results were corrected for the selective sampling of the nested cohort. Parents SDQ scores were compared to norm reference data.

Results:
A cohort of 361 children was compiled, mean age of infection 2.2 years (range 0-7.9), mean time since the infection 6.6 years. A nested cohort of 95 children was constructed. Total scores derived from the SDQ and CBCL were moderately correlated: Spearman’s rank correlation coefficient $r = 0.66$. Cohen’s Kappa coefficient was 0.47, indicating moderate agreement between the SDQ and CBCL. Sensitivity was 0.51, specificity 0.92. PPV was 0.62, NPV 0.91. In the total cohort of 361 children parents of 62 children (17.6 %) reported behavior in abnormal range, compared with 9.7% in the population sample ($p$-value <0.001).

Conclusion:
The SDQ can provide effective support in the evaluation of children at risk of behavioral problems, especially to identify those children without problems. Further, emotional and behavioral problems are a relevant and not to be underestimated problem in children with a history of BM.
INTRODUCTION

Although decreasing in incidence in the Western world, bacterial meningitis (BM) in childhood is still a severe infectious disease with often devastating consequences in the short- and long-term.\(^1\)\(^-\)\(^3\)

Besides prevention of BM by vaccination and a spontaneous decrease of *Neisseria meningitidis* serogroup B infections, treatment of the disease also improved by advances in antibiotic therapy and critical care. Still, mortality is up to 5% in pediatric patients, and even higher in neonates.\(^1\)\(^-\)\(^2\)\(^,\)\(^5\)\(^,\)\(^6\) In survivors the incidence of morbidity is high: severe (neurological) sequelae as spasticity, paresis, epilepsy, mental retardation and hearing loss occur in 7-23% of survivors of childhood BM.\(^1\)\(^-\)\(^7\)\(^,\)\(^9\) In the last two decades researchers paid an increasing attention to more subtle sequelae as cognitive, academic and behavioral problems. It appeared that these outcomes have an alarming high incidence: several studies report incidences of more than 20%.\(^10\)\(^-\)\(^13\)

Focusing on behavior, Koomen et al. reported a compound incidence of academic and behavioral problems of 32% in a large cohort of school-age survivors of BM.\(^12\) Ritchi et al. disentangled the behavioral problems from the academic limitations in this cohort, reporting 9% of the children as having behavioral problems at school-age.\(^14\) Some other studies found higher incidences of 17-46%.\(^3\)\(^,\)\(^11\)\(^-\)\(^17\)

Behavioral problems are a challenging subject for research, particularly due to poor definitions of “abnormal behavior”. Many questionnaires have been developed for the assessment of behavioral problems in children. The tool mostly used in literature is the Child Behavior Checklist (CBCL). This is a widely used and extensively validated questionnaire designed to measure behavioral problems.\(^18\)\(^-\)\(^20\) Although highly valuable the CBCL seems less useful for screening purposes because of its length and the relatively large number of items not relevant for most children.

As an alternative, Goodman developed the Strengths and Difficulties Questionnaire (SDQ)\(^21\)\(^,\)\(^22\). This is a brief, user-friendly screening questionnaire on child’s behavior, available in more than 70 languages. It is extensively validated and being widely used in epidemiological and clinical research.\(^23\)\(^-\)\(^27\) Multiple studies, including a systematic review, reported the CBCL and SDQ scores to be highly correlated.\(^28\)\(^,\)\(^29\)

Despite its advantages, the SDQ has not often been used for assessment of behavioral problems of BM survivors. One study by Halket et al. investigated parental and teacher’s perception of the effects of BM in infancy on subsequent teenage behavior using the SDQ. They found this group to have significantly more problems than matched controls, even up to 46% in teenagers with a history of infant BM with and 38% in those without complications.\(^17\)

This study aimed to assess the diagnostic value of the SDQ to identify behavioral problems compared with the CBCL. The second aim was to determine the prevalence of behavioral problems in a Dutch cohort of school-age survivors of BM, using the SDQ.
PATIENTS AND METHODS

Study sample and procedure

The cohort used for this study was primarily constructed for external validation of a clinical prediction rule (CPR) for academic or behavioral limitations after childhood BM\textsuperscript{12}. Next, it was used for secondary research questions. From 2005 to 2007 a cohort of school-age children with a history of non-Haemophilus influenzae type b (Hib) BM was compiled, using the database of the Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM) which collects strains from approximately 90% of all Dutch meningitis cases\textsuperscript{30}. All Dutch children born between January 1993 and December 1995 who suffered from BM between January 1997 and December 2001 were eligible for inclusion. Exclusion criteria were: meningitis caused by Hib or other less common pathogens, a complex onset of BM (defined as: meningitis secondary to immunodeficiency states, central nervous system surgery, cranial trauma or cerebrospinal fluid shunt infection, or relapsing meningitis), and pre-existing cognitive or behavioral problems or severe handicaps. BM was diagnosed by a positive CSF culture or by the presence of bacterial antigens using latex agglutination. Pediatricians in all Dutch hospitals where the patients were originally treated were requested to forward the parents (or guardians) an invitation letter to participate in the study. After informed consent, the parents were asked to fill in the SDQ and other questionnaires regarding health, learning and behavior (School Achievement Rating Scale (SAR) and Functional Status II (FS-II)). The School Achievement Rating Scale is a questionnaire for parents on school performance. It provides information about complaints regarding the child’s achievements, concentration, behavior, speed, motivation and mood at school. The Functional Status II is a questionnaire measuring health status using behavioral statements about children with chronic physical conditions. Both questionnaires are described in more detail in the original publications by Koomen et al. These report parental perception of educational, behavioral and general health problems and the development of a CPR for academic or behavioral limitations after childhood BM\textsuperscript{12,31-33}.

For both the development and the validation of this CPR a nested cohort approach was used: in this design only a subset of cases and controls are selected for further analysis, which decreases the necessary time and financial resources resulting in an improved efficiency\textsuperscript{34}. Because only the nested cohort included children with both a completed SDQ and CBCL, this cohort was used for the intra-individual comparison of SDQ and CBCL scores. Based on the results of the FS-II, SAR and the (absence of) necessity for special education the cohort was divided in two groups: using a cut-off point of scores below the 10\textsuperscript{th} percentile on the SAR or the FS-II, or the need for special education the children were classified as suspect for academic or behavioral limitations or not. From both groups equal samples of children were randomly selected. For the validation study of the CPR the children were invited for extensive tests on academic and behavioral performance. The CBCL was used for assessment
of behavioral limitations, and these data were used in this study for comparison with the results of the SDQ.

For the second part of this study, in which the prevalence of behavioral problems after childhood BM was determined, the original cohort of all children with a completed SDQ was used. The study was approved by the medical ethics committee of the VU University Medical Center in Amsterdam. Written informed consent was obtained from the parents or guardians of all children and from the children themselves if they were 12 years of age or older.

**Assessment methods: Strengths and Difficulties Questionnaire**

The SDQ is a brief screening questionnaire on behavior, covering the most important domains of child psychopathology. The SDQ can be completed in five minutes by the parents or teachers of children aged 4 to 16. Children aged 11 to 16 can independently complete the questionnaire. In this study, the parent version of the Dutch SDQ 4-16 was used. The questionnaire consists of 25 items, divided into five scales: emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems, and pro-social behavior. The first four of these scales rate negative aspects of behavior where the fifth scale rates positive aspects. Parents use a three-point Likert scale to answer each question with “not true”, “somewhat true”, or “certainly true”. Higher scores on the pro-social behavior scale reflect strengths, whereas higher scores on the other scales reflect difficulties. A total difficulties score can be calculated by summing the scores on the emotional symptoms, conduct problems, hyperactivity and peer relationship problems scales. Scores for each scale can be classified as normal, borderline and abnormal. For this study, norm data from a British national sample were used, since reliable Dutch norms are not yet available. British population norms are available at www.sdqinfo.com. In this norm data a total difficulties score of ≥17 is considered as “abnormal”, based on the 90th percentile of the norm group. A score of 14-16 is considered as “borderline”, representing the 85th-90th percentile. The psychometric properties of the SDQ have been examined in different studies and evidence has been collected for the validity of the SDQ. The SDQ scores correlate substantially with other psychopathology questionnaires such as the Child Behavior Checklist. As mentioned earlier, reliable Dutch norm data are yet not available.

**Assessment methods: Child Behavior Checklist (CBCL)**

The Child Behavior Checklist for ages 6-18 (CBCL/6-18) is a parent-report questionnaire for children of 6 to 18 years in which the child is rated on various behavioral and emotional problems. In the first part parents give information for 20 competence items covering their child’s activities, social relations, and school performance. Part two consists of 118 items that describe specific behavioral and emotional problems. Parents rate their child for how true each item is using the following Likert scale: “not true”, “somewhat true”, or “very true or often true”. Eight subscale scores can be calculated: withdrawn, somatic complaints, anxious-depressed,
social problems, thought problems, attention problems, delinquent behavior and aggressive
behavior. Two domains of the psychopathology are measured: first “externalizing” (withdrawn,
somatic complaints, anxious-depressed) which reflects behavioral problems and second “in-
ternalizing” (delinquent and aggressive behavior) which reflects emotional problems 18, 37, 38.
Higher CBCL scores reflect higher levels of problems.
The reliability and validity of the CBCL established by Achenbach were repeatedly validated
and confirmed for the Dutch translation. Several studies with large cohorts of children from
the general population and from clinically referred situations show good to excellent cross-
cultural correlations between American and Dutch results of the parent CBCL 39-46. In this
study, the Dutch validated and standardized version of the questionnaire was used 19, 47-49. Raw
scores were converted to total problem scores (T-scores). The T-score can be classified as nor-
mal, borderline and clinical (abnormal) range. We used the total problem T-score to compare
results with the SDQ. Behavioral problems were defined as a T-score ≥64, which corresponds
with the 90th percentile of the healthy Dutch norm group. Borderline abnormal was defined as
a T-score of 60-63 (85th-90th percentile) 19.

Data analysis

Diagnostic value of the SDQ

To assess the diagnostic value of the SDQ compared to the “gold standard” CBCL, the cor-
relation between the SDQ total difficulties-score and CBCL T-score was calculated using
Spearman’s rank correlation coefficient \( r \). An \( r \leq 0.3 \) was considered to represent weak, \( >0.3 \)
and \( \leq 0.7 \) moderate and \( >0.7 \) strong correlation. Based on the aforementioned literature it was
hypothesized that a strong correlation with a coefficient of \( \geq 0.7 \) could be expected.
Because interest lies mainly in the clinical range of problems (scores >90th percentile), the
results of both questionnaires were dichotomized in the classification “normal/borderline”
or “abnormal” behavior. Agreement between the two questionnaires regarding these clas-
sifications was defined with a Cohen’s Kappa for the level of agreement. A Kappa \( \leq 0.2 \) was
considered as poor, \( >0.2 \) and \( \leq 0.4 \) as fair, \( >0.4 \) and \( \leq 0.6 \) as moderate, \( >0.6 \) and \( \leq 0.8 \) as good
and \( >0.8 \) as very good agreement 50, 51. The observed proportion of agreement was calculated
for the composite categories and for the two categories (“normal/borderline” or “abnormal”)
separately.
Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of
the SDQ questionnaire in comparison with the CBCL (gold standard) were assessed for the
dichotomized SDQ and CBCL total scores (“normal/borderline” versus “abnormal behavior).
All measures were calculated for the group suspect and for the group not suspect for limita-
tions. To estimate the value in the whole cohort, they were corrected for the selected sam-
pling of the nested cohort: pooled, weighted averages were calculated with correction for the
sampling fraction.
Determination of the prevalence of behavioral problems and comparison with norms

The SDQ scores were calculated according to standard instructions. The means of the subscales and the total difficulties score were compared with the British means of the norm group with the determination of mean difference and effect size (mean difference divided by standard deviation (SD)). Then, the children were classified as having “normal/borderline” or “abnormal” behavior using the abovementioned cut-off points. Differences in prevalences of abnormal behavior between the children in the cohort and the norm group were analyzed using the χ² test and a relative risk (RR) was calculated.

The CBCL consistently report girls to have higher scores on somatic complaints and anxious or depressed emotions, but lower scores on attention problems, delinquent behavior, and aggressive behavior than boys. Therefore the differences in mean SDQ scores and in prevalences of abnormal behavior between boys and girls were compared with independent sample t-test and χ² test respectively.

All differences were considered to be statistically significant if their two-tailed p-values were 0.05 or below, mean differences and 95% confidence intervals (95% CI) were calculated where applicable.

All data were analyzed using SPSS Statistics 20.0 (IBM Corporation, Somers, NY) and Prism 5 (GraphPad Software, Inc., La Jolla, CA).

RESULTS

Primarily, 1036 children met the criteria for inclusion. Finally, 361 completed SDQ questionnaires were returned. Figure 1 presents a flow chart of patient inclusion.

Table 1 presents the basic patients characteristics of the original cohort. The cohort consists of significantly more boys (n=200) than girls (n=161), but characteristics are distributed equally between the sexes.

From the original cohort of 361 children a nested cohort was constructed as described above. From 3 children (0.8%) incomplete FS-II or SAR led to exclusion. Based on results of the FS-II, SAR and the (absence of) necessity for special education the original cohort was divided into two groups: the first group consisted of 131 children (36.3%) suspect for academic or behavioral limitations. The second group (n=227, 62.9%) were children without problems. From both groups, equal samples of children with (n=80) and without (n=80) these problems were randomly selected. Of the 80 invited children with suspected limitations, 47 participated in this study. Forty-four of these children completed this assessment. Forty-nine children in the group of children without suspected problems completed the tests. The parents of two children did not want to participate in this part of the validation study, but sent us the completed CBCL, resulting in a total of 95 children with completed SDQ and CBCL questionnaires. Table 2 presents the basic patients characteristics of the
1036 BM patients eligible for inclusion

- 693 (67%) - invitation letter
- 228 (22%) - no cooperation pediatrician
- 22 (2%) - died
- 93 (9%) - missing or incorrect address data

- 414 (40%) - informed consent
- 22 (2%) - refusal parents
- 257 (25%) - no response

- 40 (4%) - questionnaires not returned
- 13 (1%) – exclusion after second check criteria

361 (35%) - included

Figure 1: Patient inclusion flow chart
Diagnostic value of the SDQ

Table 3 presents the agreement between both questionnaires for the two categories “normal/borderline” vs. “abnormal” behavior.

Table 4 presents all results of the comparison between SDQ and the CBCL in both groups of children suspect or not suspect for limitations, and their pooled values. The inverse of the sampling fractions were used as weighing factors, correcting for the selective sampling in the nested cohort. For the children suspect for limitations this correcting factor was 131/47, for the children not suspect it was 227/48.
Table 2: Patient characteristics of the nested cohort used for SDQ vs CBCL comparisons

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total n=95</th>
<th>Suspect for limitations n=47</th>
<th>Not suspect n=48</th>
<th>p-value b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No c</td>
<td>No c</td>
<td>No c</td>
<td></td>
</tr>
<tr>
<td>Male sex d</td>
<td>95</td>
<td>47 (49.5)</td>
<td>47 (57.4)</td>
<td>48 (41.7)</td>
</tr>
<tr>
<td>Mean age at infection (years)e</td>
<td>95</td>
<td>2.6 (1.8)</td>
<td>2.4 (1.7)</td>
<td>2.7 (1.9)</td>
</tr>
<tr>
<td>Mean age at assessment (years)e</td>
<td>95</td>
<td>9.2 (2.2)</td>
<td>9.0 (1.9)</td>
<td>9.4 (2.5)</td>
</tr>
<tr>
<td>Time after bacterial meningitis (years)e</td>
<td>95</td>
<td>6.7 (1.6)</td>
<td>6.6 (1.5)</td>
<td>6.7 (1.7)</td>
</tr>
<tr>
<td>Causative pathogens d</td>
<td>95</td>
<td>47</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>N. meningitidis</td>
<td>79</td>
<td>38 (80.9)</td>
<td>41 (87.2)</td>
<td>0.55</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>14</td>
<td>9 (19.1)</td>
<td>5 (10.6)</td>
<td>0.23</td>
</tr>
<tr>
<td>E. coli</td>
<td>0</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>n.a.</td>
</tr>
<tr>
<td>S. agalactiae</td>
<td>2</td>
<td>0 (0.0)</td>
<td>2 (4.2)</td>
<td>0.16</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>n.a.</td>
</tr>
<tr>
<td>Hearing impairment a,d</td>
<td>95</td>
<td>12 (12.6)</td>
<td>9 (19.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>Known pre-existing behavioral problems a,d</td>
<td>95</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

a Based on parental information provided by the questionnaires on FS-II and SAR screening questionnaires
b p-value: independent sample t-test for continuous data; χ²-test for nominal data
c Number of subjects the variable was obtained from
d Number of subjects (%)
e Mean (standard deviation)
* Statistical significant (2-tailed p-value of ≤0.05)

Table 3. Agreement between SDQ and CBCL

3.1. Children suspect for limitations

<table>
<thead>
<tr>
<th>CBCL</th>
<th>Normal / borderline</th>
<th>Abnormal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDQ</td>
<td>score ≤63 (64)</td>
<td>≥64</td>
<td></td>
</tr>
<tr>
<td>Normal / borderline</td>
<td>≤16</td>
<td>28</td>
<td>6</td>
</tr>
<tr>
<td>Abnormal</td>
<td>≥17</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>34</td>
<td>13</td>
<td>47</td>
</tr>
</tbody>
</table>

3.2. Children not suspect for limitations

<table>
<thead>
<tr>
<th>CBCL</th>
<th>Normal / borderline</th>
<th>Abnormal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDQ</td>
<td>score ≤63 (64)</td>
<td>≥64</td>
<td></td>
</tr>
<tr>
<td>Normal / borderline</td>
<td>≤16</td>
<td>43</td>
<td>2</td>
</tr>
<tr>
<td>Abnormal</td>
<td>≥17</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>44</td>
<td>4</td>
<td>48</td>
</tr>
</tbody>
</table>
Determination of the prevalence of behavioral problems and comparison with norms

Based on British normative data of the SDQ, the severity of behavioral problems in this cohort was assessed. For the total group, for boys and girls, effect sizes were small for total difficulties scores and for all subscales indicating no relevant differences in scores. The results are presented in Table 5.

Based on the cut-off point discussed above (a total difficulties score of ≥17) the children were classified as having “normal/borderline” vs. “abnormal” behavior. The subscales of the SDQ were also scored (Table 6). Parents of 62 children (17.6%) reported behavioral problems in abnormal range in their children, compared with 9.7% in the British population sample. When children with borderline behavior are also included in the group with abnormal behavior (total difficulties score ≥14), prevalence is 89 children (25.3%), including 34 girls (21.7%) and 56 boys (28.7%) versus 17.9% in the norm group (not in table). Except for the conduct problems scale, SDQ ratings of BM survivors indicated a greater prevalence of abnormal behavior for all subscales. These results are consistent when boys and girls are compared.

Comparison of boys and girls

The scores of boys and girls were compared with the results on the dichotomized results “normal/borderline” vs. “abnormal” behavior. Boys had on average a significant higher total difficulties-score than girls and appeared to have more conduct problems, problems with hyperactivity or inattention and with pro-social behavior. When cut-off points were applied the
results were comparable for the three subscales mentioned, but not for the total difficulties scores. Results are presented in table 7.

**DISCUSSION**

In the first part of this study comparison of intra-individually SDQ and CBCL total scores of 95 BM survivors showed a significant but moderate correlation (r=0.66, p-value <0.0001). These results are consistent with those of previous studies regarding the diagnostic value of the SDQ that concluded that SDQ scores correlate substantially with other indexes of psychopathology such as the CBCL 28, 29. Regarding the diagnosis “abnormal” behavior the Cohen’s Kappa coefficient for level of agreement between the two questionnaires was 0.47, which means there is moderate agreement. The composite observed proportion of agreement between
CBCL and SDQ was good: 0.87. Observed proportion of agreement was high in the “normal/ borderline” category: 0.84, in the “abnormal” category it was fair: 0.39. Assigning the status “gold standard” to the CBCL, sensitivity of the diagnosis “abnormal” by the SDQ was 0.51 and specificity 0.92. PPV was 0.62 and NPV 0.91. A good specificity and NPV indicates that, compared with the CBCL, the SDQ has a good ability to identify children that do not have behavioral problems. But with low sensitivity and PPV, it seems not an optimal tool to detect children with behavioral problems in this population. Goodman et al. reported that the SDQ provides a quick and effective way of measuring behavior of children 23. This study shows that the SDQ can be useful when a brief and user-friendly questionnaire is needed to screen for the absence of behavioral problems, but limitations lie in low sensitivity and PPV. When the children are classified by the SDQ as having “abnormal” behavior, further testing by the CBCL might be indicated.

### Table 6. Number of children classified as having “abnormal” behavior: community vs. BM-survivors

<table>
<thead>
<tr>
<th>Parent SDQ</th>
<th>Cut-off point for abnormal</th>
<th>Population abnormal (%)</th>
<th>BM survivors abnormal (%)</th>
<th>No *</th>
<th>p-value b</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All children</strong></td>
<td></td>
<td>n=10298</td>
<td>n=361</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional symptoms</td>
<td>≥5</td>
<td>1174 (11.4)</td>
<td>74 (20.7)</td>
<td>358</td>
<td>&lt;0.01*</td>
<td>2.0</td>
<td>1.5 - 2.5</td>
</tr>
<tr>
<td>Conduct problems</td>
<td>≥4</td>
<td>1308 (12.7)</td>
<td>48 (13.4)</td>
<td>359</td>
<td>0.71</td>
<td>1.1</td>
<td>0.8 - 1.4</td>
</tr>
<tr>
<td>Hyperactivity / inattention</td>
<td>≥7</td>
<td>1514 (14.7)</td>
<td>79 (21.9)</td>
<td>360</td>
<td>&lt;0.01*</td>
<td>1.6</td>
<td>1.3 - 2.0</td>
</tr>
<tr>
<td>Peer relationship problems</td>
<td>≥4</td>
<td>1215 (11.8)</td>
<td>57 (16.0)</td>
<td>357</td>
<td>0.02*</td>
<td>1.1</td>
<td>1.1 - 1.8</td>
</tr>
<tr>
<td>Pro-social behavior</td>
<td>≤4</td>
<td>237 (2.3)</td>
<td>23 (6.4)</td>
<td>358</td>
<td>&lt;0.01*</td>
<td>2.7</td>
<td>1.8 - 4.1</td>
</tr>
<tr>
<td>Total difficulties</td>
<td>≥17</td>
<td>999 (9.7)</td>
<td>62 (17.6)</td>
<td>352</td>
<td>&lt;0.01*</td>
<td>1.9</td>
<td>1.5 - 2.5</td>
</tr>
<tr>
<td><strong>Girls</strong></td>
<td></td>
<td>n=5145</td>
<td>n=161</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional symptoms</td>
<td>≥5</td>
<td>623 (12.1)</td>
<td>40 (25.0)</td>
<td>160</td>
<td>&lt;0.01*</td>
<td>2.3</td>
<td>1.6 - 3.3</td>
</tr>
<tr>
<td>Conduct problems</td>
<td>≥4</td>
<td>530 (10.3)</td>
<td>15 (9.4)</td>
<td>160</td>
<td>0.70</td>
<td>0.9</td>
<td>0.5 - 1.5</td>
</tr>
<tr>
<td>Hyperactivity / inattention</td>
<td>≥7</td>
<td>504 (9.8)</td>
<td>25 (15.5)</td>
<td>161</td>
<td>0.02*</td>
<td>1.7</td>
<td>1.1 - 2.5</td>
</tr>
<tr>
<td>Peer relationship problems</td>
<td>≥4</td>
<td>520 (10.1)</td>
<td>24 (15.1)</td>
<td>159</td>
<td>0.04*</td>
<td>1.6</td>
<td>1.0 - 2.4</td>
</tr>
<tr>
<td>Pro-social behavior</td>
<td>≤4</td>
<td>82 (1.6)</td>
<td>6 (3.8)</td>
<td>160</td>
<td>0.04*</td>
<td>2.3</td>
<td>1.1 - 5.1</td>
</tr>
<tr>
<td>Total difficulties</td>
<td>≥17</td>
<td>396 (7.7)</td>
<td>24 (15.3)</td>
<td>157</td>
<td>&lt;0.01*</td>
<td>2.1</td>
<td>1.4 - 3.2</td>
</tr>
<tr>
<td><strong>Boys</strong></td>
<td></td>
<td>n=5153</td>
<td>n=200</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional symptoms</td>
<td>≥5</td>
<td>551 (10.7)</td>
<td>34 (17.2)</td>
<td>198</td>
<td>&lt;0.01*</td>
<td>1.7</td>
<td>1.2 - 2.4</td>
</tr>
<tr>
<td>Conduct problems</td>
<td>≥4</td>
<td>778 (15.1)</td>
<td>33 (16.6)</td>
<td>199</td>
<td>0.57</td>
<td>1.1</td>
<td>0.8 - 1.6</td>
</tr>
<tr>
<td>Hyperactivity / inattention</td>
<td>≥7</td>
<td>1005 (19.5)</td>
<td>54 (27.1)</td>
<td>199</td>
<td>0.01*</td>
<td>1.5</td>
<td>1.1 - 2.0</td>
</tr>
<tr>
<td>Peer relationship problems</td>
<td>≥4</td>
<td>691 (13.4)</td>
<td>33 (16.7)</td>
<td>198</td>
<td>0.19</td>
<td>1.3</td>
<td>0.9 - 1.8</td>
</tr>
<tr>
<td>Pro-social behavior</td>
<td>≤4</td>
<td>155 (3.0)</td>
<td>17 (8.6)</td>
<td>198</td>
<td>&lt;0.01*</td>
<td>2.8</td>
<td>1.8 - 4.5</td>
</tr>
<tr>
<td>Total difficulties</td>
<td>≥17</td>
<td>608 (11.8)</td>
<td>38 (19.5)</td>
<td>195</td>
<td>&lt;0.01*</td>
<td>1.8</td>
<td>1.2 - 2.5</td>
</tr>
</tbody>
</table>

a Number of subjects in the BM survivor cohort the variable was obtained from  
b p-value: χ² test  
c 95% CI  
* Statistical significant (2-tailed p-value of ≤0.05)
The second part of this study found that parents of school-age BM survivors reported a significantly higher prevalence of behavioral problems with the Strengths and Difficulties Questionnaire than the (British) norm population (17.6 % versus 9.7%). Further analysis indicated that, except for the conduct problems scale, BM survivors appear to have a greater prevalence of abnormal behavior on all subscales. Boys had a significant higher total difficulties-score than girls and appeared to have more conduct problems, problems with hyperactivity or inattention and with pro-social behavior.

Behavioral problems after childhood BM are reported by numerous studies, but the reported prevalence has a large variation from 9-46% ³, ¹¹, ¹³-¹⁷. To understand how to place our results among these studies it is important to realize there are important differences between the studies. For example, Grimwood et al. reported 23% of BM survivors to have behavioral problems versus 7% in the control group ⁵². The assessment was done with the CBCL and the Teacher’s Report Form (TRF, the teacher’s version of the CBCL), and a cut-off point of ≥60 was used, including borderline problems in the clinical range. The median age at admission was lower compared to our group: 1.4 versus 2.2 years ⁵². Sumpter et al. found 32.3% behavioral problems diagnosed by the parent SDQ in children after BM and viral meningitis.

### Table 7. Comparison of SDQ scores: Girls vs. Boys

<table>
<thead>
<tr>
<th>Parent SDQ</th>
<th>Girls</th>
<th>No</th>
<th>Boys</th>
<th>No</th>
<th>p-value</th>
<th>Mean difference</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=161</td>
<td></td>
<td>n=200</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional symptoms</td>
<td>2.7 (2.4)</td>
<td>160</td>
<td>2.3 (2.4)</td>
<td>198</td>
<td>0.09</td>
<td>0.4</td>
<td>0.1 - 0.9</td>
</tr>
<tr>
<td>Conduct problems</td>
<td>1.1 (1.6)</td>
<td>160</td>
<td>1.7 (1.9)</td>
<td>199</td>
<td>&lt;0.01</td>
<td>0.6</td>
<td>0.2 - 1.0</td>
</tr>
<tr>
<td>Hyperactivity / inattention</td>
<td>3.1 (2.9)</td>
<td>161</td>
<td>4.3 (3.2)</td>
<td>199</td>
<td>&lt;0.01</td>
<td>1.3</td>
<td>0.6 - 1.9</td>
</tr>
<tr>
<td>Peer relationship problems</td>
<td>1.3 (1.9)</td>
<td>159</td>
<td>1.5 (2.1)</td>
<td>198</td>
<td>0.57</td>
<td>0.1</td>
<td>-0.3 - 0.5</td>
</tr>
<tr>
<td>Pro-social behavior</td>
<td>8.9 (1.5)</td>
<td>160</td>
<td>8.1 (2.1)</td>
<td>198</td>
<td>&lt;0.01</td>
<td>0.7</td>
<td>0.4 - 1.1</td>
</tr>
<tr>
<td>Total difficulties</td>
<td>8.2 (6.8)</td>
<td>157</td>
<td>9.8 (7.3)</td>
<td>195</td>
<td>0.05</td>
<td>1.5</td>
<td>0.0 - 3.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Abnormal vs. normal</th>
<th>Cut-off point for abnormal</th>
<th>p-value</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emotional symptoms</td>
<td>≥5</td>
<td>0.07</td>
<td>1.6</td>
<td>1.0 - 2.7</td>
</tr>
<tr>
<td>Conduct problems</td>
<td>≥4</td>
<td>0.05</td>
<td>0.5</td>
<td>0.3 - 1.0</td>
</tr>
<tr>
<td>Hyperactivity / inattention</td>
<td>≥7</td>
<td>0.01</td>
<td>0.5</td>
<td>0.3 - 0.8</td>
</tr>
<tr>
<td>Peer relationship problems</td>
<td>≥4</td>
<td>0.69</td>
<td>0.9</td>
<td>0.5 - 1.6</td>
</tr>
<tr>
<td>Pro-social behavior</td>
<td>≤4</td>
<td>0.06</td>
<td>0.4</td>
<td>0.2 - 1.1</td>
</tr>
<tr>
<td>Total difficulties</td>
<td>≥17</td>
<td>0.30</td>
<td>0.7</td>
<td>0.4 - 1.3</td>
</tr>
</tbody>
</table>

Table 7. Comparison of SDQ scores: Girls vs. Boys

- Number of subjects in the BM survivor cohort the variable was obtained from
- p-value: Independent-Sample t-test
- 95% CI
- p-value: χ² test
- Statistical significant (2-tailed p-value of ≤0.05)
Bedford et al. found 11.9% behavioral problems compared with 3.3% in matched controls. All children survived BM before their first year of life. It is notable that they did not use a validated questionnaire for the assessment of behavioral problems, but designed one themselves. This makes comparison of the results very difficult. Both Grimwood et al. and Bedford et al. included all children after meningitis, where in our cohort only children without severe sequelae were assessed because the cohort was constructed for validation of a CPR for more subtle sequelae. The Swedish group of Berg et al. found 16% behavioral problems in BM survivors and 6% in matched controls. They also only included children without major neurological sequelae, and the age at infection and at assessment was comparable with our cohort. They used the Conners Parent Questionnaire, which is difficult to compare with the SDQ. In the study by Vartzelis et al. a cohort of BM survivors that had the disease at the age of >6 months were tested at late school-age or as a teenager. The range of the age at assessment was higher than in our study. The CBCL was used, with also the borderline clinical range included. Reported behavioral problem were 26.7% with a background risk of 16.7% in controls.

These examples illustrate how difficult it is to compare reported prevalences of behavioral problems, due to different patient characteristics of the cohorts (bacterial or also viral meningitis, all or only uncomplicated cases, infant BM or all childhood BM), the time period between disease and assessment, age of assessment, the questionnaires used and the cut-off point chosen. Our findings regarding a low sensitivity make a good comparison of prevalences measured by the CBCL and the SDQ not very reliable.

But, despite of these differences the prevalences found are quite in the same range, except for striking discrepancies between our results and those found in two studies: first, Halket et al. included children aged 13 years old who had had meningitis during the first year of life, using the SDQ. They found 46% of the children with a complicated and 38% with an uncomplicated course of the disease to have SDQ scores outside normal range (total difficulties score ≥14). When we also include children with “borderline” behavior in the “abnormal” group the prevalence is 25.3% in our study, compared to 17.6% when only “abnormal” behavior is included. Background risks are comparable: Halket et al. report 21% of borderline or abnormal behavior in their controls, where the British norm population we used reports 18%. The main reason for the difference in incidence may be found in the age at infection: Halket et al. included only infants, where we included all school-age children with a history of BM, with a mean age 2.2 years. Meningitis in infancy is a known risk factor for increased severity of disease and for poor prognosis regarding sequelae in the short- and long-term.

Second, Ritchi et al. found behavioral problems in 9% of the post meningitis children what is on the lowest end of the spectrum and within the range of the normal population. It is a strikingly discrepant with our results, in particular since their cohort was originally constructed for the development of the same prediction rule that we aimed to validate with our cohort. Behavioral problems were defined by a CBCL Total-score ≥64 (90th percentile).
Again, our results show that a good comparison of incidences measured by CBCL and SDQ is not very reliable, but the difference remains remarkable.

The strengths of this study lie in the fact that we were able to prospectively assess the outcome measure in a large cohort of BM survivors. Using the files of the NRLBM we were able to address a representative sample of children. Further, Warnick et al. stated in 2008 that the most critical limitation of their systematic review was the lack of head-to-head studies that would have allowed a direct comparison of the CBCL and the SDQ. A study like this gives the best results with regards to direct comparison of two questionnaires.

There are some limitations of this work that should be addressed as well. First, in the inclusion process from eligible to inclusion selection bias may have occurred. It is thinkable that parents who are more concerned about their children’s are more willing to participate. Then, this study relies on parental reporting in both the SDQ and the CBCL. The possibility that parents overestimate the problems must be considered. This is also supported by the British SDQ norm data, were the teacher’s version consistently finds lower scores than the parent SDQ. On the other hand, parents know their children best, and it is also plausible to think that the teachers underestimate the problems.

A nested cohort design was used, in which only a subset of cases and controls are randomly selected for further analysis. This is a known and appreciated methodology that results in more efficiency with reference to time and financial resources, and it was used for the original purpose of this cohort: validation of a CPR. This stepwise construction may have led to differences in case mix between the original and the nested cohort, but with the use of weighted pooling we avoided this problem as much as possible.

At last, reliable Dutch SDQ norms are not available: the Dutch translation of the parent SDQ was tested, but was not validated yet. Therefore we used mean scores and cut-off points from a large, representative British sample. Even though both countries are in many points comparable Western societies, it is presumable that distribution of scores and therefore cut-off points may differ.

Therefore, more studies (not necessarily only in BM survivors) that compare SDQ and CBCL are necessary. Such studies should also compare the teacher SDQ with the Teacher Report Form (TRF).

In conclusion, the results of this study show that the SDQ can provide effective support in the screening of children at risk of behavioral problems, especially to identify those children without problems. But caution is required, and with a positive result on the SDQ or when in doubt further evaluation is advised. Further, emotional and behavioral problems are a relevant and not to be underestimated problem in children with a history of BM. Reliable Dutch SDQ norm scores must be developed and validated.
REFERENCES


