

# Neuropsychological Sequelae in 91 Cases of Pneumococcal Meningitis

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During the years 1966 to 1976, 164 children and adults with pneumococcal meningitis were admitted to our hospital. By 1980, 91 of the 111 survivors were assessed with neuropsychological tests to detect cognitive deficits. The 58 adults (age range 18 to 83 years) were divided into groups with and without alternative etiologic factors (mainly head trauma with skull fracture) and compared separately with 141 normal controls. In addition to group comparisons, we made individual assessments of impairment in adults by comparing the observed data with those predicted from regression analysis. The data from 33 children were evaluated without control. In group comparisons, a deficit in the adult group was found in visuomotor speed tests. Individual assessment revealed unequivocal cognitive impairment in three patients

with meningitis as the only etiologic factor. Our results indicate that detectable and sometimes serious cognitive impairment does occur in survivors from pneumococcal meningitis, although it is probably infrequent.

Meningeal bacterial infection may be caused by a number of organisms, of which *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Hemophilus influenzae* account for the vast majority of diagnosed cases. During the first decade of life, *S. pneumoniae* usually ranks third in frequency; it is second to *N. meningitidis* in older childhood and young adulthood, but in older adults the pneumococcus is the most common pathogen (Geiseler, Nelson, Levin, Reddi, & Moses, 1980).

Pneumococcal meningitis was usually fatal before the introduction of antibiotics. Today it is survived by about 80% of the patients. An important question is the quality of life of the survivors.

The incidence of neurological sequelae on discharge after pneumococcal meningitis approximates a mean of 25% for all age groups (Harris, Sokalski, & Levin, 1978; Weiss, Figueroa, Shapiro, & Flippin, 1967), but is higher in neonates and the elderly. In our hospital, sequelae on discharge had been noted in 13.6% of the pneumococcal cases (against 5.6 and 2.8% in cases with meningococcal and *H. influenzae* meningitis; Bohr, Hansen, Jessen, et al., 1983).

In this article, we present the findings on neuropsychological examination 5 to 14 years after pneumococcal meningitis in 91 survivors (both children and adults) among 164 cases. The patients also had a neurological (Bohr, Paulson, & Rasmussen, 1984) and an otological (Rasmussen, Johnsen, & Bohr, 1991) examination, and a computer tomogram (CT) of the brain. Cumulated evaluations of sequelae of pneumococcal meningitis based on all four examinations and related to various clinical findings and conditions during the acute illness have been published previously (Bohr et al., 1985).

## METHODS

### Patients

During the period 1966 to 1976, 164 children and adults with a final diagnosis of pneumococcal meningitis were admitted to the Copenhagen University Department of Infectious Diseases. Neonates were not received in this department, but admitted to a pediatric ward. Lumbar puncture and blood cultures were performed immediately upon admission on all directly admitted patients and in most transferred cases. The diagnosis was based on findings of *S. pneumoniae* in the cerebrospinal fluid (CSF) by culture and/or microscopy of the CSF, or in blood. In four cases the bacteria were cultured from septic foci, such as the middle ear. Treatment (adult daily dosages) of bacterial meningitis initially consisted of 2

mill. IU of penicillin given intramuscularly; sulfamethiazole, 4 g intramuscularly, or sulfadiazine, 4 g orally, and streptomycin, 1.5 g orally. When *S. pneumoniae* was identified, penicillin (2 mill. IU  $\times$  2-4) and sulfonamides (2 g  $\times$  4) were continued, but streptomycin was discontinued. Further details of the diagnostic measures were previously reported (Bohr et al., 1983).

Of the 164 cases of pneumococcal meningitis, 31 died during the hospitalization, and another 22 died during the observation period of 4 to 14 years ending on January 1, 1980. Of the remaining 111 patients, 108 answered a questionnaire (Bohr, Hansen, Kjersem, et al., 1983), and 93 (84%) of these returned to the hospital for follow-up examinations. Judging from the questionnaires returned by the nonparticipants in the follow-up examination, their state of health did not differ from that of the 93 examined. Data from two patients were discarded from all analyses (an 89-year-old patient and a deaf child).

The age distributions (at the time of acute disease) of fatalities, survivors, and re-examined cases, and of re-examined cases by sex and age (at the time of re-examination), are shown in Figure 1. Nonparticipants were distributed evenly over the age groups. Results will be presented for three subgroups: children (6 to 15 years;  $n = 33$ ) and adults (18 to 83 years) with ( $n = 20$ ) and without ( $n = 38$ ) histories of alternative etiologic factors.

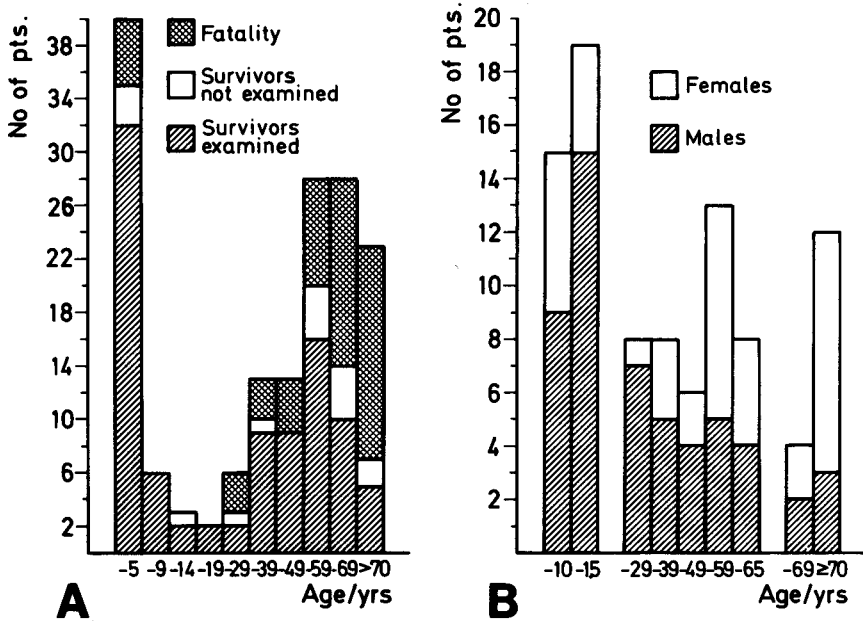


FIGURE 1 (A) 162 cases of pneumococcal meningitis. Fatalities (during hospitalization and observation period), surviving patients not reexamined, and patients with neuropsychological examination grouped according to their age at the acute illness. (B) 93 cases with neuropsychological examination. Distribution of sex and age at reexamination.

## Predisposing and Unrelated Other Diseases

Because it was our aim to identify cognitive impairment attributable to the meningitis, we examined subgroups of patients with and without alternative etiologies of potential significance. In the following, we describe all other nontrivial diseases encountered in our sample, followed by a listing of those considered important for group allocation. Seventeen patients had sustained head trauma before their meningitis, and seven had suffered from trauma in the observation period. Six of the head traumas occurring after the meningitis were mild concussions; whereas those occurring before meningitis were generally more serious, involving cranial fracture. Ten patients had recurrent meningitis; in nine of these cases prior head trauma was seen. Two patients with liquoré had histories of head trauma and had suffered two or three attacks of meningitis. Six patients suffered recurrent otitis media, and six had recurrent respiratory tract infections. Patients with systemic diseases with expected decreased resistance to infections included one case of diabetes mellitus and three cases of alcohol abuse. Two patients had suffered from strokes.

Decisions of group assignment were made retrospectively, but without knowledge of neuropsychological results. The 20 patients in whom alternative etiologic factors were judged to be present (group W) included 17 patients with head trauma, 1 patient with alcohol abuse, and the 2 stroke patients. This may be an arbitrary assignment, as it is hard to evaluate the significance of these parameters.

The children were treated as one group, as only one case had suffered head trauma (concussion) and other existing diseases were judged to be unimportant for cognitive development.

## Controls

Of the 141 normal subjects who served as controls, 120 were patients without central nervous system (CNS) involvement, from the Departments of Orthopedic Surgery and Neurosurgery in our hospital. They were screened by interviewing for the presence of psychiatric or neurological history, or for systemic medical disorders of potential significance for test performance. Details of the exclusion criteria and sample characteristics were reported by Gade, Mortensen, and Bruhn (1988). The age range of this subsample was 20 to 73 years.

To equate the age range of the controls with that of patients, a second control group of healthy elderly subjects (54 to 84 years old) from the community was studied. These individuals were recruited among participants in a longitudinal medical study (Appleyard, 1989), and they were screened with the same exclusion criteria as the main control sample. In addition, the elderly controls were given a CT of the brain.

In data analysis, all controls were treated as one group.

## Neuropsychological Test Battery

The neuropsychological assessment was conducted in a single session during an outpatient visit. The neuropsychologist was not aware of the results of other examinations, nor of details of the patients' hospitalization for meningitis.

Some 30 children (6 to 15 years old) were tested with the Wechsler Intelligence Scale for Children (WISC, Danish version), scored according to the Danish standardization (Danish Psychological Association, 1975). All children except one deaf child and four 6-year-old children were also tested with two learning and memory tests, two tests of memory span, and the Trail Making Test.

All patients older than 16 years of age were examined with the following battery of tests: (a) Symbol Digit Modalities Test (SDMT, Smith, 1973), (b) Trail Making Test A & B (Reitan, 1955), (c) Associate Learning and Retention of 15 Word Pairs (Andersen, 1976), (d) Visual Gestalt Test (Andersen, 1976), (e) Digit Span Forwards and Backwards, (f) Sentence Repetition (Spreeen & Benton, 1969), (g) a modified Block Design Test, (h) Proverb Interpretation, and (i) a classification test modified from the Kasanin-Hanfman Concept Formation Test (Lezak, 1983).

In order to reduce the number of scores and to increase reliability (Gade, Mortensen, Udesen, & Bruhn, 1985), highly correlated test scores presumably measuring similar abilities were averaged in factor scores. The combination of test scores to factor scores was based on the correlations observed in the normal control subjects. Raw scores were converted to standard scores (T scores with a mean of 50 and a standard deviation of 10 in the normal controls). A final summary score of the mean of the 13 test scores in the 9 tests is termed the mean BB T score (Basic Battery).

## Methods of Analysis

Analysis of both group and individual data was based on an objectification of the decision rules normally used in clinical neuropsychological assessments to correct for the effect of age and education. All aspects of the assessment reported here were analyzed in an automated fashion, using T scores. Test data from the 141 normal subjects were subjected to regression analysis with age, education, sex, age<sup>2</sup>, and Age  $\times$  Education as the independent variables, as described elsewhere in detail (Mortensen & Gade, 1992). The resulting regression equations were used to compute expected individual T scores in patients, and differences (residuals) between the expected and the observed scores were calculated. Group mean values in Difference Scores were tested for deviation from zero by *t* tests. In individual patients, each Difference Score was likewise tested for significant deviation from zero by computing an appropriate *t* statistic.

## RESULTS

### Children

Of 33 children examined, verbal and performance WISC IQs were determined for 30 children (2 were missing, and 1 child with poor vision was not given performance subtests). Mean verbal IQ (113.1, *SD* 15.2) and performance IQ (112.4, *SD* 14.2) were similar, and both were above the expected mean. Mean scaled scores ranged from 10.9 in the Object Assembly subtest to 12.8 in the Similarities subtest. Mean scaled scores above 12 were also found in the Picture Completion and Block Design subtests.

Other test data were obtained in 28 children (mean age 12.1 years). No age norms exist. The children achieved better mean scores than the adult meningitis patients in 6 of the 10 variables on the adult tests, and better mean scores than the normal adult controls in Associate Learning and Retention of Visual Gestalts. Their mean scores on the Trail Making Test were 53.7 sec for version A, and 98.7 sec for version B.

### Adults

The analyses were based on Difference factor scores in the groups without and with alternative etiologic factors. The results from the two subgroups separately and combined are shown in Table 1, where positive values indicate better performance and negative values indicate poorer performance than expected on the basis of regression equations. In the two groups combined, Visuomotor Speed was significantly ( $-3.7$  T-score points;  $p < .01$ ) below that expected. Although the deficit was of approximately equal size in the two groups, it was significant ( $p < .05$ ) only in patients without alternative etiologic factors. Difference scores in the other factors and in the summary measure mean BB did not deviate significantly from zero.

### Individual Assessment

Table 2 shows the percentage of individuals in each group who were significantly impaired on each of the five factor scores and in the summary measure. Three individuals in the patients-WO group scored 22, 27, and 33 T-score points below expectation in the mean of all tests, suggesting severe impairment. The distributions of Difference Scores in the remaining patients were symmetrical around zero.

## DISCUSSION

This study was motivated by our interest in the quality of life of survivors of pneumococcal meningitis. We also hoped to contribute to improved patient care by identifying adverse prognostic factors during the acute illness (Bohr et al.,

TABLE 1  
Mean Difference Factor Scores and Summary Scores in Patients  
Without (WO) and With (W) Alternative Etiologic Factors and  
in the Two Groups Combined

Factor <sup>a</sup>		Patients WO	Patients W	Combined
A	$\bar{x}$	-2.1	+3.9	-0.2
	SD	11.8	10.6	11.7
MS	$\bar{x}$	-0.3	-0.2	-0.3
	SD	9.2	8.3	8.8
VL	$\bar{x}$	+0.8	-2.2	-0.3
	SD	8.9	7.6	8.5
V-S(M)	$\bar{x}$	-1.1	-0.7	-1.0
	SD	9.3	9.3	9.2
V-MS	$\bar{x}$	-4.0*	-3.2	-3.7**
	SD	9.9	9.7	9.8
$\bar{x}$ BB	$\bar{x}$	-2.6(*)	-1.1	-2.1(*)
	SD	9.5	7.6	8.9

<sup>a</sup>The factors included the following tests: A (Abstraction), Proverb Interpretation and Classification Test; MS (Memory Span), Digits Forwards and Backwards; Sentence Repetition; VL (Verbal Learning), Associate Learning and Retention; V-S(M) (Visuospatial [memory]), Block Design and Visual Gestalts, learning and retention; V-MS (Visuomotor Speed); SDMT and Trail Making Test

\* $p < .05$ . (\*) $p < .10$ . \*\* $p < .01$ .

1985). Our results indicate that, although mortality rates are still high in pneumococcal meningitis, neuropsychological evidence of permanent brain damage in survivors may be found only in few cases. In the estimation of late neuropsychological sequelae, the sensitivity of the neuropsychological tests may represent the greatest limitation to the validity of our findings. We believe the problem of sensitivity may be greatest in the case of children, in whom a retarded development rather than loss of acquired abilities might follow meningitis, and for whom we have no normal values for tests other than the WISC.

TABLE 2  
Percentage of Subjects Impaired on Each Summary or Factor Variable

Factor	Patients WO	Patients W	Controls
A	16	0	6
MS	11	0	3
VL	8	10	6
V-S[M]	8	15	4
V-MS	18	20	2
$\bar{x}$ BB	11	10	5

Note. The actual impairment in T-score units below expectation required for significance ( $p < .05$ ) varied according to the reliability and predictability of each measure. The units required were -10 ( $\bar{x}$  BB), -12 (V-S[M] and V-MS), -13(A), -14(MS), and -15(VL).

## Children

Previous follow-up studies of childhood meningitis have in some instances reported on IQs, but cases of pneumococcal meningitis were either not included or not reported separately. Lorber (1961) reported on the long-term follow-up of 100 children recovered from tuberculous meningitis, 6 of whom were profoundly retarded (IQ < 50). This outcome has not been encountered in any of the series of pneumococcal meningitis, including this one, and may be specific to the disease processes of tuberculous meningitis. Kresky, Buchbinder, and Greenberg (1962) found a normal distribution of IQ in 50 children, of whom only 6 were known to have had pneumococcal meningitis. Of the 50 children, 5 were designated as "brain injured." Sillanpää, Peltonen, and Nurmikko (1977) studied 183 survivors among 244 cases of childhood meningitis. Of 39 pneumococcal cases, 27 survived. One of these was mildly retarded, and another three were subnormal. There was some indication in the total group that prognosis was better for older children than for neonates and infants, and after the neonatal period *H. influenzae* meningitis seemed to cause disability more often than *N. meningitidis* and *S. pneumoniae*. *H. influenzae* meningitis was also studied by Sell, Merrill, Doyne, and Zimsky (1972), who followed up on 56 children. Their results indicated that 29% had severe or significant handicaps, and IQs ranged from 20 to 140, with a mean of 84. In a subsequent study (Sell, Webb, Pate, & Doyne, 1972), 21 survivors after *H. influenzae* meningitis were matched to a near-age, non-meningitic sibling. The mean IQ of the postmeningitic children was 86; that of the control children, 97. Comparison of each subject with his or her control showed that 6 were at least 15 IQ points below the control. In the same study, another 25 children with previous bacterial (5 pneumococcal) meningitis considered to be normal at school were compared to carefully matched controls. The meningitic children were significantly inferior to their controls on tests of psycholinguistic abilities and vocabulary.

In the latest and best controlled study of sequelae of *H. influenzae* meningitis, Taylor et al. (1990) found much less severe or pervasive consequences. In this study, 97 children treated for *H. influenzae* a mean of 8 years earlier were compared to a nearest-age sibling on a number of standardized cognitive, academic, and behavioral measures. There were no significant group differences in IQ, WISC subtests, or neuropsychological measures, but the index children did have poorer reading skills than their siblings.

As far as we know, our study is the first one to report psychological results from an exclusively pneumococcal meningitis group. We found in our group of 33 children a mean verbal IQ of 113 and a mean performance IQ of 112. Although both the results of Sell and co-workers and a likely increase in IQ since the standardization of the WISC (Teasdale & Owen, 1987) must make us cautious in our interpretation, we feel it unlikely that these higher-than-average scores can represent a significant decline in intellectual potential. Only two children were clinically suspected of intellectual dysfunction, and one child was felt to be patho-



logically hyperactive. Comparing our results with those of others, it may be significant that fatality rates among children with bacterial meningitis in our hospital (5.3% for all etiologies; Bohr, Hansen, Jessen, et al., 1983) were lower than those reported in these other studies. In two adult learning tests, our meningitic children obtained better mean scores than normal adult controls. No child norms are available for these tests, but the results certainly do not indicate that learning disabilities are common problems in these children.

### Adult Patients

We are aware of no previous reports of neuropsychological sequelae in adult pneumococcal meningitis, or in other forms of meningitis. Our choice of tests was guided by an expectation that potential impairment might be associated with diffuse, rather than focal, brain damage. This was true in the three cases of definite impairment found; also, in the other cases with performance below expectation, the test results did not suggest focal involvement. Yet it must be acknowledged that the study was not designed to detect specific disabilities. On neurological examination, gait ataxia was found in 16 patients (Bohr et al., 1984). It is unresolved whether unsteady gait and dizziness after pneumococcal meningitis reflect cerebellar or vestibular dysfunction (Schwartz, 1972). There is no evidence for the involvement of any specific cerebral area in pneumococcal meningitis.

In the total group of 58 adult meningitis patients and in the group of patients without alternative etiologic factors, we found a nonsignificant tendency to performance deficits in the summary measure (mean BB, mean of all tests, see Table 1). The only significant group result was slow visuomotor performance. In our test battery, these tests are the most sensitive to diffuse brain lesions (Gade, Mortensen, & Bruhn, 1988), and the slowness may thus be a marker of mild general impairment.

In individual assessments based on regression equations, three individuals with meningitis as the only etiologic factor were found to be clearly below the normal range. A discrepancy exists between this low incidence and that found on clinical impression (Bohr et al., 1985). We believe to have previously underestimated the normal age decline on the tests used (Gade, Mortensen, & Bruhn, 1988). The age factor was effectively controlled in this study. We had expected to find a greater incidence of neuropsychological impairment in elderly meningitis patients, but this hypothesis was clearly not supported by our data.

The patients with alternative etiologic factors did not perform worse than those without. Head traumas figured prominently in this group. The association between head trauma and meningitis is well known (Appelbaum, 1960; Hand & Sanford, 1970; Levin, Nelson, Spies, & Lepper, 1972). A low mortality in meningitis following head trauma has been noted previously (O'Toole & Thornton, 1971), possibly due to infections with less virulent strains or to the stimulation

of protective antibody. The absence of significant neuropsychological deficit in this group may also be related to the fact that the factor in head trauma that may dispose for meningitis is skull fracture, rather than brain contusion. CT (not shown) showed (frontal) hypodense areas in only two of these patients.

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