Cognitive impairment in adults with good recovery after bacterial meningitis
van de Beek, D.; Schmand, B.A.; de Gans, J.; Weisfelt, M.; Vaessen, H.; Dankert, J.; Vermeulen, M.

Published in:
The Journal of Infectious Diseases

DOI:
10.1086/344229

Citation for published version (APA):
vан де Бек, Д., Сханд, Б., де Ганс, Ж., Вейслет, М., Вассен, Х., Данкерт, Ј., & Вормелен, М. (2002).
Cognitive impairment in adults with good recovery after bacterial meningitis. The Journal of Infectious Diseases,
186(7), 1047-1052. DOI: 10.1086/344229

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s),
other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating
your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask
the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam,
The Netherlands. You will be contacted as soon as possible.
Cognitive Impairment in Adults with Good Recovery after Bacterial Meningitis

Diederik van de Beek,1,2 Ben Schmand,1 Jan de Gans,1 Martijn Weisfelt,1 Heleen Vaessen,1 Jacob Dankert,2 and Marinus Vermeulen1

Subjects and Methods

Adults without neurologic sequelae after bacterial meningitis are supposed to live without restrictions. Neuropsychological outcome was assessed in 51 adults from a prospective cohort with good recovery, defined as Glasgow Outcome Scale score 5, after pneumococcal or meningococcal meningitis. Patients who recovered well after pneumococcal meningitis showed cognitive slowness ($P = .001$). A cognitive disorder was found in 27% of these patients. Patients who previously had meningococcal meningitis were not significantly different from control subjects. Scores on general health and quality of life questionnaires revealed lower scores for patients with meningitis, which were related to cognitive slowing ($R, -0.46$ to $-0.38$). In conclusion, adults surviving pneumococcal meningitis were at significant risk of neuropsychological abnormalities, even if they were clinically well recovered.

The most common etiologic agents of bacterial meningitis in adulthood are Neisseria meningitidis and Streptococcus pneumoniae, which cause 80%–85% of all cases [1, 2]. Fatality rates in patients with meningitis caused by these microorganisms are significant, with rates of 10% and 26%, respectively [1, 2]. Nevertheless, most patients survive bacterial meningitis without neurologic sequelae. In children without neurologic sequelae after the infection, learning deficits and cognitive impairment may be present [3]. In adults without neurologic sequelae after bacterial meningitis, functional outcome has never been investigated properly. In this prospective and nationwide study, we assessed cognitive outcome and quality of life in adults with good recovery after bacterial meningitis.

Subjects and Methods

This study was based on data from a prospective observational cohort study from Dutch adults with bacterial meningitis. From October 1998 to April 2000, patients with bacterial meningitis in the Netherlands were identified by use of the database of the Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM). Since 1979, the NRLBM has received cerebrospinal fluid isolates from 85% of all patients with bacterial meningitis in the Netherlands (15.8 million inhabitants in 1999) [4]. The NRLBM provided the investigators with daily information, consisting of the name of the patients with bacterial meningitis who had been admitted 2–6 days earlier. The physicians were contacted and were informed about the study. Information was collected by means of a case record form. At discharge, outcome was graded by use of the Glasgow Outcome Scale (GOS), ranging from 1 (dead) to 5 (good recovery).

Patients eligible for this follow-up evaluation were patients aged 16–65 years with bacterial meningitis due to N. meningitidis or S. pneumoniae, who were discharged with a GOS score of 5. A GOS score of 5 implies good physical and mental recovery in the sense that the treating physician expects the patient to be able to function independently and to resume activities of daily life, work included, as before contracting the disease.

For each of the patients, 1 control subject was recruited from partners, siblings, and close friends, until a control group of 25 subjects was completed with the same age range as the patient groups. Exclusion criteria for neuropsychological follow-up included serious illnesses (other than meningitis), preexisting psychiatric disorders (psychosis, mood disorder, anxiety disorder, or mental retardation), and insufficient mastery of Dutch language.

Neuropsychological evaluation was done 6–24 months after discharge. Four cognitive domains were tested: intelligence, memory, attention and executive functioning, and reaction speed. Current intelligence was tested by the Groningen Intelligence Test (abbreviated version), consisting of subtests for verbal and visuospatial reasoning and numerical ability [5]. Premorbid intelligence was tested by the Dutch Adult Reading Test [6] (this test was included as a further characteristic of the sample; it was not used in testing of the hypothesis). Verbal memory was tested by the Rey’s Auditory Verbal Learning Test and the subtest Prose Recall from the Rivermead Behavioural Memory Test [7]. Figural memory was tested by the subtest Visual Reproduction from the Wechsler Memory Scale Revised [7]. Attention and executive functioning were tested by 5 tasks: Trailmaking Test, Stroop Color-Word Test, category fluency, letter fluency, and the Wisconsin Card Sorting Test (WCST).
### Table 1. Clinical characteristics of patients in study of cognitive impairment in adults after recovery from bacterial meningitis.

<table>
<thead>
<tr>
<th>Time point, parameter</th>
<th>Meningococcal patients (n = 25)</th>
<th>Pneumococcal patients (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median days from discharge to testing (range)</td>
<td>391 (209–753)</td>
<td>426 (228–650)</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>32 (15–60)</td>
<td>47 (20–64)</td>
</tr>
<tr>
<td>Sex, male:female</td>
<td>13:12</td>
<td>12:14</td>
</tr>
<tr>
<td>Before admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predisposing factors present*</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Symptoms before admission &lt;24 h</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Presentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature &gt;38°C, headache, and neck stiffness</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>Glasgow Coma Scale &lt;8</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Focal neurologic deficits*</td>
<td>4</td>
<td>11f</td>
</tr>
<tr>
<td>Laboratoryd</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood leukocyte count &gt;10⁹ cells/L</td>
<td>23/25</td>
<td>25/26</td>
</tr>
<tr>
<td>CSF leukocyte count, cells/μL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100</td>
<td>0/24</td>
<td>1/26</td>
</tr>
<tr>
<td>100–999</td>
<td>3/24</td>
<td>5/26</td>
</tr>
<tr>
<td>≥1000</td>
<td>21/24</td>
<td>20/26</td>
</tr>
<tr>
<td>Positive blood culture result</td>
<td>14/19</td>
<td>14/23</td>
</tr>
<tr>
<td>Penicillin-resistant strain</td>
<td>0/25</td>
<td>0/26</td>
</tr>
<tr>
<td>Clinical course</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal neurologic deficitsb</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Seizures</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Cardiorespiratory failure</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Discharge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glasgow Outcome Scale score 5</td>
<td>25</td>
<td>26</td>
</tr>
<tr>
<td>Focal neurologic deficits at dischargee</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

**NOTE.** CSF, cerebrospinal fluid.

* Recent head injury, recent neurosurgery, neurosurgical device, altered immune status, alcoholism, and CSF leak.

b Defined as aphasia, cranial nerve palsy, monoparesis, or hemiparesis.

c * P = .04 vs. patients with meningococcal meningitis (Fisher’s exact test, 2-tailed).

d Data are no./no. evaluated.

e Patients had slight hemiparesis.

---

[7]. Reaction speed was tested by simple and 2-choice reaction time measurements [7]. The tests are described in the Appendix.

For determination of general health and quality of life, the RAND-36 questionnaire was used [8, 9]. Because of the possible bias of depressive mood disorder, mood was determined with the Profile of Mood States (POMS) [7].

We hypothesized the existence of clinically significant cognitive impairment for patients with good recovery after pneumococcal meningitis. Therefore 1-tailed P values were used for cognitive testing. Cognitive assessment was analyzed by multivariate analysis of variance for each domain separately with covariates age and education where applicable, with post hoc pairwise comparisons tests with Bonferroni-corrected P values. For nonparametric testing, Mann-Whitney U, Kruskal-Wallis, and Fisher’s exact statistics were used; correlations are given by Pearson correlation coefficients.

### Results

Altogether, 471 adults with meningitis were identified by the NRLBM. A filled-in case record form was received from 374 (79%) patients, and 151 (40%) of those were potentially eligible for cognitive testing (GOS score 5; 93 with meningococcal meningitis and 58 with pneumococcal meningitis); 58 consecutive patients were contacted for participation in this study. Fifty-one patients were tested (25 patients with meningococcal meningitis and 26 with pneumococcal meningitis); 3 patients had insufficient mastery of Dutch language, 2 patients had serious somatic illnesses, and 2 patients refused to travel to Amsterdam. Demographic characteristics for patients eligible for testing (n = 151) and those tested (n = 51) were similar.

Clinical characteristics are shown in table 1. Patients with meningococcal meningitis were significantly younger than patients with pneumococcal meningitis. Patients with pneumococcal meningitis had a higher rate of neurologic deficits (defined as aphasia, cranial nerve palsy, monoparesis, or hemiparesis) on presentation (P = .04) than did patients with meningococcal meningitis. However, the number of patients developing neurologic deficits during admission was similar. Laboratory examination showed no significant differences between groups. Antibiotic therapy was noted in 50 case record forms. Initial treatment consisted of penicillin or amoxicillin for 19 patients (38%), third-generation cephalosporins for 9 (18%) patients, and a combination of penicillin or amoxicillin with a third-generation cephalosporin for 15 (30%)
patients; 7 patients (14%) received other antibiotic regimens. Susceptibility testing of the 51 isolates showed that all were penicillin-susceptible.

Test scores on neuropsychological assessment of control subjects (n = 25) and patients are shown in table 2. Multivariate analysis of covariance showed significant overall group differences in the domains of intelligence (Pillais’ Trace, $P = .02$), attention and executive functioning ($P = .03$), and reaction speed ($P = .03$) but not in the domain of memory ($P = .28$). Post hoc analysis showed lower scores for the subtest visuospatial reasoning for patients who had pneumococcal meningitis than for patients who had meningococcal meningitis and control subjects. In the domain of attention and executive functioning, pneumococcal patients took more time to perform the Trailmaking B test and had lower scores on the category fluency test. They also tended to be slower on the Stroop and letter fluency tests. In the domain of reaction speed, patients who had pneumococcal meningitis were slower than control subjects on all tests, and they were slower than patients who had meningococcal meningitis on the binary choice reaction task. Neuropsychological test scores were not related to days since illness.

To explore relations between cognitive disorders and disease characteristics, we formed a speed composite measure for each patient by the mean of Z-transformed values of tests in which cognitive speed is important (category fluency, Trailmaking B, and simple and 2-choice). Patients who had pneumococcal meningitis showed cognitive slowness, compared with patients who had meningococcal meningitis and control subjects ($P = .001$). We defined a patient cognitively disordered if speed composite scores were worse than the fifth centile of the control group, after correction for age. One patient (4%) who had meningococcal meningitis and 7 (27%) who had pneumococcal meningitis were cognitively disordered ($P = .02$). No differences were found between patients above or below the fifth centile, with respect to cytobiochemical parameters. However, a trend was observed between the presence of focal neurologic deficits during admission and cognitive slowness ($P = .07$). Among the pneumococcal meningitis patients with or without focal neurologic deficits, 5 patients (38%) of 13 and 2 patients (15%) of 13, respectively, had speed composite scores below the fifth centile of control subjects.

Scores on general health and quality of life (RAND-36) re-
vealed lower scores for patients with pneumococcal meningitis (compared with reference data, n = 1063; table 3) [8, 9]. Patients who had pneumococcal meningitis experienced impairment of everyday functioning due to physical and emotional problems and, additionally, loss of vitality, resulting in lower levels of experienced general health. Meningococcal patients had scores in between those of the pneumococcal patients and the control population. Correlation between the general speed composite and subscales of RAND-36 within the group of meningitis patients showed significant correlation with physical functioning (−0.46; P = .0005), role impairment due to physical functioning (−0.43; P = .001), and vitality (−0.38; P = .004). Other subscores were not related to cognitive speed. The POMS showed higher scores on the item “depression” for meningitis patients than for control subjects (P = .04), irrespective of the causative microorganism. No relationship was found between neuropsychological test scores and high scores on the item depression. No differences were found in other subscores of the POMS (anger, fatigue, vigor, and tension).

**Discussion**

Adults with good recovery after pneumococcal meningitis appeared to have significant neuropsychological abnormalities. The main cognitive impairment in these patients was loss of cognitive speed. Cognitive slowness was related to impairment of everyday functioning. These cognitive disorders were found in 27% of patients after pneumococcal meningitis but in only 4% of patients after meningococcal meningitis and in 4% of control subjects. *S. pneumoniae* is one of the most frequent microorganisms causing bacterial meningitis in adults, responsible for 35%–40% of all adult cases. Therefore, large numbers of survivors have cognitive problems attributable to their illness.

Results of neuropsychological evaluation of adult patients after bacterial meningitis have been described in only a few studies [10–13]. In these studies, highly selected groups of adult patients, of whom 54%–70% had neurologic sequelae, were examined retrospectively. Psychometric findings included decreased speed of cognitive and psychomotor performance, reduction in visuoconstructive capacity, and high scores on depression scales, all which were comparable to our findings [10–13]. However, the studies described impairments in almost all neuropsychological domains, and cognitive impairment was correlated with presence of neurologic sequelae.

All patients in the present study had a maximum GOS score of 5, assessed at discharge. This does not imply the recovery of all normal functions, because there may be some sequelae. The patient is supposed to be able to participate in normal social life and to resume work (although he or she may not have done so) [14]. Because outcome was assessed at discharge and recovery may continue thereafter, patients could change in outcome category; for example, patients can move up from moderate recovery at discharge to good recovery 6 months later. However, it is unlikely that patients with good recovery would move down to moderate recovery. Therefore, the percentage of patients with a cognition disorder might be underestimated by this study.

Patients evaluated in this study are a representative sample of adults with acute bacterial meningitis who recovered well. The study was nationwide, and a high percentage of patients gave informed consent for inclusion in the cohort. At baseline, demographic characteristics of patients potentially eligible for cognitive testing and patients evaluated in the study were similar. With exception of the expected difference in age between patients with meningococcal and pneumococcal meningitis, the 3 tested groups remained similar for sociodemographic characteristics, including premorbid intelligence and education.

Patients who had meningitis had higher scores on the POMS depression subscale than did control subjects. Higher scores do not necessarily mean a depressive mood disorder. No relation between depressed mood with neuropsychological test scores nor with quality of life was found; therefore, there was no confounding of cognitive test results by depression. The high scores for this subscale are most likely caused by the impact of meningitis, similar to the case in patients who underwent surgical procedures [15].

**Table 3.** Scores on general health and quality of life (RAND-36) for adult patients recovered from meningitis.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control subjects (n = 25)</th>
<th>Meningococcal patients (n = 25)</th>
<th>P*</th>
<th>Pneumococcal patients (n = 26)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>81.9</td>
<td>83.6 (16.7)</td>
<td>1.0</td>
<td>79.6 (17.8)</td>
<td>1.0</td>
</tr>
<tr>
<td>Social functioning</td>
<td>86.9</td>
<td>83.9 (17.7)</td>
<td>1.0</td>
<td>75.5 (30.1)</td>
<td>3</td>
</tr>
<tr>
<td>Role impairment due to physical problems</td>
<td>79.4</td>
<td>61.9 (43.7)</td>
<td>.3</td>
<td>54.8 (44.2)</td>
<td>.02</td>
</tr>
<tr>
<td>Role impairment due to emotional problems</td>
<td>81.4</td>
<td>69.8 (42.0)</td>
<td>.5</td>
<td>74.4 (39.2)</td>
<td>1.0</td>
</tr>
<tr>
<td>Mental health</td>
<td>76.8</td>
<td>73.7 (12.9)</td>
<td>.5</td>
<td>75.5 (22.1)</td>
<td>1.0</td>
</tr>
<tr>
<td>Vitality</td>
<td>76.4</td>
<td>63.1 (15.7)</td>
<td>.001</td>
<td>57.5 (22.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pain</td>
<td>79.4</td>
<td>76.7 (20.3)</td>
<td>1.0</td>
<td>80.1 (24.8)</td>
<td>1.0</td>
</tr>
<tr>
<td>Experienced general health</td>
<td>72.7</td>
<td>68.3 (13.1)</td>
<td>.5</td>
<td>67.1 (13.6)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**NOTE.** Data are mean or mean (SD), unless otherwise noted.

* 1-Tailed P values, Bonferroni-corrected (t test); subscales of RAND-36 of meningococcal and pneumococcal meningitis patients vs. national reference data.
Doctors should be aware of cognitive impairment in patients after pneumococcal meningitis, even in those patients who have a favorable clinical outcome. Our findings have important implications for information given to patients and their relatives.

Acknowledgments

We thank Cox J. J. M. Schouten for assistance in data management, Claudia van der Lugt for assistance in neuropsychological evaluation, and Cornelieke van de Beek for helpful comments. We are indebted to many physicians in the Netherlands for their cooperation.

Appendix: Neuropsychological Tests and Mood and Health Rating Scales

**Dutch Adult Reading Test (DART)**. Fifty words with irregular spelling have to be read aloud. The number of correctly read words is transformed into an estimate of verbal intelligence. The DART is the Dutch counterpart of the National Adult Reading Test (NART). This test gives an estimate of premorbid verbal intelligence, because it correlates highly with other tests of verbal intelligence although it is relatively insensitive to cognitive deterioration due to neurologic disorders. Scores are intelligence quotients (population mean, 100; SD, 15).

**Groningen Intelligence Test (GIT), subtest Verbal Reasoning**. The subject has to choose 1 word from 5 possibilities that correctly completes a $3 \times 2$ matrix of logical semantic relations (e.g., black-white, high-low, hot-?). Raw scores are converted to age-corrected T scores (population mean, 50; SD, 10).

**GIT, subtest Visuospatial Reasoning**. The subject has to decide which of several smaller geometric shapes are needed to fill a larger geometric figure (in a way similar to the oriental game of Tangram, but without actually manipulating the shapes). Raw scores are converted to age-corrected T scores.

**GIT, subtest Numerical Speed**. The subject completes as many written additions as possible in 1 min. Raw scores are converted to age-corrected T scores.

**Rey’s Auditory Verbal Learning Test (AVLT)**. The subject has to memorize a series of 15 words in 5 learning trials. After a 20-min delay, the subject is asked to recall the word list. Raw scores are used.

**Logical Memory of the Rivermead Behavioural Memory Test (RBMT)**. Two 21-item news messages are read to the subject, who repeats as many items as he can remember. After a 20-min interval, the subject is asked to recall the messages again. Score is the number of items recalled.

**Subtest Visual Reproduction of the Wechsler Memory Scale—Revised (WMS-R)**. Four geometric figures of increasing complexity are shown to the subject for 10 s each. Immediately after presentation of each figure and after a 30-min delay, the subject is asked to draw the figures from memory. The quality of the drawings is scored by use of 41 criteria, resulting in a raw score range of 0–41. Raw scores are converted to age-corrected T scores.

**Stroop Color Word Test**. This test measures perceptual interference, response inhibition, and selective attention by having the subject name the color of ink of 100 words when the words are printed in a nonmatching colored ink. Score is time to completion in seconds. Score distributions were modified before statistical testing by an inverse transformation ($1/s$).

**Trailmaking Test part B**. The task is to connect numbers alternating with letters on a sheet of paper. This is a test of visual scanning, visuomotor and conceptual tracking, mental flexibility, and motor speed. Score is time to completion in seconds. Before statistical testing score distributions were modified by a square root transformation ($\sqrt{s}$).

**Wisconsin Card Sorting Test (WCST)**. This test uses a deck of cards on which different numbers of different forms in different colors are shown. The task is to sort the cards according to 1 of 3 possible sorting rules (color, number, or form). These rules are not told but must be determined by the subject. After each sort, feedback is given on whether or not it was correct. Once a sorting rule has been found (10 correct sorts on a row), the subject has to change to a different rule. Of particular interest are perseverative errors of the kind where the subject keeps sorting according to a previously correct rule or to a rule that was wrong in the immediately preceding sort. The WCST is a test of concept formation and set shifting. Scores used in this study are the raw numbers of perseverations.

**Category fluency**. For 1 min, the subject has to say as many words that belong to a particular semantic category. Two trial were done (animals and occupations). Numbers of words produced were converted to age-corrected T scores.

**Letter fluency**. For 1 min, the subject has to say as many words that begin with a given letter. Three trials with different letters were done. Score is raw number of words in 3 min.

**Simple reaction speed**. Simple reaction speed was tested for the dominant and nondominant hands separately with use of visual stimuli (e.g., white square on a black computer screen, press space bar, 30 trials for each hand). Scores are median reaction times in milliseconds.

**Two-choice reaction speed**. Two-choice reaction speed was tested with use of both hands and visual stimuli (e.g., push left button with left hand if square appears to the left of the screen, and vice versa for right hand, 60 trials). Scores are median reaction times in milliseconds.

**Profile of Mood States (POMS)**. During the test session, an abbreviated version of the POMS was filled out by the patient. This is a list of 32 adjectives clustered in 5 subscales (depression, anger, fatigue, vigor, and tension) by which subjects describe their mood during the week preceding the assessment.

**RAND-36**. The RAND-36 is a questionnaire of general health and quality of life. It has been standardized for the Neth-
erlands on a sample of subjects (n = 1063) that is roughly comparable to the present groups with respect to age and education.

References