LETTER TO THE EDITOR

Reply: neuropsychological sequelae of bacterial meningitis: the influence of alcoholism and adjunctive dexamethasone therapy

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Van de Beek *et al.* present new important data concerning the clinical outcome of patients with alcoholism and pneumococcal meningitis. The data was derived from a subgroup analysis of the patient population of their comparative key study on neuropsychological sequelae after pneumococcal versus meningococcal meningitis (van de Beek *et al.*, 2002).

With respect to our paper, they raised three issues:

(i) Absence of statistically significant differences between patients after *Streptococcus pneumoniae* and *Neisseria meningitidis* meningitis in our study.

Van de Beek *et al.* reported that only 2 of 26 patients of the pneumococcal meningitis group who were actually examined neuropsychologically suffered from alcoholism. In contrast to our findings (Schmidt *et al.*, 2006), van de Beek *et al.* found significant neuropsychological differences between patients who survived pneumococcal and meningococcal meningitis. Before we received the information from van de Beek *et al.* by this communication, we presumed that one of several possible reasons for this discrepancy was the different proportion of patients with alcoholism in our study versus those in van de Beek's study. This now can be ruled out.

Searching for further explanations, van de Beek *et al.* suggest that different Glasgow Outcome Scores (GOS) or differing intervals between hospital stay and re-examination of the respective meningitis group might have led to this discrepancy. Patients examined after pneumococcal meningitis in our study had a significantly lower mean GOS value than patients examined after meningococcal meningitis. Therefore, the differences should have been even more pronounced. The interval between hospital admission and neuropsychological testing was not significantly different in our pneumococcal and meningococcal patient groups.

Van de Beek *et al.* pointed out that a group size of 16 patients per group might not yield enough statistical power to discriminate differences. This is true, especially for domains with only limited inter-group differences.

We think that the reported difference between meningococcal and pneumococcal meningitis patients in van de Beek's study (or in other terms the non-existing difference in our study) might be a result of different statistical approaches:

In contrast to our colleagues' work we compared the groups using two-sided tests (not assuming *a priori* one group to be more severely affected than the other). This approach results in an alpha error twice as high as with one-sided testing. If one-tailed tests are used, it is recommended to calculate with half the alpha error that would have been used with a two-tailed study [according to the ICH topic E9 (EMEA, 1998)]. Applying a *P*-value of 0.025, only 3 out of 14 neuropsychological examinations for which van de Beek *et al.* gave mean *T*-values with standard deviations were significantly different (Visuospatial reasoning, WMS-R immediate memory, Trailmaking B) after their univariate analysis of covariance.

Comparing the *T*-values of van de Beek's groups in our way with two-sided *t*-tests for independent samples, only the items Visuospatioal reasoning and Trailmaking B yielded statistically significant differences in van de Beek's study groups.

Contrary to our analysis of alertness functions (performed after age-related transformation into *z*-values), reaction speed (dominant/non-dominant hand) and a two-choice paradigm in van de Beek's paper were significantly slower for the pneumococcal than for the meningococcal meningitis group. In contrast to all other domains, for the comparison of the reaction speed, a transfer of the raw data into age-adapted *z*- or *T*-values (derived from age-matched controls or with the standard values from the respective test manuals) was not

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performed. It is well known, however, that the reaction time declines considerably with age. The mean age of the *Neisseria* meningitis patients in van de Beek's work was significantly lower than that of the *S. pneumoniae* patients. Hence, it would be interesting to determine whether age-corrected *T*-values or *z*-values for reaction speed were actually significantly different in van de Beek's study population.

In conclusion, both studies applied different statistical approaches, which is in our opinion the most likely explanation for the observed discrepancies.

According to the ICH guidelines (EMEA, 1998), we have chosen the more conservative way of two-tailed *t*-tests in order not to obtain too many false-positive group differences. We are aware that thereby we have increased the risk of missing true differences.

(ii) Glucocorticoids.

Seven out of 118 patients in our bacterial meningitis group received concomitant glucocorticoid treatment, and two of them had been on glucocorticoids before the onset of meningitis due to other medical conditions.

Another patient suffering from meningococcal meningitis had received glucocorticoids several days after the onset of the disease because of evolving coxitis. Only four patients (3 patients with *N. meningitidis* and one with *S. pneumoniae* meningitis) were treated with dexamethasone just before or with the first dose of antibiotic treatment.

Since the number of patients treated with glucocorticoids was small, we did not include a subgroup analysis of them. Such an analysis would lack statistical power. However, we are presently carrying out further follow-up examinations on patients after bacterial meningitis using the identical test design and hope to be able to present the effect of glucocorticoids on neuropsychological performance as soon as enough patients for a reasonable group size have been collected.

(iii) Regional atrophy in conjunction with visuo-constructive difficulties.

For this study, we manually measured supranuclear brain volumes without further differentiation of brain regions. We are currently working on voxel-based morphometric measurements (Schmidt *et al.*, 2005) combined with masking various brain regions, and hope thus to provide the data van de Beek *et al.* requested by this summer.

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