Cognitive outcome in adults after bacterial meningitis

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ABSTRACT

Objective: To evaluate cognitive outcome in adult survivors of bacterial meningitis

Methods: Data from three prospective multi-center studies were pooled and re-analyzed, involving 155 adults surviving bacterial meningitis (79 after pneumococcal and 76 after meningococcal meningitis) and 72 healthy controls.

Results: Cognitive impairment was found in 32% of the patients and this proportion was similar for survivors of pneumococcal and meningococcal meningitis. Patients after pneumococcal meningitis performed worse on memory tasks ($P < 0.001$) and tended to be cognitively slower than patients after meningococcal meningitis ($P = 0.08$). We found a diffuse pattern of cognitive impairment, in which cognitive speed played the most important role. Cognitive performance was not related to time since meningitis; however, there was a positive association between time since meningitis and self-reported physical impairment ($P < 0.01$). The frequency of cognitive impairment and the numbers of abnormal test results for patients with and without adjunctive dexamethasone were similar.

Conclusions: Adult survivors of bacterial meningitis are at risk for cognitive impairment, which consist mainly of cognitive slowness. The loss of cognitive speed is stable over time after bacterial meningitis; however, there is a significant improvement of subjective physical impairment in the years after bacterial meningitis. The use of dexamethasone was not associated with cognitive impairment.

INTRODUCTION

The estimated annual incidence of bacterial meningitis is 4-6 per 100.000 adults and *Streptococcus pneumoniae* (pneumococcus) and *Neisseria meningitidis* (meningococcus) are the causative bacteria in 80% of cases.[1,2] Fatality rates in patients with pneumococcal meningitis (26%) and meningococcal meningitis (7%) are significant.[1-3] Even in patients with apparent good recovery, cognitive impairment occurs frequently,[4] especially after pneumococcal meningitis.[4-6] The cognitive functions affected by bacterial meningitis differ between studies, most likely because of the limited numbers of patients examined, and the lack of uniformity across studies in assessment methods and in definition of cognitive impairment.[4-10] We therefore pooled data on cognitive outcome after bacterial meningitis from three of our previous studies to more clearly determine which cognitive functions are affected by bacterial meningitis, and to identify which patients are at risk for developing cognitive impairment.

METHODS

Selection of patients

Data on neuropsychological evaluations were derived from three long-term follow-up studies embedded in two research projects: the European Dexamethasone Study (EDS) and the Dutch Meningitis Cohort (DMC).[1,11] The total number of patients that underwent neuropsychological evaluation in these studies was 155 (79 patients after pneumococcal and 76 patients after meningococcal meningitis).[4,6,10] A group of 72 healthy subjects formed the control group. The distribution of scores on the Glasgow Outcome Scale (GOS) was as follows: 129 patients had a GOS score 5 (good recovery), 25 patients had a GOS score of 4 (moderate disability) and one patient had a GOS score of 3 (severe disability). Participants gave written informed consent and all studies were approved by the local ethics committee.[1,4,6,10,11]

The EDS was a randomized placebo-controlled and double blind trial of adjunctive dexamethasone therapy in adults with bacterial meningitis; 301 patients were included between June 1993 and December 2001.[11] Part of this sample (n=87; 38 pneumococcal and 49 meningococcal patients) participated in a long-term follow-up study on cognitive outcome.[6] Patients eligible for this neuropsychological study were survivors of pneumococcal or meningococcal meningitis, confirmed by cerebrospinal fluid culture, who were aged >17 years; exclusion criteria were other serious illness (interfering with cognitive testing), pre-existing psychiatric disorders, insufficient mastery of the Dutch language, and evidence of alcohol or other substance abuse. Eighty-one patients had a GOS score of 5 (35 after pneumococcal and 46 after meningococcal meningitis), 5 patients had a GOS score of 4 (2 after pneumococcal and 3 after meningococcal meningitis) and one pneumococcal patient had a GOS score of 3. The control subjects were partners, relatives or close friends of patients (n=50).

The DMC was a prospective observational cohort study of adults with community-acquired bacterial meningitis; 696 episodes were included between October 1998 and April 2002.[1] Two follow-up studies on neuropsychological outcome were conducted in part of this cohort.[4,10] Patients were aged

16-65 and exclusion criteria were as mentioned above. Forty-eight patients had a GOS score of 5 (21 after pneumococcal and 27 after meningococcal meningitis) and 20 patients had a GOS score of 4 (all after pneumococcal meningitis). The total number of participants was 68 patients (41 after pneumococcal and 27 after meningococcal meningitis). A group of control subjects consisted of partners, relatives or close friends (n=25). Three patients and 3 controls were included in both studies.[4,10]

Neuropsychological evaluation

In each study patients were tested with an identical battery of standardized neuropsychological tests, which was described previously.[4,6,10] The battery included the following tests:

1. Memory: Rey's Auditory Verbal Learning Test,[13] Rivermead Behavioral Memory Test subtest Story Recall and Wechsler Memory Scale Revised subtest Visual Reproduction.[14]
2. Attention/Executive functions: color-word card of the Stroop test,[15] numerical speed of the Groningen Intelligence Test (GIT), Trail Making Test part B,[16] Category fluency, Letter fluency and Wisconsin Card Sorting test.[17]
3. Psychomotor functions: Trail Making Test part A,[16] word and color cards of the Stroop Test, simple and 2-choice reaction tasks.
4. Intelligence: Abbreviated version of the GIT[18] containing verbal and visuo-spatial reasoning. The Dutch Adult Reading Test (DART) was used as an estimator of premorbid intelligence.[19]
5. Questionnaires: The Profile of Mood States (POMS)[20] was used to identify the presence of depressive mood disorders. Additionally, the RAND-36[21,22] was administrated to evaluate quality of life and general health.

Statistical analysis

All test scores were expressed as T-scores corrected for age and education with the control group as reference. Outliers of individual test scores of the control group were excluded (<1% of raw neuropsychological data points). Skewed score distributions were normalized with appropriate transformations. Linear multiple regression analyses were conducted with the raw (or transformed) test score of the controls as dependent variable, and age and educational level as independent variables. The resulting regression formulas were used to calculate expected test scores for each subject on each test. The differences between expected and observed scores were divided by the standard error of the estimate and transformed to T-scores (mean = 50 and SD = 10; a higher score indicating better performance).

To examine relative differences between groups multivariate analyses of variance (Manova's) were performed within each cognitive domain using T-scores. If these Manova's revealed significant results (Pillais' Trace 2-tailed P <0.05), t-tests with Bonferroni correction for the number of comparisons were conducted to evaluate single neuropsychological measures within each cognitive domain. Subsequently we evaluated the cognitive profile of meningitis patients; an individual test score was defined as impaired if it was at least two standard deviations below the mean normative score of our control group (T-score < 30). Cognitive impairment was considered to be present if performance, reflected by the number of impaired test results, was worse than the fifth percentile of our control group. To compare cognitive speed between groups a speed composite score was calculated for each participant by taking the mean T-score of tests in which cognitive speed is important as described previously.[10]

For nonparametric testing, Mann-Whitney U, χ^2 or Fisher's exact statistics were used. Spearman correlations were calculated between cognitive performance and depression, GOS-score, time since meningitis and physical functioning.

We performed a logistic regression analysis to identify determinants of cognitive impairment. Independent variables in this analysis were clinical and demographic characteristics and the dependent variable was presence of cognitive impairment.

RESULTS

Clinical characteristics

Patients with pneumococcal meningitis were admitted with a higher severity of disease, as reflected by lower scores on the Glasgow Coma Scale (Table 1). Laboratory examination showed no significant

differences between groups. Initial antimicrobial treatment consisted of penicillin or amoxicillin for 70% of episodes, third-generation cephalosporins in 8%, cephalosporins in combination with penicillin or amoxicillin in 17% of episodes, and another regimen in 5%; 30% received adjunctive dexamethasone treatment.

Table 1 Clinical characteristics of patients with pneumococcal and meningococcal meningitis.

	Pneumococcal patients (n=79)	**Meningococcal patients** (n=76)	***P****
Presentation			
Glasgow Coma Scale score	11 ± 3	12 ± 3	0.03
Coma	10 (13)	8 (11)	0.62†
Median heart rate (bpm)	100 ± 16.8	88 ± 18.9	<0.001
Diastolic blood pressure <60 mmHg	8 (10)	16 (21)	0.12
Focal cerebral deficits‡	18 (23)	11 (14)	0.22†
Cranial nerve palsies	16 (20)	5 (7)	0.02†
Laboratory results on admission			
CSF Leukocyte count (x10^3 cells/mm^3)	18 ± 25	19 ± 28	0.42
CSF Protein level (g/l)	4.3 ± 2.7	4.9 ± 3.4	0.43
CSF Glucose level (mg/dl)	1.2 ± 1.4	1.4 ± 1.9	0.62
Positive blood culture	54 (68)	56 (74)	0.99†
Focal neurological abnormalities at discharge			
Focal cerebral deficits	4 (5)	2 (3)	0.68†
Cranial nerve palsies	22 (28)	9 (12)	0.02†
GOS score 3 or 4/5 at discharge	23/56	3/73	<0.001†
Months between illness and cognitive testing	54.7 ± 44.0	68.8 ± 49.4	0.10

Values represent number (%) or mean ± SD
CSF denotes cerebrospinal fluid
* 2-tailed p-value of U-test; † χ2-test
*‡ aphasia, mono- or hemiparesis

Cognitive impairment

Patients and controls

Patients did not differ from controls with respect to age (P = 0.72), years of education (P = 0.66) and premorbid intelligence (P = 0.81) (Table 2).

Table 2 Demographic characteristics of patients and controls

	Pneumococcal patients (n=79)	**Meningococcal Patients** (n=76)	**Controls** (n=72)	***P****
Age at follow-up	52.3 ± 13.6	38.9 ± 16.6	46.6 16.0	<0.01
Years of education	12.4 ± 2.4	13.3 ±1.8	13.1 1.5	0.01
Premorbid IQ	98.6 ±16.7	98.0 ±15.8	99.4 ±16.7	0.97
Male/Female	40/39	40/36	21/50	0.01†

Values represent mean ± SD or number
* 2-tailed p-value of ANOVA; † χ2-test

We found significant differences between patients and controls. Manova's within each cognitive domain showed significant overall group differences between patients and controls for 'attention/executive functions' (Table 3; P = 0.03) and for 'psychomotor functions' (P = 0.03) but not for 'intelligence' (P = 0.77) and 'memory' (P = 0.21). Patients performed worse than controls on TMT part B (P < 0.01), Color-Word Card of the Stroop (P < 0.01) and Simple reaction time for the dominant hand (P < 0.01). The frequency of cognitive impairments was higher in the patient group compared to the control group (50 of 155 [32%] vs. 4 of 72 [5.5%], P < 0.001). Patients had significantly lower speed scores than controls (T-scores of 46.4 vs. 50.0, P = 0.03). No differences were found between patients and controls on the POMS depression scale (5.4 vs. 5.7, P = 0.48). Also on the questionnaires patients had worse scores than controls. They had lower scores than controls on

the subscales 'Bodily pain' (69.6 vs. 80.0, $P = 0.04$) and 'Role limitations due to physical health problems' (72.7 vs. 84.9, $P < 0.01$) of the RAND-36.

Table 3 T-scores of neuropsychological tests in survivors of bacterial meningitis

Neuropsychological measure	Pneumococcal patients (n=79)	Meningococcal patients (n=76)	*P* A* P vs M	*P* B* P vs C	*P* C* M vs C
Intelligence					
Visuo-spatial reasoning (GIT)	50.5 (10.9)	50.0 (11.4)	0.77	0.78	0.97
Verbal reasoning (GIT)	50.8 (10.5)	51.2 (10.6)	0.79	0.62	0.45
Attention/Executive functioning					
Stroop color-word card	44.1 (13.8)	45.9 (11.1)	0.39	0.01	0.04
TMT part B	40.4 (17.4)	45.6 (12.6)	0.04	0.00	0.05
Numerical ability (GIT)	46.8 (10.4)	51.8 (10.5)	<0.01	0.06	0.31
Category fluency	50.9 (10.8)	48.9 (12.6)	0.30	0.63	0.55
Letter fluency	47.4 (10.7)	48.1 (7.9)	0.67	0.14	0.21
WCST categories	48.0 (13.4)	46.4 (11.0)	0.42	0.40	0.07
WCST errors	49.8 (10.8)	48.1 (10.5)	0.34	0.92	0.28
WCST perseverative errors	46.9 (12.2)	46.3 (10.2)	0.74	0.11	0.03
Memory					
RMBT immediate recall	50.4 (9.2)	50.6 (12.1)	0.92	0.78	0.73
RMBT % retained	48.5 (13.0)	46.3 (13.3)	0.33	0.30	0.04
WMS immediate recall	47.0 (14.2)	48.6 (11.8)	0.48	0.16	0.46
WMS % retained	45.7 (15.9)	51.5 (9.3)	<0.01	0.06	0.36
AVLT immediate recall	48.2 (10.2)	48.8 (10.2)	0.72	0.10	0.21
AVLT % retained	48.8 (13.6)	48.0 (13.0)	0.81	0.66	0.48
Psychomotor functions					
TMT part A	43.0 (14.6)	47.7 (11.3)	0.03	0.00	0.37
Stroop word-card	43.9 (14.4)	45.6 (13.3)	0.46	0.00	0.03
Stroop color-card	43.2 (11.1)	43.7 (12.3)	0.80	0.00	0.00
SRT dominant hand	40.6 (18.0)	44.8 (13.3)	0.12	0.00	0.02
SRT non dominant hand	43.3 (17.2)	45.9 (11.2)	0.31	0.02	0.05
2-choice reaction time	47.2 (17.2)	48.4 (12.1)	0.65	0.31	0.44
Speed score	45.3 (8.8)	47.5 (6.7)	0.08	<0.01	0.06
Number of impaired tests	2.2 (2.3)	1.6 (2.1)	0.10	<0.01	<0.01

Values represent mean (SD)

* 2-tailed p-value of t-test. P-value A= comparison pneumococcal/meningococcal patients; P-value B= comparison pneumococcal patients/controls; p-value C= comparison meningococcal patients/controls; GIT= Groningen Intelligence Test; TMT= Trail Making Test; WCST= Wisconsin Card Sorting Test; RBMT= Rivermead Behavioral Memory Test; WMS=Wechsler Memory Scale; AVLT=Rey Auditory Verbal Learning Test; SRT= Simple reaction time

Causative organism

Pneumococcal patients were older ($P < 0.001$) and had a slightly lower level of education compared to meningococcal patients ($P = 0.02$); although, premorbid intelligence did not differ between both patient groups ($P = 0.84$) (Table 2). T-scores of neuropsychological tests, corrected for age and education, for both patient groups are shown in Table 3 (by definition, mean T-scores in the control group are 50 [SD = 10]). Manova's within the cognitive domains showed significant group difference between pneumococcal and meningococcal patients for 'memory' ($P = 0.05$) but not for 'intelligence' ($P = 0.90$), 'attention/executive functions' ($P = 0.24$) and 'psychomotor functions' ($P = 0.24$). Pneumococcal patients performed worse than meningococcal patients on WMS-R Visual

Reproduction percentage retained. Pneumococcal patients tended to have lower speed composite scores than meningococcal patients ($P = 0.08$).

The numbers of abnormal test results for both patient groups and controls are presented in Table 4. Subjects with three or more impaired test results were considered to be 'cognitively impaired'. A total of 50 patients (32%) were cognitively impaired. The frequency of cognitive impairment was similar for pneumococcal and meningococcal patients (29 of 79 [37%] vs. 21 of 76 [28%], $P = 0.24$).

Table 4 Impaired test results per subject group

Number of abnormal tests	Pneumococcal patients (n=79)	Meningococcal patients (n=76)	Control subjects (n=72)
0	24 (30)	34 (45)	38 (54)
1	17 (22)	13 (17)	22 (31)
2	9 (11)	8 (10)	7 (10)
≥ 3	29 (37)	21 (28)	5 (6)

Values represent number of patients (%)

The frequency of abnormal test results across the various cognitive domains is shown in Figure 1. Pneumococcal patients had significantly more impaired test results in the cognitive domains of attention/executive functions ($P < 0.001$), memory ($P < 0.001$) and psychomotor functions ($P < 0.001$) compared to controls. Meningococcal patients had more impaired test results than controls on attention/executive functions ($P = 0.03$) and psychomotor functions ($P = 0.03$). Pneumococcal patients tended to have more impaired test results in the cognitive domain of memory than meningococcal patients ($P = 0.06$).

Figure 1 Percentage of subjects with one or more abnormal test results across cognitive domains.

Pneumococcal patients had higher scores on the depression scale of the POMS compared to meningococcal patients (7.1 vs. 5.3, $P = 0.05$). No significant correlations (Ps > 0.17) between POMS depression score and the number of impaired test results or speed score were found in both patient groups; nor between the GOS-score and number of impaired test scores. Pneumococcal patients had lower scores on the subscale physical functioning of the RAND-36 compared to meningococcal patients (78.7 vs. 88.1, $P < 0.01$). Ratings of physical functioning (RAND-36) and the speed composite score were not significantly correlated (r =0.15; $P = 0.08$).

Interval between onset of illness and cognitive testing

The median interval between onset of illness and cognitive testing was 49.5 months (range 5-164 months) and did not correlate with performance on the speed composite score (r = 0.09; $P = 0.25$) and number of abnormal test results (r = -0.05; $P = 0.54$). Scores on the subscale physical functioning (RAND-36) correlated significantly with time since meningitis (r = 0.30; $P < 0.001$). In addition, physical functioning was negatively correlated with number of impaired test results (r = -0.20; $P = 0.02$).

Adjunctive dexamethasone therapy

The influence of dexamethasone therapy was recently described in a long-term follow-up study of the EDS.[6] Within data of the EDS, MANOVAs of neuropsychological domains showed no significant overall group differences between both treatment groups for 'intelligence' ($P = 0.35$), 'memory' ($P = 0.29$), 'attention/executive functioning' ($P = 0.11$), and 'psychomotor speed' ($P = 0.71$); scores on the speed composite score for placebo and dexamethasone treated patients were also similar ($P = 0.37$).

In the current analysis with pooled data all analyses were performed for patients with and without adjunctive dexamethasone therapy separately; no differences were found in these sub analyses (data not shown). However, MANOVAs showed significant overall differences in the domains "memory" ($P = 0.02$) and 'attention/executive function' ($P < 0.001$); and not in 'intelligence' ($P = 0.10$) and not in 'psychomotor speed' ($P = 0.41$). Patients who were treated with steroids had better scores on the

WMS immediate recall (T-scores, 51.8 *vs.* 46.2, $P = 0.02$); however, they had more errors on the WCST (T-scores, 52.8 *vs.* 47.3, $P < 0.001$) and lower scores on numerical ability of the GIT (T-scores, 46.4 *vs.* 50.3, $P = 0.04$). Importantly, there were no significant differences between patients with and without adjunctive dexamethasone therapy within the different causative organisms. The frequency of cognitive impairment for patients with and without adjunctive dexamethasone therapy was similar ($P = 0.42$), as were numbers of abnormal test results (Table 5).

Table 5 Impaired test results per treatment group

Number of abnormal tests	Dexamethasone (n = 46)	No dexamethasone (n = 109)
0	16 (35)	42 (39)
1	8 (17)	22 (20)
2	5 (11)	12 (11)
≥ 3	17 (37)	33 (30)

Predictors of cognitive impairment

Nine most important potential predictors for cognitive impairment were submitted to a logistic regression analysis: causative pathogen, sex, years of education, premorbid intelligence, age, Glasgow Coma Scale on admission, presence of cranial nerves palsies at discharge, presence of focal cerebral deficits at discharge, and interval between onset of illness and cognitive testing. Male patients after bacterial meningitis were at higher risk for cognitive impairment (odds ratio [OR] = 3.08; 95% confidence interval [CI] = 1.33- 7.13; P <0.01). Patients with cranial nerve palsies at discharge were also at higher risk for cognitive impairment (OR = 4.73; CI = 1.37-16.28; $P = 0.01$). The Hosmer-Lemeshow Goodness of Fit test confirmed the validity of the final multivariate model (chi-square = 3.6, df = 8, p = 0.90).

DISCUSSION

Our study shows that patients after bacterial meningitis are at high risk for cognitive impairment. Cognitive impairment was found in one-third of patients, so large numbers of patients will continue to have complaints attributable to their illness after the acute phase of disease.

The prevalence of cognitive impairment between patients after pneumococcal and meningococcal meningitis was similar. This is in contrast with our previous studies, in which we described cognitive impairment after pneumococcal meningitis only;[4,6,10] but it is consistent with a recent retrospective study.[9] The discrepancy between the present study and our previous reports may well be explained by larger numbers of patients and controls, which has resulted in more statistical power and superior normative reference scores from controls.

We found a diffuse pattern of cognitive impairment, in which cognitive speed played the most important role. Previous studies on cognitive outcome after bacterial meningitis have described impairment of memory, decreased psychomotor performance, impaired attention/executive functions, and reduction in visuoconstructive capacity.[5,7,9] A previous retrospective study involving 59 adults younger than 70 years, 1-12 years after recovery from bacterial meningitis, found poorer performance in subtests that required plan formation and learning strategies.[9] The findings of executive deficits in this may also have been associated with a decline in cognitive speed.

The most important limitation of our study was selection bias. First, patient who could reliably assessed with the neuropsychological test battery were excluded; i.e. those with severe disability and low scores on the GOS. Low GOS might also reflect severe neuropsychological deficits. Thus, severe cases of neuropsychological deficits might not be represented in this study. Secondly, a considerable number of patients was tested in follow-up study of in a randomized, controlled trial, so all of these patients met specific inclusion criteria. However, baseline characteristics of patients in the European Dexamethasone Study were similar to those included in our nation-wide cohort of adults with culture-proved bacterial meningitis.[1,11] Therefore, patients included in the European study are likely to be a

representative sample of adults with bacterial meningitis. Thirdly, all patients included in this neuropsychological evaluation underwent lumbar puncture. Negative cerebrospinal fluid cultures occur in 11 to 30% of patients with bacterial meningitis.[1,2] No significant differences in clinical presentation have been reported between patients with culture-positive bacterial meningitis and those with culture-negative bacterial meningitis.[1] Therefore, it is unlikely that this factor confounded our results.

Patients reported a significant improvement of physical impairment in the years after meningitis, while cognitive outcome was not related with time. We found no confounding by higher scores on the depression scale. Although speculative, this might imply that patients adapt to their cognitive impairments, even if these impairments remain stable. The effect of cognitive impairment after bacterial meningitis on longer-term outcome (>10 years) and the potential influence on the development of dementia remains to be elucidated.

The use of dexamethasone was not associated with cognitive impairment. This has also recently been reported by a follow-up study of the European Dexamethasone Study.[6,11] Results of an experimental meningitis model raised concerns about a possible harmful effect of adjunctive dexamethasone therapy on cognition in patients after bacterial meningitis.[23] This study in infant rats showed that adjunctive dexamethasone aggravated neuronal apoptosis in the hippocampal dentate as compared to antibiotic therapy alone.[23] Since adjunctive dexamethasone therapy should be routine in adults with bacterial meningitis this is important information.[2,6,11,24]

In sum, our results showed that about one third of adult survivors of bacterial meningitis experience subtle cognitive impairment which consists mainly of slight mental slowness. Male sex and cranial nerve palsy at discharge were risk factors for cognitive impairment. Over the years, patients tended to report fewer complaints, but the cognitive impairment, if present, does not seem to improve once the subacute phase has elapsed.

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COMPETING INTERESTS

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REFERENCES

1. van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M. Clinical features and prognostic factors in adults with bacterial meningitis. *N Engl J Med* 2004;351:1849-59.
2. van de Beek D, de Gans J, Tunkel AR, Wijdicks EF. Community-acquired bacterial meningitis in adults. *N Engl J Med* 2006;354:44-53.
3. Weisfelt M, van de Beek D, Spanjaard L, Reitsma JB, de Gans J. Clinical features, complications, and outcome in adults with pneumococcal meningitis: a prospective case series. *Lancet Neurol* 2006;5:123-29.
4. van de Beek D, Schmand B, de Gans J, et al. Cognitive impairment in adults with good recovery after bacterial meningitis. *J Infect Dis* 2002;186:1047-52.
5. Merkelbach S, Sittinger H, Schweizer I, Muller M. Cognitive outcome after bacterial meningitis. *Acta Neurol Scand* 2000;102:118-23.
6. Weisfelt M, Hoogman M, van de Beek D, Gans J, Dreschler W, Schmand B. Dexamethasone and long-term outcome in adults with bacterial meningitis. *Ann Neurol* 2006;60:456-68.
7. Bohr V, Rasmussen N, Hansen B, et al. Pneumococcal meningitis: an evaluation of prognostic factors in 164 cases based on mortality and on a study of lasting sequelae. *J Infect* 1985;10:143-57.
8. Naess A, Halstensen A, Nyland H, et al. Sequelae one year after meningococcal disease. *Acta Neurol Scand* 1994;89:139-42.
9. Schmidt H, Heimann B, Djukic M, et al. Neuropsychological sequelae of bacterial and viral meningitis. *Brain* 2006;129:333-45.
10. Weisfelt M, van de Beek D, Hoogman M, Hardeman C, de Gans J, Schmand B. Cognitive outcome in adults with moderate disability after pneumococcal meningitis. *J Infect* 2006;52:433-9.
11. de Gans J, van de Beek D. Dexamethasone in adults with bacterial meningitis. *N Engl J Med* 2002;347:1549-56.
12. van de Beek D, Weisfelt M, Hoogman M, de Gans J, Schmand B. Neuropsychological sequelae of bacterial meningitis: the influence of alcoholism and adjunctive dexamethasone therapy. *Brain* 2006;129:E46.
13. Rey A. L'examen clinique en psychology. *Paris: Presses Universitaires de France*, 1964.
14. Wilson B, Cockburn J, Baddeley A. Rivermead behavioral memory test. Reading. *UK: Thames Valley Test Company*, 1985.
15. Stroop J. Studies of interference in serial verbal reactions. *J Exp Psychol* 1935;18:643-62.
16. Reitan R. Trail Making Test. Manual for administration and scoring. *Tuscon: Reitan Neuropsychological Laboratory*, 1992.
17. Alpherts WCJ, Aldenkamp AP. Fepsy. *Heemstede: Instituut voor epilepsiebestrijding*, 1994.
18. Lutelijn F, van der Ploeg F. Groningen Intelligentie Test. *Lisse: Swets and Zeitlinger*, 1983.
19. Schmand B, Lindeboom J, van Harskamp F. De Nederlandse Leestest voor volwassenen. *Lisse: Swets and Zeitlinger*, 1992.
20. Lezak MD, Howieson BD, Loring DW. Neuropsychological assessment, 4th ed. *New York: Oxford University Press*, 2004.
21. Brazier JE, Harper R, Jones NMB, et al. Validating the Sf-36 Health Survey Questionnaire - New Outcome Measure for Primary Care. *BMJ* 1992;305:160-4.
22. van der Zee K, Sanderman R. Het meten van de algemene gezondheidstoestand met de RAND-36. *Groningen: Groningen University*, 1993.
23. Leib SL, Heimgartner C, Bifrare YD, Loeffler JM, Täuber MG. Dexamethasone aggravates hippocampal apoptosis and learning deficiency in pneumococcal meningitis in infant rats. *Pediatr Res* 2003;54:353-7.
24. van de Beek D, de Gans J. Dexamethasone in adults with community-acquired bacterial meningitis. *Drugs* 2006;66:415-27.