Neuropsychological sequelae of bacterial and viral meningitis

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Survivors of meningitis often complain about neurological and neuropsychological consequences. In this study, the extent of these sequelae was quantified and correlated to MRI findings. Neurological, neuropsychological and neuroradiological examinations were performed with adult patients younger than 70 years, 1–12 years after recovery from bacterial meningitis (BM; n = 59), or from viral meningitis (VM; n = 59). Patients with other potential causes for neuropsychological deficits (e.g. alcoholism) were carefully excluded. Patients were compared to 30 healthy subjects adjusted for age, gender and length of school education. With the exception of attention functions, both patient groups showed more frequently pathological results than the control group for all domains examined. Applying an overall cognitive sum score, patients after BM did not differ significantly in their performance from patients after VM. Separate analyses of various cognitive domains, however, revealed a higher rate of persistent disturbances in short-term and working memory after BM than after VM. Moreover, patients after BM exhibited greater impairment of executive functions. Associative learning of verbal material was also reduced. These deficits could not be ascribed to impaired alertness functions or decreased motivation in BM patients. Applying a logistic regression model, the neuropsychological outcome was related to the neurological outcome. Patients with a Glasgow Outcome Scale (GOS) of <5 had more frequently impaired test results for non-verbal learning and memory. GOS was also correlated with performance in executive functions. Brain volume was lower and ventricular volume was higher in the bacterial than in the VM group, and cerebral volume and the amount of white matter lesions of patients after BM were negatively correlated with short-term and working memory. In conclusion, patients after BM with a GOS ≤4 led to decreased activities of daily living but only a minority of patients were disabled in a way that social functions were affected. The extent of neuropsychological sequelae of BM might have been overestimated in earlier studies which often had not been controlled for comorbidity factors such as alcoholism.

Keywords: bacterial meningitis; viral meningitis; neuropsychological sequelae; neurological sequelae; MRI

Abbreviations: AAT = Aachen Aphasia Test; BM = bacterial meningitis; CVLT = California Verbal Learning Test; GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Scale; HAWIE-R = Hamburg-Wechsler Intelligenztest für Erwachsene-R; SD = standard deviation; SNRS = Scripps Neurological Rating Scale; VM = viral meningitis; VV = ventricular volume; WMS-R = Wechsler Memory Scale-R

Introduction

Survivors of bacterial meningitis (BM) often complain of neurological (Durand et al., 1993) and neuropsychological (Bohr et al., 1983) sequelae. The overall mortality rate can reach 20% (van de Beek et al., 2004). Cognitive deficiencies after BM in children (predominantly persistent difficulties in learning, deficits in short-term memory, behavioural problems and poorer academic performance) (Grimwood et al., 2000) have been described. In adults, to our knowledge, only
two systematical neuropsychological follow-up studies with a sufficient number of participants have been published (Merkelbach et al., 2000; van de Beek et al., 2002). Unfortunately, both studies performed comparisons only with healthy subjects, and the participating patients were not controlled for alcoholism or any other substance abuse. Alcoholism, however, is a predisposing factor for bacterial infections (Huang et al., 2002), especially due to streptococci (Siboni et al., 1989) and Listeria monocytogenes (Siboni et al., 1989; Aladro Benito et al., 1995). Without information about the cognitive status before onset of BM, it is not possible to differentiate between cognitive dysfunction caused by alcohol and that caused by meningitis. A Dutch study group (van de Beek et al., 2002) demonstrated that patients after Streptococcus pneumoniae meningitis often suffered long-lasting cognitive impairment, whereas patients who had survived meningococcal meningitis were hardly affected. Secondary brain lesions caused by brain oedema, increased intracranial pressure, vasospasm, vasculitis, cerebral venous thrombosis and primary brain cell death due to neurotoxicity of bacterial products or proinflammatory mediators (Bohr et al., 1983; Pfister et al., 1993; Nau et al., 2004) are responsible for persisting deficits after BM. Brain damage induced by BM could be demonstrated in both post-mortem (Nau et al., 1999) and MRI examinations (Free et al., 1996). Although MRI alterations after BM such as global atrophy (Davidson and Steiner, 1985) or focal hippocampal atrophy (Free et al., 1996) have been reported, they have not been related to cognitive disturbances. The present study was designed to examine the neuropsychological impact of BM in humans. Therefore, through the use of strict selection criteria the study population was selected to minimize concomitant disease which could potentially influence cognitive assessments.

Methods

Patients

All files of patients who were coded as ‘suspected meningitis’ at admission to the University Hospital, Göttingen, during the past 12 years were screened. The diagnosis of ‘suspected meningitis’ was made clinically when patients presented with headache, fever, neck-stiffness, qualitative or quantitative disturbances of consciousness, photophobia, vomiting or signs of systemic inflammation in the blood tests. Only patients who had received a lumbar puncture and with a sufficient clinical documentation were eligible for the inclusion/exclusion algorithm of our study as described in Fig. 1A. The study was approved by the Ethics Committee of the University of Göttingen.

Control group

Thirty healthy subjects without a medical history of neurological disease selected to match the age, gender and length of school education of the study population served as a neuropsychological control group. In order to rule out neurological impairment, they underwent a physical neurological examination which had to be normal. To ensure the reliability of our statements on normal and pathological results of the patient groups, the test results of the control group were transformed into Z-values. They served as a standard to identify pathological results in both patient groups.

Inclusion/exclusion criteria

Patients with definite bacteriological (positive culture result or positive Gram stain) or ≥2 distinctive laboratory signs of bacterial infection of the CNS (CSF leucocyte count ≥1000/µl, CSF lactate concentration ≥3.0 mmol/l, CSF protein concentration ≥1000 mg/l) in addition to clinical signs of meningitis, were assigned to the BM group. Patients with meningitis at admission were assigned to the viral meningitis (VM) group if there were a CSF pleocytosis <1000/µl, CSF protein concentration <1000 mg/l and CSF lactate <3.0 mmol/l. The microbiological examination of the CSF which included microscopy and bacterial culture had to be negative, and the plasma C-reactive protein concentration was required to be <100 mg/l. Cut-off values were derived from previous studies on the differential diagnosis of BM (Karandanis and Shulman, 1976; Berg et al., 1982; Ilanson et al., 1993; Leib et al., 1999). Patients eligible for the VM group who had received prior antibiotic treatment were excluded in order to prevent contamination of this group with patients suffering from mild BM. Exclusion criteria for both patient and control groups were as follows:

- age under 15 years
- evidence for alcoholism (as gained by information from the patients themselves, their relatives or by typical laboratory findings)
- any other addictive disorders
- age over 70 years
- poor skills in German (non-native German speakers were only included if their German was fluent)
- ambiguous clinical results concerning the differential diagnosis (see above)
- any known affective or other psychiatric disease
- known neurological disorders potentially affecting the CNS
- severe recent life events that might have interfered with neuropsychological testing
- known systemic neoplasms
- use of sedatives or neuroleptic medication.

In Fig. 1A, the inclusion/exclusion tree of the study is depicted. Fig. 1B and C show the composition of the bacterial and VM group, respectively. After application of the exclusion/inclusion algorithm, eligible patients were contacted by an informal letter describing the project. If patients did not refuse to be approached, they were called by telephone. A standardized telephone interview adapted from the Malt questionnaire (Malt et al., 1989) was performed. Patients were invited for a follow-up examination in our outpatients clinic. Fifty-nine patients with BM and 59 with VM were recruited.

Physical condition

A physical and neurological examination was performed by two physicians (M.D. and H.S.). Existing outcome scales for neurological function after meningitis are brief for reasons of clinical feasibility (Bohr et al., 1984, 1985). Therefore, we applied the Scripps Neurological Rating Scale (SNRS), originally developed for the evaluation of multiple sclerosis patients (Sipe et al., 1984), which met our needs for thorough documentation and reproducibility. In addition, the Nottingham scale of activities of daily living (Nouri and Lincoln, 1987), quality of life scores/psychic well-being (SCL-90-R GSI, PSI) (Olsen et al., 2004) were applied. We extracted Glasgow Coma Scale...
Neuropsychological evaluation
The neuropsychological test battery focused on attention, mnemonic and executive cognitive functions. General intelligence measurements were omitted in favour of more concise testing in the above-mentioned domains. Attention functions were measured with the 'Testbatterie zur Aufmerksamkeitsprüfung' (TAP) (Zimmermann and Fimm, 1994; Becker et al., 1996) focusing on selective attention (TAP subtest 'alertness'), stimulus selectivity (TAP subtest 'go-no-go') and divided attention (TAP subtest 'divided attention'). Short-term and working memory were assessed with the German version of the 'Wechsler Memory Scale-R' (WMS-R) [subtests digit span forward/backward (fw/bw); blockspan fw/bw; logical memory (LM), part I] (Harting et al., 2000), and the first trial of the 'California Verbal Learning Test' (CVLT) (Delis et al., 1988). Verbal learning and long-term memory were tested with WMS-R (subtests 'verbal pair association; LM', part II), CVLT (Delis et al., 1988) and with the 'Verbal Learning Test' (VLT) (Sturm and
Willmes, 1999b). Non-verbal learning and memory were measured with the WMS-R (subtest visual pair association), the complex Rey figures test (Osterrieth, 1944), the 'Non-Verbal Learning Test' (NVLT) (Sturm and Willmes, 1999a) and 'Lern- und Gedächtnistest 3' (LGT-3, subtest city map) (Bauml, 1974). Executive functions were examined by verbal fluency tasks ('Regensburger Wortflussigkeitstest' [RWT, subtests lexical fluency with and without alterations, subtests semantic (sem.) fluency with and without alterations] (Aschenbrenner et al., 2000), figural fluency (FF) tasks [Ruff's FF test (Ruff, 1988)], a verbal concept formation (CF) task ('Hamburg-Wechsler Intelligenztest für Erwachsene-R', HAWIE-R (Tewes, 1991); subtest 'Gemeinsamkeiten finden'; similarities), CVLT clustering and a figural concept formation task [Wisconsin Card Sorting Test, WCST (Nelson, 1976)]. In addition to attention, mnemonic and executive functions, we tested visuo-constructive functions (HAWIE-R subtest Mosaic test and Rey complex figure copy) and language functions ['Aachen Aphasia Test' (Huber et al., 1983) AAT subtest Token test]. The following domains and cut-off values for pathological results were defined (please see Appendix for the listing of constitutive subtests): attention (pathological: ≥2 subtests below \( z = -1.5 \)), executive functions (pathological: ≥2 subtests below \( z = -1.5 \)), short-term/working memory (pathological: ≥2 subtests below \( z = -1.5 \)), verbal learning/verbal memory (pathological: ≥3 subtests below \( z = -1.5 \)), non-verbal learning/non-verbal memory (pathological: ≥2 subtests below \( Z = -1.5 \)) and visuo-constructive functions (pathological: ≥1 subtest below \( Z = -1.5 \)).

**Psychosomatic/psychiatric evaluation**

Beck’s depression scale (Beck et al., 1961) and SCL-90R questionnaire (Olsen et al., 2004) were used to control for possible influences exerted by mood or personality alterations on cognitive performance, general social, psychical and physical functions. These self-assessment questionnaires were sent to the participant after the first telephone contact, i.e. before clinical presentation, to allow him/her to fill in the answers in a familiar environment.

**Neuroradiological examination**

**Image acquisition**

For each patient group, a \( T_1 \) volume of three-dimensional (3D) gradient echo acquisitions with a slice thickness of 1.3 mm in sagittal volume excitation was created (\( T_E = 24.03 \) ms, \( T_R = 6 \) ms, flip angle = 30°, matrix 256 \( \times \) 256) to provide the basis for exact

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**Fig. 1** (A) Study inclusion/exclusion diagram. (B) Exclusion diagram for the BM group. (C) Exclusion diagram for the VM group.
structural differentiation. In addition, an image set of 20 transverse images in fluid attenuated inversion recovery (FLAIR) technique ($T_2$ 6000 ms, $T_1$ 100 ms) was chosen to evaluate the frequency and severity of white matter changes. The field of view for all MR studies was adjusted parallel to the orbito-meatal line. All measurements were performed on a 1.5 T Gyrosan Philips MRI scanner.

**Image processing**
Sagittal $T_1$ scans were applied for the manual slice-by-slice outlining of cerebrum and basal ganglia. The acquired areas were multiplied by the slice thickness and the number of the slices. The volume of the ventricles was measured using the same procedure. The investigator performing the planimetry was a trained physician in clinical neurology (C.M.), blinded for the respective patients’ diagnosis. The software Osiris, Version 4 was used (Ligier et al., 1994). The landmark dividing the cerebrum and basal ganglia from the upper brainstem was defined as a line from the superior border of the superior colliculus to the lower margin of the root of the mamillary bodies drawn in the mid-sagittal plane (Edwards et al., 1999). ‘Ventricular volume’ (VV) was defined as the sum of both lateral ventricles and third ventricle without the fourth ventricle. Relative VV was calculated as the ratio of VV and cerebral volume. FLAIR sequences were used for the neuroradiological rating of atrophy, white matter and cortical lesions to categorize these into ‘normal’, ‘pathological probably due to meningitis’ or ‘pathological probably due to other causes’. The neuroradiological evaluation was carried out by a neuroradiologist who also was blinded for the diagnosis (C.F.).

**Statistics**
Data were described as mean ± standard deviations (SD). Statements on pathological alterations were made cautiously. They were not only based on significant group differences but required $Z$-values of less than −1.5 (Sreen and Strauss, 1998; Arnau et al., 2004). The normative data for this cut-off value were derived from the control group by $Z$-transformation of raw data. Whenever only VM and BM groups were compared [e.g. GCS at admission, brain volume (BV), etc.] we used $t$-tests for independent samples for normally distributed data, and $U$-tests when Gaussian distribution was not present. When both patients and control groups were used, we compared ANOVA or ANOVA on ranks (Kruskal-Wallis $H$-test) followed by Bonferroni’s or Dunn’s post hoc test for multiple testing, respectively. Frequencies were compared with either $\chi^2$- or Fisher’s exact-test in the case of small group size. Multivariate analysis was performed with MANOVA testing. We used Pearson’s correlation coefficient for normally distributed parameters, and Spearman’s rank correlation coefficient for data not being normally distributed. A logistic step-wise regression model was used for the identification of both clinical and neuropsychological outcome parameters. The calculations were performed with SPSS 11.0 software (SPSS, Inc., Chicago, IL, USA).

**Results**

**Sociodemographic data**
According to the study inclusion diagram (Fig. 1A), 250 patients with BM and 246 patients with VM were potential candidates for this study. In the BM group, significantly more patients had died or were not trackable than in the VM group ($n = 39_{BM}$ versus $n = 6_{VM}$; $\chi^2$-test $P < 0.01$). As expected, in the overall BM group, significantly more patients suffered from alcoholism or intravenous drug abuse than in the VM group ($n = 11$ versus $n = 2$; $\chi^2$-test $P < 0.01$), and were therefore excluded. The exclusion tree for the BM and VM group is given in Fig. 1B and C. We recruited 59 individuals for the BM group, 39 VM and 30 control subjects. Neither gender distribution (m/f: $34/25_{BM}$, $34/25_{VM}$, m/f: $17/13_{CONTROL}$; $\chi^2$-test $P = 0.99$) nor age distribution at the time of this investigation ($44.6 \pm 14.9_{BM}$, 40.4 ± 11.6$_{VM}$, 46.3 ± 13.1 control years; $H$-test $P = 0.12$) was different. The age of VM and BM group members at hospital admission ($38.6 \pm 15.4_{BM}$, 34.4 ± 11.7$_{VM}$ years, $t$-test $P = 0.14$) and the interval between meningitis and assessment ($6.0 \pm 3.5_{BM}$, 6.3 ± 5.1$_{VM}$, $t$-test $P = 0.93$) were comparable between the groups. The handedness did not differ between the groups ($\chi^2$-test $P = 0.44$). The duration of school education was similar among the control, the VM and BM groups ($H$-test $P = 0.52$). However, more patients after BM (13 out of 59) than after VM (4 out of 59) were either unemployed or retired (Fisher’s exact test $P = 0.03$). In our control group, 4 out of 30 persons were retired but none because of medical conditions.

**Neurological examination**
On hospital admission, BM patients exhibited significantly lower GCS scores than VM patients ($13.1 \pm 2.7_{BM}$; $14.9_{VM} \pm 0.4$; $U$-test $P < 0.01$). Only 1 VM patient had a GCS of ≤12, none of the VM patients displayed a GCS < 9, whereas 13 BM patients showed a GCS of ≤12 and 6 BM patients showed a GCS of <9. Neurological deficits (other than headache and neck stiffness on admission) that could be safely ascribed to meningitis were observed in 48 BM patients. At the time of this study, the frequency of neurological deficits differed significantly between patients after bacterial and VM ($\chi^2$-test $P < 0.01$). Only in 11 BM versus 40 VM patients was the neurological examination without abnormalities. The SNRS was lower for BM patients than for VM patients ($91.0 \pm 12.4_{BM}$ versus 96.1 ± 13.6$_{VM}$; $t$-test $P = 0.04$). The GOS on re-examination was significantly higher for VM than for BM patients ($\chi^2$-test $P < 0.01$). No one in the VM group had a diminished GOS, while 11 patients in the BM group had a GOS of ≤5.

**Complications of BM**
Cerebral complications of BM have been described in detail (Pfister et al., 1993). In the BM patients studied here, significant brain swelling was observed in 14 out of 59 (24%), ischaemic cerebral lesions in 5 out of 59 (10%), signs for small vessel vasculitis in 8.5%, impairment of CSF circulation (mostly hydrocephalus aresorptivus), in 4 out of 59 (7%), sinus thrombosis in 2 out of 59 (3%), cerebritis/abscess...
Table 1 Distribution of causative bacteria in adult patients with bacterial meningitis

<table>
<thead>
<tr>
<th>Bacterium</th>
<th>All BM patients n (%)</th>
<th>Study population n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Streptococcus pneumoniae</strong></td>
<td>64 (26)</td>
<td>16 (27)</td>
</tr>
<tr>
<td><strong>Neisseria meningitidis</strong></td>
<td>27 (11)</td>
<td>16 (27)</td>
</tr>
<tr>
<td><strong>Staphylococcus aureus</strong></td>
<td>18 (7)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Streptococci</td>
<td>13 (5)</td>
<td>8 (13)</td>
</tr>
<tr>
<td><strong>Listeria monocytogenes</strong></td>
<td>8 (3)</td>
<td>3 (5)</td>
</tr>
<tr>
<td><strong>Haemophilus influenzae</strong></td>
<td>3 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>4 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Mycobacterium tuberculosis</strong></td>
<td>29 (12)</td>
<td>0 (0)†</td>
</tr>
<tr>
<td><strong>Borrelia spp.</strong></td>
<td>15 (6)</td>
<td>0 (0)†</td>
</tr>
<tr>
<td><strong>Not identified</strong></td>
<td>69 (29)</td>
<td>18 (31)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>250</td>
<td>59</td>
</tr>
</tbody>
</table>

*Culture proven and clinically probable cases of tuberculous meningitis. †Exclusion criterion.

Formation in 2 out of 59 (3%) and intracranial haemorrhage in 1 out of 59 patients (1.7%). No such complications occurred in the VM patients.

**Neuroradiological evaluation**

**Planimetry**

BVIs were significantly smaller in the BM than the VM group (1114 ± 113 cm³BM versus 1158 ± 88 cm³VM; U-test P = 0.03). Conversely, the VVs were larger after BM than after VM (22 ± 26 cm³BM versus 11 ± 9 cm³VM; U-test P = 0.03).

**Neuroradiological evaluation**

For the blinded neuroradiologist, it was difficult to distinguish white matter lesions after meningitis from those induced by small-vessel atherosclerosis. In 12 out of 58 patients after BM, lesions in the FLAIR scans were diagnosed as being probably induced by meningitis. In another 25 patients, the radiologist found alterations but was unable to classify them as specific for BM. Nevertheless, in his final diagnosis, none of the VM patients was classified as having 'MRI lesions probably caused by meningitis' (χ²-test P < 0.01). Except for the number of white matter lesions and the extent of brain atrophy that were negatively correlated to the performance in short-term memory (both P = 0.03), none of the other substests was associated to MRI alterations.

**Psychopathological evaluation**

All psychopathological data were derived from self-assessment questionnaires which the patients had completed before presenting themselves for re-examination.

**Depression**

The Beck’s depression index did not differ between the three groups, nor between BM and VM patients (4.9 ± 5.6BM, 5.2 ± 5.9VM, and 2.5 ± 2.5CONTROL; H-test P = 0.26). According to the given cut-off values for the Beck’s depression index (<11: ‘not depressive’), most of the patients considered themselves to be ‘not depressive’. Differences in prevalence of depression between the groups could be ruled out as a cause for differences in the neuropsychological test performance.

**General physical, psychical functioning and psychic well being**

We analysed results from the Nottingham ADL, and the scales GSI and PST from the SCL-90-R questionnaire. Patients after bacterial but not after VM were more likely to experience difficulties in their daily global functioning compared to healthy control persons. ANOVA and post hoc analysis again displayed lower scores for BM patients as compared both with the VM and the control group. The VM patients did not differ from the control group in this respect (83.3 ± 9.4BM, 86.8 ± 2.9VM (U-test P = 0.02), versus 87.1 ± 2.5CONTROL; ANOVA P < 0.01). GSI [Z-values in mean −1.4 ± 1.9BM, −1.9 ± 3.0VM (U-test P < 0.01), versus 0.0 ± 1.0CONTROL; ANOVA P < 0.01] and PST scores [−0.8 ± 1.3BM, −1.1 ± 1.7VM (U-test P < 0.01)] were significantly lower in both patient groups than in the control group (0.0 ± 1.0CONTROL; ANOVA P < 0.01).

**Cognitive evaluation**

**Frequency of cognitive dysfunctions**

The relative frequencies of patients with impaired performances for each domain in each group are listed in Table 2. Except for alertness functions, in all domains the patient groups displayed significantly higher proportions of pathological results than the healthy control group. In spite of consistent differences in favour of the VM group, only the domain of short-term and working memory was significantly more often impaired in BM than in VM patients (Fisher’s exact test P < 0.01) (Table 2).

**Global cognitive sum score**

The ‘global cognitive sum score’ was derived from the number of subtests of pathological domains. Whenever the majority of the domains were pathological the global cognitive score was considered ‘pathological’. Calculating and comparing this score, both patient groups showed significantly lower global cognitive sum scores than the controls (ANOVA P ≤ 0.01), while the differences of the frequencies of pathological global cognitive sum scores in the BM and the VM groups did not reach statistical significance (χ²-test P = 0.75).

**Multivariate analysis**

As an important pre-requisite for the comparison of both patient groups, attention functions for VM, BM and control groups were comparable (MANOVA P = 0.13). In all other domains meningitis groups showed lower mean Z-values than the control group. However, only in two neuropsychological tests in the BM group, the mean Z-values were below −1.5 (Rey-figure copy and HAWIE-R similarities, Fig. 2).
Analysing the differences between the patient groups, the scores for executive functions were significantly lower in the BM than in the VM group (MANOVA $P < 0.01$). Mean Z-values for visuo-constructive abilities were significantly lower in BM patients (MANOVA $P < 0.01$). Short-term and working memory was more impaired in BM than in VM patients (MANOVA $P < 0.01$). Concerning the language domain, BM but not VM patients showed significantly lower Z-values in the AAT token test levels 4 and 5 than healthy control subjects ($-1.0 \pm 2.3_{BM}$ versus $-0.2 \pm 1.4_{VM}$; U-test $P = 0.02$ and 0.47, respectively; MANOVA $P < 0.01$). Since the AAT token test (AAT 4 more than AAT 5) is dependent on short-term and working memory functions, the lower scores for language functions could be an effect of the observed differences between VM and BM in short-term/working-memory functions. The domains of verbal learning/memory (MANOVA $P < 0.01$) but not of non-verbal learning/memory (MANOVA $P = 0.15$) were significantly different. When analysing the non-verbal recall functions (Rey figure delayed recall (del. recall), city map test and WMS-R visual pair association, part II) separately, patients after BM performed significantly worse than after VM (MANOVA $P < 0.01$) (Fig. 2). In addition to the frequencies of impaired test results in the respective groups, Tables 2 and 3 provide a summary of MANOVA and post hoc testing in the various domains.

### Predictive factors

#### Neuropsychological outcome

When applying a logistic regression model, only the age at re-examination was predictive for the neuropsychological result. When controlling for age, the neurological status at the time of re-examination expressed as SNRS was predictive for an impaired neuropsychological outcome in patients after BM. Taken separately in a univariate comparison, the only clinical parameter that differed significantly for BM patients with pathological versus those with a normal neuropsychological outcome was the VV heralding brain atrophy (U-test $P = 0.04$).

#### Social impact

Four of 59 BM patients but none of the VM patients had to retire as a consequence of the disease (Fisher’s exact test $P = 0.05$). The retired BM patients were significantly older than BM patients who were able to continue their work ($33.1 \pm 4.2$ versus $37.6 \pm 15.4$ years; U-test $P = 0.04$). Three of 4 retired patients had an impaired GOS and their SNRS was significantly lower than the SNRS of non-retired BM patients ($81.5 \pm 9.0$ versus $91.7 \pm 12.4$, U-test $P = 0.02$).

#### Subgroup analysis for BM

In patients with a culture- or microscopically proven bacterial aetiology of meningitis, the most frequent causative pathogens were $S. pneumoniae$ and *Neisseria meningitidis*, both $n = 16$. When comparing these two groups, we found characteristic differences such as mean younger age at admission ($N. meningitidis$ versus $S. pneumoniae$ 21.8 ± 10.9 versus 42.3 ± 11.2 years; t-test $P < 0.01$) and higher GOS at discharge for $N. meningitidis$ patients (Fisher’s exact test $P = 0.02$). All patients after $N. meningitidis$ meningitis had a normal GOS on discharge, whereas 10 out of 16 patients after $S. pneumoniae$ meningitis had a GOS of 4 (Fisher’s exact test $P = 0.02$). For the following analysis of psychopathological and cognitive function we took into account the significant difference in age (this analysis used Z-values from the normative data). Sociodemographic determinants such as educational system or duration of education at the time of our study did not differ. In the multivariate analysis of psychometric data, neither the domain for physical and social functioning nor the domain of psychic well being revealed differences between patients after meningococcal and pneumococcal meningitis. The comparison between meningococcal and pneumococcal meningitis did not exhibit differences for the number of cognitive domains (Fisher’s exact test $P = 0.43$), except for the domain of verbal memory, in which patients after *N. meningitidis* meningitis achieved lower Z-values than patients after pneumococcal meningitis (MANOVA $P = 0.02$). Comparing VVs, pneumococcal meningitis patients had significantly higher volumes than patients after meningococcal meningitis. Since both groups differed in ages, and higher age was accompanied by physiological brain atrophy, these differences could at least be in part the result of group-based bias. MRI examinations of patients after pneumococcal meningitis were more frequently classified as ‘pathological’ (12 versus 6) and ‘pathological probably due to meningitis’ (6 versus 0) than those of patients after meningococcal meningitis (Fisher’s exact test $P < 0.01$).

### Table 2 Frequencies of impaired domain functions for BM and VM patients

<table>
<thead>
<tr>
<th>Domain</th>
<th>BM (%) versus control</th>
<th>VM (%) versus control</th>
<th>Control group (%)</th>
<th>$P$-value $^{BM}$ versus $VM$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>39.0$^a$</td>
<td>42.6$^a$</td>
<td>20.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Executive functions</td>
<td>63.6$^a$</td>
<td>48.3$^a$</td>
<td>25.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Short-term/working memory</td>
<td>58.6$^a$</td>
<td>39.5$^a$</td>
<td>15.4</td>
<td>$&lt; 0.01$</td>
</tr>
<tr>
<td>Verbal learning/memory</td>
<td>31.0$^a$</td>
<td>25.0$^a$</td>
<td>10.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Non verbal learning/memory</td>
<td>21.1$^a$</td>
<td>13.3$^a$</td>
<td>6.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Visuo-constructive functions</td>
<td>74.6$^a$</td>
<td>59.0$^a$</td>
<td>26.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Global cognitive sum score</td>
<td>37.2$^a$</td>
<td>15.2$^a$</td>
<td>3.0</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

All comparisons made with two sided Fisher’s exact test, Bonferroni corrected P-values; $^a$ denotes $P < 0.05$. 

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*Neuropsychological sequelae and MRI changes after meningitis*  
*Brain (2006), 129, 333–345*
Discussion

BM can cause persistent neurological (Durand et al., 1993) and cognitive impairment, i.e. attention deficits, mnemonic problems, learning disabilities in children (D’Angio et al., 1995; Hugosson et al., 1997; Grimwood et al., 2000) and adults (Zahner et al., 1995; Merkelbach et al., 2000; van de Beek et al., 2002). In comparison to healthy control persons, Merkelbach et al. found a high proportion of persisting...
cognitive deficits (over 70%) resembling subcortical cognitive impairment which was not correlated to the respective neurological outcome (Merkelbach et al., 2000). Van de Beek et al. also reported cognitive slowing in patients after BM (van de Beek et al., 2002), especially in patients after S. pneumoniae meningitis, whereas patients after meningococcal meningitis displayed almost normal test results in this cohort.

Apart from attention functions, our reappraisal of cognitive dysfunctions after long-term survival of bacterial and VM revealed poorer cognitive functioning in both patient groups in many subtests when compared to an age-adapted control group of healthy adults. These impairments of cognitive functions had substantial social consequences only for a minority of BM patients. The Z-values given in the literature have been obtained by testing subjects through only a single test, whereas our array of tests usually took >3 h. For this study, as a common ground for normative values, the results were interpreted in relation to Z-values determined by a group of healthy adults who had undergone the same time-consuming test procedure. In this way, we ruled out that the differences between the normative data and the patient groups were partly just a result of fatigue. Nevertheless, for the evaluation of long-term sequelae in BM patients, it is probably more important to look at the comparison with the age-matched VM group having a comparable clinical history. Serious life events such as meningitis can have a critical long-term impact on psychic and mood stability (Twamley et al., 2004; Bremner et al., 2004). Serious life events can induce depression with its negative effects on cognition (Penick et al., 1994). These direct and indirect cognitive disturbances are difficult to distinguish from primary impairment caused by the disease itself. Because the frequency of cognitive dysfunctions (and MRI alterations) increases with age, we only allowed patients up to 70 years to participate in this study. Probably most important, we carefully excluded patients with alcoholism (or other substance abuse), a frequent cause of cognitive derangement (Goldstein et al., 2004). Alcohol abuse impairs frontal executive functions (Dao-Castellana et al., 1998) and affects memory functions (Parsons, 1994). Alcoholism—with or without related medical diseases—is one of the predisposing factors for streptococcal, including pneumococcal diseases (Siboni et al., 1989; Huang et al., 2002). Failure to exclude these patients can produce a bias with respect to cognitive functions in patients after pneumococcal meningitis and may be responsible for the high rate of severe neuropsychological abnormalities in one previous study (Merkelbach et al., 2000).

Although we controlled for the variable alcoholism by studying the patients’ files for typical laboratory signs of alcoholism, and by thoroughly interviewing the patients themselves and/or their relatives, our analysis may still have underestimated the true rate of alcoholism, since the rate of excluded patients in our VM group was a little lower (2%) than the 3% reported for alcoholism in the German population (Singer and Teyssen, 2001).

Our patient and control groups were well balanced with respect to age, gender and education. The results showed all groups to be homogeneous concerning their personality traits and depression scores. Long-term psychological and cognitive disturbances after VM without encephalitis have been reported (Hotopf et al., 1996; Lepow et al., 1962; Muller et al., 1958). These disturbances have been described as subtle. In this study, the neuropsychological outcome for VM patients was significantly poorer than for the healthy control group. Yet, most of the Z-values of the VM group were in mean greater than −1.5. These Z-values greater than or equal to −1.5 are in the lower normal range and might in part be a result of having experienced a serious life disruption by VM. This hypothesis is supported by the fact that the scores for psychic well being for both VM and BM were significantly lower than for the healthy control group.

We did not find a significant difference between BM and VM patients with regard to a general cognitive sum score, or when referring to the healthy control—or to the controls from the literature as the reference. Not until separate cognitive domains had been analysed in detail, was it possible to determine valid differences between the BM and VM group. BM patients more often exhibited pathological deficits in short-term and working memory. The direct comparison showed distinctively poorer results for executive tasks in the BM patients, particularly when learning strategies and control of mnemonic interference were required. Patients after BM made more mistakes in the AAT token test (domain language) than those after VM and performed significantly poorer in the domain of visuo-constructive functions. The difference between the test performance of BM and VM patients in the domains of short-term and working memory was significant, irrespective of the mode of analysis (frequencies of pathological test results (χ²); mean Z-values ± SD (MANOVA)).

While the domains of verbal learning and non-verbal learning/memory did not differ in total, especially in subtests which required plan formation and learning strategies, we saw significantly poorer performance of the BM group. The differences in the visuo-constructive performance and language domain can be specific but could also be in part caused by executive deficits due to poorer concept formation.

We ruled out with certainty deficits of attention as a cause for these differences since the respective test results equalled each other. In spite of these differences, only a small subgroup of those BM patients surviving BM with a GOS ≥4 (thus qualifying them for our neuropsychological testing) experienced socially significant impairment leading to retirement or disability (4 out of 39 patients).

Except for one domain, in our culture proven cases, MANOVA analysis did not show relevant differences between patients after S. pneumoniae and N. meningitidis meningitis. One explanation for this discrepancy between the findings reported previously (van de Beek et al., 2002) and ours probably was the fact that we rigorously excluded
patients after \textit{S. pneumoniae} meningitis with concomitant conditions—such as alcoholism—having a negative impact on cognitive functions.

For the interpretation of this study, the findings of van de Beek \textit{et al.} are very important, since these authors provided age-corrected neuropsychological data presented as $t$-values. Considering our definition of an impaired test performance, the results of both studies are very similar. In van de Beek’s neuropsychological investigation of BM patients there was no item with a mean $t$-value of less than 40, i.e. none of the given normalized domains displayed mean $Z$-value lower than $-1$. Although there is no common cut-off $Z$-value for the definition of a pathological test result, $Z$-values below $-1.5$ are considered as impaired test performance (Sreen and Strauss, 1998; Arnaiz \textit{et al.}, 2004). For their cognitive sum score, van de Beek \textit{et al.} considered results below the fifth

<table>
<thead>
<tr>
<th>Domain</th>
<th>BM Z-values (mean ± SD)</th>
<th>VM Z-values (mean ± SD)</th>
<th>Control group raw values (Mean ± SD)</th>
<th>Comparison (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive functions</td>
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<tr>
<td>MANOVA</td>
<td></td>
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<td>&lt;0.01</td>
</tr>
<tr>
<td>Lexical verbal fluency</td>
<td>$-0.8 ± 1.0^\dagger$</td>
<td>$-0.7 ± 0.9^\dagger$</td>
<td>$17.4 ± 4.5$</td>
<td>n.s.</td>
</tr>
<tr>
<td>Semantic verbal fluency</td>
<td>$-0.6 ± 0.8^\dagger$</td>
<td>$-0.5 ± 0.8^\dagger$</td>
<td>$14.5 ± 3.6$</td>
<td>n.s.</td>
</tr>
<tr>
<td>Semantic verbal fluency; alternations</td>
<td>$-0.9 ± 1.0^\dagger$</td>
<td>$-0.6 ± 1.1^\dagger$</td>
<td>$25.4 ± 5.1$</td>
<td>n.s.</td>
</tr>
<tr>
<td>Verbal concept formation</td>
<td>$-0.6 ± 0.9^\dagger$</td>
<td>$0.0 ± 1.0^\dagger$</td>
<td>$14.9 ± 3.3$</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>WCST errors</td>
<td>$-1.1 ± 1.0^\dagger$</td>
<td>$-0.8 ± 1.1^\dagger$</td>
<td>$36.9 ± 9.2$</td>
<td>n.s.</td>
</tr>
<tr>
<td>WCST perseverations</td>
<td>$-0.4 ± 1.2$</td>
<td>$-0.2 ± 1.1$</td>
<td>$4.8 ± 1.7$</td>
<td>n.s.</td>
</tr>
<tr>
<td>CVLT semantic clustering</td>
<td>$-0.9 ± 0.7$</td>
<td>$-0.4 ± 1.1^\dagger$</td>
<td>$2.4 ± 2.7$</td>
<td>n.s.</td>
</tr>
<tr>
<td>Visuo-constructive functions</td>
<td></td>
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<td>&lt;0.01</td>
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<tr>
<td>MANOVA</td>
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<tr>
<td>HAWIE-R mosaic test</td>
<td>$-1.0 ± 1.5^\dagger$</td>
<td>$-0.6 ± 1.4$</td>
<td>$35.3 ± 7.3$</td>
<td>n.s.</td>
</tr>
<tr>
<td>Rey figure copy</td>
<td>$-2.6 ± 4.1^\dagger$</td>
<td>$-1.1 ± 2.7^\dagger$</td>
<td>$35.5 ± 0.9$</td>
<td>0.02§</td>
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<tr>
<td>Language</td>
<td></td>
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<tr>
<td>AAT token test</td>
<td>$-1.0 ± 2.3^\dagger$</td>
<td>$-0.2 ± 1.4$</td>
<td>$0.1 ± 0.5$</td>
<td>n.s.</td>
</tr>
<tr>
<td>Short-term and working memory</td>
<td></td>
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<td>?&lt;0.01</td>
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<tr>
<td>MANOVA</td>
<td></td>
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<tr>
<td>Digit span forward</td>
<td>$-0.7 ± 1.2$</td>
<td>$-0.5 ± 1.0^\dagger$</td>
<td>$7.0 ± 2.4$</td>
<td>n.s.</td>
</tr>
<tr>
<td>Block span forward</td>
<td>$-0.6 ± 0.8^\dagger$</td>
<td>$-0.3 ± 0.8$</td>
<td>$8.9 ± 1.8$</td>
<td>0.05</td>
</tr>
<tr>
<td>Block span backward</td>
<td>$-0.6 ± 1.0^\dagger$</td>
<td>$-0.6 ± 1.0^\dagger$</td>
<td>$8.6 ± 1.9$</td>
<td>n.s.</td>
</tr>
<tr>
<td>CVLT 1st trial</td>
<td>$-0.9 ± 0.8^\dagger$</td>
<td>$-0.6 ± 0.8^\dagger$</td>
<td>$8.2 ± 2.4$</td>
<td>0.03</td>
</tr>
<tr>
<td>WMS logical memory part I</td>
<td>$-1.0 ± 1.2^\dagger$</td>
<td>$-0.8 ± 1.1^\dagger$</td>
<td>$33.1 ± 5.8$</td>
<td>n.s.</td>
</tr>
<tr>
<td>Verbal learning and memory</td>
<td></td>
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<tr>
<td>MANOVA</td>
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<tr>
<td>CVLT trial 1–5</td>
<td>$-1.2 ± 1.1$</td>
<td>$-0.8 ± 1.3$</td>
<td>$59.6 ± 10.6$</td>
<td>n.s.</td>
</tr>
<tr>
<td>CVLT free recall</td>
<td>$-0.1 ± 1.1$</td>
<td>$-0.1 ± 1.2$</td>
<td>$1.4 ± 0.5$</td>
<td>0.01</td>
</tr>
<tr>
<td>CVLT cued recall</td>
<td>$-1.0 ± 1.1^\dagger$</td>
<td>$-0.5 ± 1.0^\dagger$</td>
<td>$13.2 ± 2.6$</td>
<td>0.02</td>
</tr>
<tr>
<td>CVLT delayed free recall</td>
<td>$-0.9 ± 1.2^\dagger$</td>
<td>$-0.5 ± 1.0^\dagger$</td>
<td>$13.0 ± 2.6$</td>
<td>0.03</td>
</tr>
<tr>
<td>CVLT delayed cued recall</td>
<td>$-1.1 ± 1.3^\dagger$</td>
<td>$-1.1 ± 1.3^\dagger$</td>
<td>$13.3 ± 2.3$</td>
<td>0.02</td>
</tr>
<tr>
<td>CVLT recognition hits</td>
<td>$-0.9 ± 1.4^\dagger$</td>
<td>$-1.0 ± 2.1^\dagger$</td>
<td>$15.4 ± 1.1$</td>
<td>n.s.§</td>
</tr>
<tr>
<td>CVLT recognition errors</td>
<td>$-0.6 ± 1.5$</td>
<td>$-0.2 ± 1.7$</td>
<td>$0.6 ± 1.1$</td>
<td>n.s.§</td>
</tr>
<tr>
<td>WMS verbal association part I</td>
<td>$0.2 ± 2.1$</td>
<td>$-0.0 ± 0.4$</td>
<td>$2.2 ± 2.8$</td>
<td>n.s.§</td>
</tr>
<tr>
<td>WMS visual association part I</td>
<td>$-1.4 ± 2.1$</td>
<td>$-0.6 ± 1.5^\dagger$</td>
<td>$7.7 ± 0.5$</td>
<td>0.02§</td>
</tr>
<tr>
<td>WMS logical memory part II</td>
<td>$-1.2 ± 1.2^\dagger$</td>
<td>$-0.9 ± 1.2^\dagger$</td>
<td>$30.6 ± 6.1$</td>
<td>n.s.</td>
</tr>
<tr>
<td>Non-verbal learning and memory</td>
<td></td>
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<tr>
<td>MANOVA</td>
<td></td>
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</tr>
<tr>
<td>Rey figure delayed recall</td>
<td>$-1.1 ± 1.3^\dagger$</td>
<td>$-0.7 ± 1.1^\dagger$</td>
<td>$63.4 ± 16.8$</td>
<td>n.s.</td>
</tr>
<tr>
<td>NVLT difference right positive/false positive</td>
<td>$-0.7 ± 0.8$</td>
<td>$-0.6 ± 0.8^\dagger$</td>
<td>$18.7 ± 5.1$</td>
<td>n.s.</td>
</tr>
<tr>
<td>WMS visual association part I</td>
<td>$-0.1 ± 1.1$</td>
<td>$0.2 ± 1.0$</td>
<td>$17.0 ± 3.1$</td>
<td>n.s.</td>
</tr>
<tr>
<td>WMS visual association part II</td>
<td>$-1.0 ± 2.0^\dagger$</td>
<td>$-0.3 ± 1.3$</td>
<td>$5.8 ± 0.5$</td>
<td>&lt;0.01§</td>
</tr>
</tbody>
</table>

Comparisons were performed with two-sided t-tests unless otherwise denoted. §Comparison of the control group versus normal values derived from the tests’ handbooks or from the literature. †Significantly different as compared with the healthy control group. n.s.: standardised Z-values not available in the literature. §Comparison with U-test.
percentile as pathological. Applying this cut-off value, 16% of their study patients displayed a pathological cognitive sum score. With the same definition of the cut-off value, only 10% of our BM group would have been characterized as abnormal.

In contrast to a previous report (Merkelbach et al., 2000), the neurological outcome at re-examination in our study group was correlated to impaired overall cognitive abilities, as well as to lower executive, non-verbal learning and non-verbal memory functions.

As an expression of atrophy, cerebral volumes in BM patients were smaller, VVs were higher and MRI scans were more often classified as abnormal due to atrophy and/or white matter lesions than in VM patients. For the entire patient group, only dysfunction of short-term and working memory but not a reduced global cognitive sum score or any other domain of learning and memory was correlated with lower cerebral volumes. At first glance, the lack of a tighter correlation of BV with overall cognitive functions seems surprising but corresponds well to the finding that the BV does not clearly correlate with memory functions in healthy persons (Torres et al., 1997).

In patients after VM without encephalitic signs, the achieved Z-values were mostly lower than zero, i.e. poorer than the results of our healthy control subjects (and poorer than the control groups given in the literature and in the test manuals). Whether this confirms that VM may induce lasting, cognitive limitations (Hotopf et al., 1996; Iushchuk et al., 2001) or whether this might be a mere effect of the serious life event these patients have experienced (resulting in decreased psychic well-being) remains to be elucidated by further studies.

In conclusion, the extent of neuropsychological impairment after VM is measurable but probably has only limited social impact for these patients. The damage of cognitive functions by BM is more severe but might have been overestimated in some previous studies due to the inclusion of patients with causes of cognitive deficits other than meningitis. Many adult long-term survivors of BM who were able to present themselves for clinical re-evaluation, showed unimpaired cognitive performance. Short-term/working memory and executive functions are the domains which are affected most frequently and most severely after BM. The executive deficits have a secondary impact on other neuropsychological functions (memory recall, visuo-constructive functions and language). These neuropsychological impairments are correlated to poor clinical outcome. Examinations of short-term/working memory and of executive functions can represent important end-points for future outcome studies evaluating new treatment options for BM in humans.

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References
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Appendix: domains

Attention

- TAP tonic alertness: median reaction time, SD reaction time.
- TAP phasic alertness: median reaction time, SD reaction time.
- TAP stimulus selectivity: median reaction time, SD reaction time.
- TAP divided alertness: median reaction time, SD reaction time, missing items.

Executive functions

- ‘Regensburger Wortflüssigkeitstest’: Verbal lexical fluency with and without alternations, sem. (category) fluency with and without alternations.
- Ruff FF test.
- HAWIE-R ‘Gemeinsamkeiten finden’ (similarities): CF.
- WCST: concepts, errors, perseverations.
- CVLT: sem. clustering.

Short-term memory/working memory

- WMS-R digit span: fw, bw.
- WMS-R block span: fw, bw.
• CVLT: 1st trial.
• WMS-R LM: part I.

Verbal learning/memory
• CVLT: sum score of 1st and 5th trial, slope, free recall after interference, cued recall after interference, free late recall after interference, free cued recall after interference, correct recognition hits, recognition errors.
• VLT: difference right-positive/false-positive.
• WMS-R verbal association (VeP) recognition: part I.
• WMS-R VeP recognition: part II.
• WMS-R LM: part II.

Non verbal learning/memory
• Rey figure: del. recall.
• LGT-3: city map test.

• NVLT: difference right-positive/false-positive.
• WMS-R: Visual association (VP): part I.
• WMS-R: VP: part II.

Visuo-constructive functions
• HAWIE-R: mosaic test.
• Rey figure: copy.

Language
• AAT: Token test 4 and 5.