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Childhood bacterial meningitis: Impact of age at illness and acute medical complications on long term outcome

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Abstract

This study compared postmeningitic children ($N = 130$) with grade and sex matched controls ($N = 130$) selected from target children's schools on measures of intellectual, linguistic, learning, and reading skills. Results showed that children with a history of meningitis are at greater risk for impairment in these areas, with experience of the disease prior to 12 months of age being an important risk factor. Within the postmeningitic sample presence of medical complications was associated with poorer verbal abilities. Finally, a significant relationship was identified between depressed language skills and later educational difficulty, with these findings interpreted with respect to both developmental and neuropsychological principles. (*JINS*, 1997, *3*, 147–158.)

Keywords: Meningitis, Child development, Neuropsychological sequelae

INTRODUCTION

Bacterial meningitis in childhood is a life-threatening disease, involving infection of the membranes surrounding the brain and spinal cord. Excluding the neonatal period, the peak incidence of the disease in children occurs between 6 and 9 months of age, and then falls progressively during the preschool years (Klein et al., 1986). Before the advent of antibiotics, mortality was greater than 90%. While advances in critical care medicine and appropriate and early antibiotic treatment, have reduced mortality to approximately 5%, considerable morbidity remains (Sell, 1987; Baraff et al., 1990; Taylor et al., 1993; Grimwood et al., 1995).

By the time meningitis is clinically apparent, inflammation of cerebral blood vessels has already occurred, and may be associated with vascular occlusions, cerebral edema, hydrocephalus, and subdural effusions. Mortality and morbidity from bacterial meningitis are thought to be due to either compression and herniation of cerebral tissue or focal ischemia, resulting from altered cerebral blood flow (Herson & Todd, 1977; Klein et al., 1986; Taylor et al., 1992).

Serious sequelae identified in children surviving bacterial meningitis include physical handicap, intellectual disability, seizures, visual impairment, and deafness (Sproles et al., 1972; Lindberg et al., 1977; Feldman et al., 1982; Sell, 1983; Claesson et al., 1984; Dodge et al., 1984; Jadavji et al., 1986; Klein et al., 1986). A recent meta-analysis of 19 prospective studies, including 1602 children (Baraff et al., 1993), reported that 16.4% of survivors exhibited major impairments. However, studies investigating intellectual and neuropsychological abilities have been less conclusive. While some studies report significant differences between postmeningitic and control samples on a wide range of intellectual and academic measures (Kresky et al., 1962; Sell et al., 1972a, 1972b; Sproles et al., 1972) others have concluded that the majority of postmeningitic children have a favorable prognosis (Emmet et al., 1980; Tejani et al., 1982; Feldman & Michaels, 1988; Taylor et al., 1990). Nevertheless, subtle abnormalities in visuomotor coordination, auditory

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perception and higher cognitive functions may occur. These abnormalities are often difficult to detect in early childhood, and children surviving bacterial meningitis may be discharged from followup and assumed to be fully recovered, before such problems become evident.

While it may be that such conflicting results are the product of changes in medical care over time, methodological problems also limit the interpretation of many studies. In general, studies have involved small sample sizes, and enrolled subjects have been selected from retrospective reviews of case records. Such small studies may have had insufficient statistical power to detect even moderately large group differences. Early studies lacked controls, whereas more recent studies have employed sibling controls to reduce genetic and environmental influences. These latter children are usually older, and may be adversely affected by the presence of a sibling who receives extra attention following life-threatening illness. Although several large prospective projects have addressed outcome issues, followup has usually been restricted to 1 to 2 years, with the focus on neurological and sensory functions (Dodge et al., 1984; Jadavji et al., 1986).

It may be that inconsistencies in these results are also associated with a failure to address the specific risk factors. For example, acute medical complications such as focal neurological deficits, coma, prolonged fever, and seizures have been identified as predictors of poor outcome (Herson & Todd, 1977; Emmett et al., 1980; Igarishi et al., 1984). Others have documented factors such as a lower ratio of glucose in CSF to that in blood at time of illness (Feldman et al., 1982; Taylor et al., 1990) as being relevant to long-term outcome following bacterial meningitis.

Younger age at illness has also been suggested as a predictor of poor long-term outcome (Herson & Todd, 1977; Feigin, 1992; Franco et al., 1992). Such findings are contrary to traditional "plasticity" theories, which argue that very young children show fewer severe residual effects from brain insult because of an ability to transfer cognitive functions from damaged to undamaged brain tissue (Teuber, 1962; Lennenberg, 1967). While this may be true in instances of focal insult; for example, tumor or hemispherectomy (Dennis, 1980; Rankur et al., 1980), it is perhaps less likely where an insult is generalized, as with inflammatory processes associated with bacterial meningitis.

In recent years the relative vulnerability of the immature CNS to generalized insult has been described in a number of patient groups, including children sustaining head injury (Ewing-Cobbs et al., 1989; Kriel et al., 1989; Wrightson et al., 1995; Anderson & Moore, 1995), cyanotic heart disease (Wright & Nolan, 1994), and cranial irradiation (Eiser, 1978; Rubenstein et al., 1990; Anderson et al., 1994). To explain such findings it has been argued that cerebral insult in infancy and early childhood may interrupt ongoing development, leading to significant residual deficits. However, some of these deficits may not be initially apparent. If a cerebral area is damaged before it has become functional, then deficits may not be expected to appear until the skills for which the area is responsible would normally emerge. From a cognitive perspective, Dennis (1989) suggests that the impact of early cerebral insult may be cumulative, with established skills being maintained, but with emerging and developing skills being vulnerable to insult. For example, in the case of bacterial meningitis, where many children contract the disease in the first year of life, immature skills, or skills in a critical period of development, such as linguistic abilities, may be particularly vulnerable. The impact of cerebral insult may be to alter the rate of acquisition, the sequence of acquisition, or the mastery level of the skill.

Bacterial meningitis provides a useful model for investigating such hypotheses, occurring as it does in early childhood, during a period of rapid cerebral and cognitive development. As many children present with the illness in infancy and early childhood, it may be difficult to detect deficits in emerging skills immediately following recovery. Thus it is important to follow children over time to monitor ongoing development and mastery of new skills.

The aim of the present study was to investigate the long-term sequelae of bacterial meningitis, minimizing the methodological problems inherent in previous research. The prospective study employed a large sample of consecutive admissions for bacterial meningitis, standardized treatment protocols, including thorough documentation of medical and demographic variables during admission. Inclusion of a control group matched for school grade level and gender enabled comparisons between the groups with respect to cognitive abilities, after adjusting for age, demographic factors and developmental variation. The study evaluated children on average 6.7 years postmeningitis, when all children were attending school, and when subtle deficits, if present, would have been likely to be demonstrating functional consequences. Further, the project aimed to evaluate the relationships between specific risk factors, including age at illness and presence of acute medical complications, and long-term outcome.

METHODS

Sample

Postmeningitic patients

A cohort of all children aged between 3 months and 14 years admitted to the Royal Children's Hospital, Melbourne with bacterial meningitis was established during a 3-year period from October, 1983 to October, 1986. The diagnosis of bacterial meningitis was determined by lumbar puncture and identification of bacteria from cerebrospinal fluid. Children with documented preexisting neurological and developmental deficits, immunodeficiency states, previous central nervous system surgery, or meningitis secondary to cranial trauma or shunt infections were excluded. One hundred and sixty-six children were initially enrolled in the study. Eight children (4.9%) died during the course of their illness.

Between 1991 and 1993, 130 (82%) of the 158 survivors, who had experienced 131 episodes of meningitis, were evaluated. The remaining 28 cases were either unable to be found ($N = 26$), refused to participate ($N = 1$) or had died from unrelated causes ($N = 1$). No statistically significant differences were found between the followup sample and the group lost to followup on any of the demographic or medical measures described below. The postmeningitic sample had a mean age at testing of 8.4 years and mean time since illness of 6.7 years. The median age at illness was 17 months (range 3 months–8.5 years), and 49 children (38%) suffered their illness prior to 12 months of age.

Within the postmeningitic group there were 56 (42.8%) children who experienced one or more acute neurological complications including (1) seizures ($N = 40$, 30.5%), (2) obtundation or coma ($N = 23$, 17.6%), (3) acute hydrocephalus requiring a shunt ($N = 2$, 1.5%), (4) hemiparesis or hypotonia ($N = 12$, 9.2%), (5) cranial nerve palsies ($N = 6$, 4.6%), (6) severe visual loss ($N = 3$, 2.3%), ataxia ($N = 7$, 5.3%) and (7) sensorineural deafness ($N = 8$, 6.1%). Twenty-seven percent ($N = 35$) of children had some form of neurodevelopmental abnormality at the time of discharge.

Control participants

A comparison group ($N = 130$) was also employed in the study. Grade- and sex-matched controls were recruited from each postmeningitic child's classroom by writing to the child's school and asking the class teacher to select the next same sex student on the class roll. Where parents refused permission to approach the school, a control was selected in a similar fashion from a neighbouring school to ensure equivalent socioeconomic background. For postmeningitic children attending a special school for disabled children, controls were recruited from another school in the same region. Children included in the comparison group had no previous history of meningitis.

Table 1 describes the demographic characteristics of the two groups. No important differences between groups were found for age at testing or SES.

Table 1. Demographic characteristics of the sample

	Group	
Variable	Postmeningitic	Control
Number of subjects	130	130
Gender* (number of males)	70	71
Age at testing (years): *M* (*SD*)	8.4 (1.6)	8.7 (1.7)
Socioeconomic status#: *M* (*SD*)	4.1 (1.1)	4.0 (1.0)
Maternal education (% tertiary)	30	31
Language other than English spoken at home (%)	16.2	9.2

*Misassignment of one case for gender. #Daniel, 1983.

Measures

Socioeconomic status (SES)

SES characteristics were measured using two variables: highest level of education attained by the mother and occupational status. Occupational status was then coded using the Daniel's Scale of Occupational Prestige (Daniel, 1983). This scale is continuous with a minimum rating of 1 (*high prestige*) and a maximum rating of 7 (*low prestige*). The higher ranking parental occupation was used. Ethnicity was also noted, with language other than English spoken at home as the marker.

Illness variables

A questionnaire for presenting history, examination findings, laboratory and treatment details and clinical course was completed during hospitalization and at the discharge neurological examination. Several variables were recorded to be investigated as possible risk factors for long-term outcome. These included acute medical complications (i.e., experience of seizures, abnormal neurological signs, coma, duration of symptoms prior to diagnosis) and age at illness (greater than 12 months of age, less than 12 months of age).

Neuropsychological variables

Evaluation of outcome focused on four specific domains: (1) intelligence, (2) academic ability, (3) language skills, and (4) memory. Specific measures employed in the study are listed in Table 2. These areas of functioning were emphasized, in line with research and theoretical understandings of the effects of early cerebral insult on children's development.

Intellectual ability (Wechsler Intelligence Scale for Children–Revised; Wechsler, 1974). Verbal (VIQ), Performance (PIQ), and Full Scale Intellectual Quotients (FSIQ) were calculated. To further investigate cognition, performances on individual subtests were also examined.

Language skills

1) *Token Test for Children (Di Simoni, 1978)*: A measure of language comprehension skills, requiring subjects to follow verbal instructions of increasing complexity. Resultant scores indicate the number of correct responses.

2) *Controlled Oral Word Association Test (COWAT; adapted from Gaddes & Crockett, 1973)*: A measure of verbal fluency for abstract information. Children were asked to generate words beginning with a certain letter in a one minute period. The letters chosen were "F," "A," and "S." Children were given two rules: (1) they could not use words beginning with a capital letter, and (2) they could use each word only once. Total number of words generated over the three letter trials was recorded.

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Table 2. Neuropsychological assessment measures

Ability domain	Test	Variables
Intellectual ability	Wechsler Intelligence Scale for Children–Revised (WISC–R)	VIQ, PIQ, FIQ, Subtest scaled scores
Language function	Token Test for Children	Total number of items correct
	Controlled Oral Word Association Test (COWAT)	Total number of words generated
Memory and learning	Digits Forward	Number of digits forward
	Block Span	Number of blocks forward
	Rey Auditory–Verbal Learning Test (RAVLT)	Total number of words recalled (T1–T5)
	Story Recall	Number of items recalled
	Complex Figure of Rey, recall	Recall score
Reading ability	Neale Analysis of Reading Ability–Revised	Reading Accuracy (%)
		Reading Comprehension (%)
		Reading Rate (%)

Memory function

1) *Digits Forward (Wechsler, 1974)*: A test of short-term memory for auditory-verbal material, where children were required to repeat strings of digits of increasing length. At each difficulty level (commencing with three digits) two digit strings were presented. The resultant score (DS) indicated the maximum number of digits repeated correctly.

2) *Block Span (Milner, 1971)*: A test of short-term visual memory, involving presentation of an array of nine identical blocks, where children were required to tap a sequence of blocks of increasing length as demonstrated by the examiner. At each difficulty level (commencing with three blocks) two different sequences were presented. The score achieved (BS) reflected the maximum number of blocks tapped correctly.

3) *Rey Auditory–Verbal Learning Test (RAVLT; Rey, 1964)*: A measure of verbal learning ability. Form 1 of the test was administered according to the format described by Spreen and Strauss (1991). Total number of words recalled over five trials was recorded.

4) *Story Recall (modified from Luria's Neuropsychological Battery; Christensen, 1979)*: A measure of short-term retention of meaningful verbal material. Two stories, describing episodes relevant to a school-aged population, were read to the children who were then required to retell the stories in their own words. Each story was divided into 22 chunks, with recall of each chunk scored as 1 point. Half-points were awarded where only part of a chunk was recalled. Recall scores were obtained for each story, and a total recall score was also computed.

5) *Complex Figure of Rey, recall (CFR; Rey, 1941)*: Children were asked to draw, from memory, the Complex Figure of Rey which they had copied approximately 3 min before. A recall score was obtained, based on the accuracy of the child's production. Scoring was as described by Spreen and Strauss (1991).

Reading ability (Neale Analysis of Reading Ability–Revised; Neale, 1988). This test requires children to read aloud a series of stories, of increasing complexity, and then answer questions regarding story content. Measures derived include Reading Accuracy, Comprehension, and Rate, expressed as percentile scores.

Procedure

Children in the postmeningitic group were initially enrolled in the study once a diagnosis of bacterial meningitis had been established. These children were then recontacted with an invitation to participate in the present project. Neuropsychological assessment took place over two 1-hr sessions. The Wechsler Intelligence Scale for Children–Revised (WISC–R) was administered during the first session, with the remainder of the tasks administered in set order during the second session. All children participated in neuropsychological evaluation. However, 2 postmeningitic children were unable to complete testing due to disability, and a 3rd child was only able to complete nonverbal tasks. In each of these cases a best estimate of their scores was made. For the WISC–R, each child was assigned IQ scores of 50. On the Neale Analysis of Reading Ability, 15 postmeningitic and 5 controls scored lower than the minimum scores recorded in the test manual for their age. Each child was assigned a percentile score of 1 point less than the lowest rank for that age. A score of 2 standard deviations below the mean for age was used for all other tests.

Data Analysis

Multivariate analysis of covariance (MANCOVA), using the SAS GLM procedure, was employed to investigate differences between and within groups. These analyses were executed for a number of cognitive domains including IQ (WISC–R: Verbal Scale subtests; Performance Scale subtests), reading ability, language, short-term memory, and

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learning. All analyses included gender, age at testing, mother's level of education, parental level of occupation and ethnicity as covariates. Structural equation modeling (LISREL) was conducted to investigate the theoretical model that history of meningitis is related to poor linguistic skills which in turn impact upon language-based educational abilities.

RESULTS

Between-Group Differences

Intellectual ability

Group means and standard errors for IQs and individual subtests are presented in Table 3. For all measures of intellectual ability, postmeningitic children achieved scores within the *average* range (as described by Wechsler, 1974), and close to the test mean of 100. However, mean intellectual quotients were significantly below those of the healthy control group [$F(2,252) = 5.53$, $p < .005$]. Univariate F tests indicated this was true for both Verbal IQ [$F(1,259) = 8.66$, $p < .005$] and Performance IQ [$F(1,259) = 7.95$, $p < .005$]. Further, 12 postmeningitic children had *borderline* IQs (< 80), compared to only 1 control (OR, 12.0; CI, 1.6, 91.0; $\chi^2(6) = 9.8$, $p = .002$), and because of intellectual disability, 7 postmeningitic children were attending special classes.

The individual subtests of the WISC–R were then examined using two separate MANOVAs for Verbal and Performance subtests, with no overall differences detected. However, univariate F tests did detect significant differences for the following subtests: Information [$F(1,256) = 6.32$, $p < .05$], Vocabulary [$F(1,256) = 5.77$, $p < .05$], Comprehension [$F(1,256) = 3.94$, $p < .05$], Picture Arrangement [$F(1,256) = 3.07$, $p < .01$], and Block Design [$F(1,256) = 4.15$, $p < .05$], with the postmeningitic group recording consistently poorer scores.

Table 3. Comparison of WISC–R results for postmeningitic and control groups

	Postmeningitic (N = 130)		Controls (N = 130)	
Scale	M	(SE)	M	(SE)
Verbal IQ**	97.0	(1.5)	101.6	(1.6)
Performance IQ**	100.7	(1.5)	105.5	(1.7)
Full Scale IQ**	98.7	(1.4)	104.4	(1.5)
Information$^+$	10.3	(0.3)	11.2	(0.3)
Similarities	10.0	(0.4)	10.7	(0.4)
Arithmetic	10.3	(0.3)	10.9	(0.3)
Vocabulary$^+$	9.4	(0.3)	10.2	(0.3)
Comprehension$^+$	8.9	(0.3)	9.5	(0.3)
Digit Span	9.6	(0.3)	9.9	(0.3)
Picture Completion	9.2	(0.3)	9.6	(0.3)
Picture Arrangement*	9.8	(0.3)	10.8	(0.4)
Block Design$^+$	11.3	(0.3)	12.0	(0.4)
Object Assembly	10.7	(0.3)	10.9	(0.4)
Coding	10.1	(0.3)	10.6	(0.3)
Mazes	10.5	(0.3)	11.0	(0.4)

$^+p < .05$, $^*p < .01$, $^{**}p < .001$.

Language and learning skills

The postmeningitic group also performed consistently more poorly on language tests [$F(3,251) = 4.00$, $p < .005$]. Mean scores and standard errors for each of these measures are shown in Table 4. The Token Test [$F(1,259) = 3.98$, $p < .05$], COWAT [$F(1,259) = 3.98$, $p < .05$], and Story Recall tests [Story A: $F(1,259) = 12.84$, $p < .001$; Story B: $F(1,259) = 9.77$, $p < .005$] were all performed more poorly by the postmeningitic group. Measures of new learning skills were also reduced [RAVLT: $F(1,256) = 5.77$, $p < .05$; CFR recall: $F(1,259) = 6.58$, $p < .01$]. In contrast, there were no significant differences between the groups for tests tapping short-term recall (Digit Span, Block Span).

Academic achievement

Multivariate analysis of variance also detected significant differences between the two groups on reading measures [$F(3,251) = 4.10$, $p < .005$]. Postmeningitic children read more slowly [Rate: $F(1,259) = 6.70$, $p < .01$], were less efficient in decoding text [Accuracy: $F(1,259) = 8.04$, $p < .005$], and had poorer comprehension [Comprehension: $F(1,259) = 11.88$, $p < .001$] than control children. There were 16 cases and 4 controls who were unable to read [OR, 4.0; CI, 1.4, 11.6; $\chi^2(4) = 7.8$, $p = .005$] and a further 28 cases and 17 controls, ages 7 years and older had reading ages assessed at 2 or more years below that expected for their age (OR, 1.9; CI, 0.9, 3.9; $\chi^2(4) = 3.3$, $p = .07$). These findings indicate that children suffering from bacterial meningitis are at risk for developing school-based learning difficulties in comparison to healthy children.

Within-Group Analyses

Analyses were also conducted to determine possible risk factors for poorer outcome in the postmeningitic group. In particular, presence of acute medical complication at the time of illness and age at illness, as previously defined, were evaluated with respect to outcome.

Acute Medical Complications

Children were classified as suffering medical complications during their illness if they experienced seizures, obtundation or coma, hydrocephalus, hemiparesis, persistent hypotonia, cranial nerve palsies, ataxia, or visual or hearing loss. Of the total postmeningitic sample 56 children were categorized as experiencing acute medical complications. The mean scores on neuropsychological measures for the two groups are listed in Table 5.

Statistical analysis of neuropsychological data identified differences between postmeningitic children with and with-

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Table 4. Neuropsychological findings for postmeningitic and control groups

Ability domain	Test	Group: Postmeningitic ($N = 130$) M (SE)	Group: Controls ($N = 130$) M (SE)
Language function	Token Test: Total^{+}	50.6 (0.6)	51.9 (0.7)
	COWAT: Total^{+}	19.4 (0.7)	21.1 (0.8)
Memory and learning	Digits Forward	5.0 (1.1)	5.2 (1.1)
	Block Span^{+}	4.5 (0.1)	4.8 (0.1)
	RAVLT: Total^{+}	36.3 (1.0)	38.6 (1.0)
	Story Recall (A)**	7.4 (0.4)	8.8 (0.4)
	Story Recall (B)*	9.0 (0.5)	10.6 (0.5)
	CFR: Recall*	10.3 (0.7)	12.6 (0.8)
Reading ability	Accuracy (%)*	45.4 (3.1)	55.1 (3.3)
	Comprehension (%)**	45.9 (2.9)	57.0 (3.1)
	Rate (%)*	50.9 (2.9)	59.3 (3.1)

$^{+}p < .05$, $*p < .01$, $**p < .001$.

out complications only for Verbal IQ [$F(1,129) = 4.94$, $p < .05$]. While mean scores for children experiencing complications were consistently lower than those of the no complications group, no other differences were statistically significant.

Age at Illness

To investigate performance differences associated with age at illness, postmeningitic children were divided into children experiencing meningitis before 12 months ($N = 49$), and after 12 months ($N = 81$). These two groups were compared for presence of medical complications (as defined above), to determine any differences in illness severity. Frequency of acute medical complications did not differ for the two age at illness groups [Percentage of children with medical complications: less than 12 months = 45%, older than 12 months = 42%; $\chi^2(3) = .106$, $p = .744$]. Table 6 lists the number of children experiencing specific complications in each group. Only coma differentiated the groups, with younger age at illness associated with higher frequency of coma.

Table 5. Comparison of outcome for children with and without medical complications during meningitis

Ability domain	Measure	Complications ($N = 56$) M (SE)	No complications ($N = 74$) M (SE)
Intellectual ability	VIQ^{+}	94.2 (2.4)	99.9 (2.1)
	PIQ	97.4 (2.6)	101.3 (2.2)
Language function	Token Test: Total	49.2 (1.1)	50.5 (0.9)
	COWAT: Total	18.0 (1.1)	19.0 (1.0)
Memory and learning	Digits Forward	4.8 (1.1)	5.2 (1.2)
	Block Span	4.4 (1.2)	5.0 (0.9)
	RAVLT: Total	37.3 (1.5)	36.2 (1.3)
	Story Recall (A)	7.3 (0.5)	7.4 (0.5)
	Story Recall (B)	8.7 (0.7)	9.4 (0.6)
	CFR: Recall	9.7 (1.1)	10.3 (1.0)
Reading ability	Accuracy (%)	46.0 (4.1)	44.6 (4.1)
	Comprehension (%)	42.9 (4.6)	49.0 (4.0)
	Rate (%)	47.5 (4.6)	51.5 (4.0)

$^{+}p < .05$.

Table 6. Illness characteristics of postmeningitic children divided according to age at illness

	Age at illness		
Medical complications	<12 months ($N = 49$)	>12 months ($N = 81$)	*p* value
Abnormal neurological signs	13	15	.28
Seizures	18	22	.25
Obtundation or coma	14	9	.01

In this study, age at illness is confounded with age at testing; that is, younger postmeningitic children tend to be those who had meningitis before 12 months of age. To disentangle these two variables, and address the hypothesis that those experiencing meningitis prior to 12 months perform more poorly than expected for age, and less well than children suffering meningitis after 12 months of age, we compared children experiencing meningitis before and after 12 months of age with age-matched controls, and looked at the Group (postmeningitic *vs.* control) × Age (younger *vs.* older) interaction.

The impact of age at illness was then investigated for summary neuropsychological variables (see Table 7). Multivariate analysis of variance identified a significant effect of group [$F(1,259) = 14.75, p < .001$] and a significant Group × Age interaction for VIQ [$F(1,259) = 13.80, p < .001$]. Thus, younger postmeningitic children scored significantly more poorly than age-matched controls and older postmeningitic children. For PIQ, significant main effects for group [$F(1,259) = 10.17, p < .001$] and age [$F(1,259) = 5.31, p < .05$] were identified.

Age at illness was also associated with linguistic and memory performances. On the Token Test there was a main effect for group [$F(1,259) = 10.15, p < .01$] and age [$F(1,259) = 42.11, p < .001$], and a significant interaction effect [$F(1,259) = 4.84, p < .05$]. On other linguistic measures significant main effects were also identified [COWAT, group: $F(1,259) = 9.13, p < .01$; age: $F(1,259) = 43.41, p < .001$; Story Recall A, group: $F(1,259) = 16.62, p < .001$, age: $F(1,259) = 36.89, p < .001$; Story Recall B, group: $F(1,259) = 15.54, p < .001$; age: $F(1,259) = 41.30, p < .001$]. For measures of short-term memory there was a significant effect of age [Digits Forward: $F(1,259) = 12.42, p < .001$; Block Span: $F(1,259) = 117.31, p < .001$], but no group or interaction effect. For verbal learning, using total words recalled on the five trials of the RAVLT, significant effects of group [$F(1,259) = 6.77, p < .01$] and age [$F(1,259) = 45.01, p < .001$] were found. Significant main effects were also identified for recall of the CFR [group: $F(1,259) = 9.54, p < .001$; age: $F(1,259) = 36.40, p < .001$].

On reading tasks, significant main effects were found for rate [group: $F(1,259) = 3.84, p < .05$; age: $F(1,259) = 5.11, p < .05$] and accuracy [group: $F(1,259) = 7.84, p < .01$; age: $F(1,259) = 9.40, p < .01$]. For reading comprehension skills there was a main effect of group [$F(1,259) = 16.2, p < .001$] and a significant Group × Age interaction [$F(1,259) = 5.43, p < .05$]. In each instance, the postmeningitic children suffering their illness before 12 months of age achieved poorest results.

Table 7. Age at illness and neuropsychological performance following bacterial meningitis in childhood

		Age at illness			
Ability domain	Measure	<12 months ($N = 49$) *M* (*SE*)	Matched controls ($N = 49$) *M* (*SE*	>12 months ($N = 81$) *M* (*SE*)	Matched controls ($N = 81$) *M* (*SE*)
Intellectual ability	VIQ$^{(a^{**}, c^{**})}$	92.8 (2.7)	106.3 (1.9)	99.5 (1.4)	100.4 (1.5)
	PIQ$^{(a^{**})}$	97.7 (2.6)	105.7 (1.6)	103.1 (1.6)	107.5 (1.4)
Language function	Tokens Test: Total$^{(a^{*}, b^{**}, c^{+})}$	46.6 (1.2)	50.8 (0.7)	53.0 (0.6)	53.9 (0.5)
	COWAT: Total$^{(a^{*}, b^{**})}$	13.2 (1.0)	17.1 (1.0)	20.5 (0.8)	22.1 (0.9)
Memory and learning	Digits Forward$^{(b^{**})}$	4.5 (0.9)	4.9 (1.0)	5.3 (1.2)	5.3 (1.2)
	Block Span$^{(a,^{*} b^{**}, c^{*})}$	4.0 (1.2)	4.6 (0.6)	4.8 (0.8)	4.9 (0.7)
	Story Recall (A)$^{(a^{**}, b^{**})}$	5.9 (0.5)	7.6 (0.5)	8.3 (0.4)	10.2 (0.3)
	Story Recall (B)$^{(a^{**}, b^{**})}$	5.9 (0.6)	9.0 (0.7)	10.1 (0.6)	12.0 (0.5)
	RAVLT: Total$^{(a^{*}, b^{**})}$	29.6 (1.5)	34.0 (1.1)	38.5 (1.1)	40.9 (1.1)
	CFR: Recall$^{(a^{*}, b^{+})}$	7.4 (1.0)	10.8 (1.0)	12.9 (0.8)	16.0 (0.8)
Reading ability	Accuracy (%)$^{(a^{*}, b^{*})}$	33.6 (4.4)	51.1 (4.0)	48.4 (3.1)	56.9 (3.3)
	Comprehension (%)$^{(a^{**})}$	38.0 (4.3)	60.5 (3.6)	49.1 (3.0)	55.6 (2.9)
	Rate (%)$^{(a^{+}, b^{+})}$	43.7 (4.4)	55.9 (3.8)	52.4 (2.8)	61.7 (3.0)

$^{+}p < .05$, $^{*}p < .01$, $^{**}p < .001$; a = Group, b = Age; c = Group × Age interaction.

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On the basis of these age-related performance differences, further investigation of the relationships between language, learning, and reading abilities was undertaken. Specifically, the theoretical position that deficits in language skills, which are hypothesized to be in a rapid state of development at the time most children suffer from meningitis, may be associated with the differences in educational abilities identified between the postmeningitic and control groups. An alternative hypothesis was that either learning skills alone, or learning skills in combination with language skills, may predict educational performance. To evaluate these predictions structural equation modeling techniques (LISREL) were employed.

This model proposed that meningitis has a significant effect on language skills, as does the child's age at testing and their SES, and that language skills are closely related to reading abilities. The model used single indicators for meningitis status and child's age at testing, with the assumption of a zero error component for these two measures. Two indicators of socioeconomic status were employed: maternal education, and parental occupation. Linguistic ability was indicated by performance on the Token Test for Children and the COWAT. Raw scores for Reading Accuracy and Reading Comprehension were used as indicators of reading ability.

The model, as illustrated in Figure 1, was found to fit the data well [$\chi^2(18) = 19.34$, $p = .37$]. The adjusted goodness of fit was .983 and the root mean square residual was .058. Meningitis had a small but statistically significant effect on language skills. As would be expected the affects of SES and age at testing on language skills were larger than the effect of meningitis, as is evidenced by the path coefficients included in Figure 1.

Two other models were also investigated. The first utilized a similar structure to that depicted in Figure 1, but substituted learning (RAVLT, Story Recall) for language skills, with the hypothesis that meningitis would effect learning ability, which would in turn reduce acquisition of educational skills such as reading. This model did not fit the data well [$\chi^2(25) = 116.9$, $p < .001$]. Similarly, data did not fit a model where learning and linguistic abilities were combined as predictors of reading ability [$\chi^2(38) = 63.7$, $p = .006$]. These results provide initial support for the hypothesis that meningitis in early childhood has a significant impact on language skills, which in turn impacts on the acquisition of new skills such as reading ability.

DISCUSSION

The aim of the present study was to investigate neuropsychological sequelae of meningitis in a school-aged population, and to identify the significance of acute medical

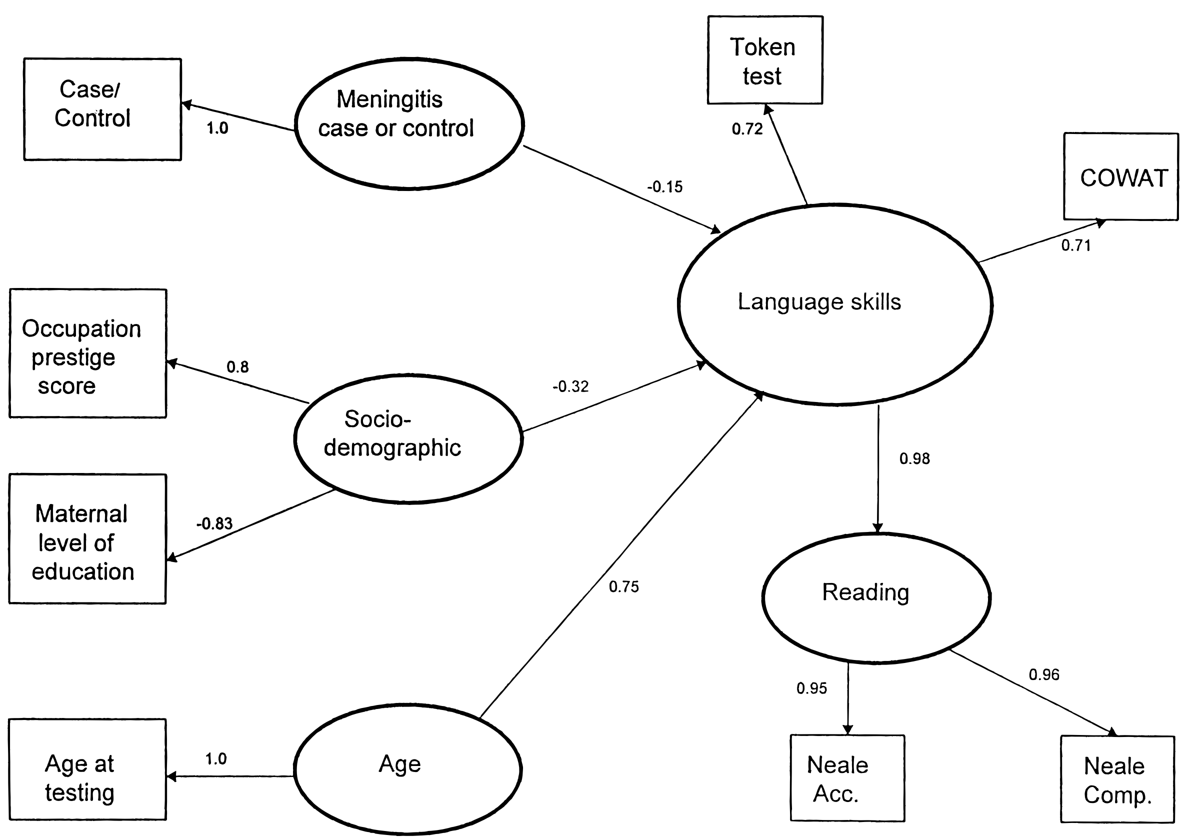

Fig. 1. Model for the relations among meningitis, language, and reading skills.

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complications and age at illness for long-term outcome. The study employed a prospective, longitudinal design and compared postmeningitic children with grade- and sex-matched controls in a number of cognitive domains including intelligence, linguistic ability, reading skills, and learning ability. Possible confounding effects of psychosocial factors, such as geographic region, parental education and occupation, and ethnicity were controlled by sampling and statistical procedures.

Results suggest that, even 6 years after their illness, children who suffer bacterial meningitis have less favorable outcomes when compared to grade- and sex-matched controls. Postmeningitic children achieved significantly lower intellectual quotients than controls, with the pattern of results suggesting greatest impairment in verbal skills and organizational capacity. Language skills, including comprehension of instructions, and verbal fluency were reduced and, while postmeningitic children showed a capacity for short-term recall of simple material, they performed more poorly when required to retain complex material, suggesting evidence for deficit/delay in the acquisition of executive abilities, indicating the effect of complexity and overload on performance. However, while postmeningitic children perform more poorly than controls in all cognitive domains, the degree of the group differences is mild to moderate, with children's performances generally within the average range.

Functional outcome measures, addressing school-based learning skills, also identified deficits for the postmeningitic children, consistent with previous research (Kresky et al., 1962; Sell et al., 1972a; Taylor et al., 1990). On measures of reading rate, accuracy, and comprehension, children with a history of meningitis performed consistently more poorly. Postmeningitic children were 4 times more likely than controls to be unable to read at all, and almost twice as likely to achieve reading ages 2 years or more below chronological age. Thus children with a history of bacterial meningitis have an increased risk for developing reading difficulties. However, as many children were assessed in the early primary school years where such skills may be developing rapidly, it is unclear whether the documented difference between the groups reflects a fixed deficit or a delay in the acquisition of educational skills.

These results support the findings of early studies (Sproles et al., 1969; Wright & Jimmerson, 1971; Sell et al., 1972b), and contradict more recent reports (Klein et al., 1986; Taylor et al., 1990). In particular, a seminal study by Taylor et al. (1990) has suggested that children surviving meningitis have a mainly favorable outcome. They failed to identify significant differences between postmeningitic children and sibling controls on intellectual and neuropsychological measures, and found only small differences on educational measures. Further evaluation of the results reported by Taylor et al. (1990) suggests a similar pattern in the two studies, with the Taylor et al. sample showing a trend for postmeningitic children to exhibit slightly lower scores on all measures, but with differences not reaching statistical significance. Interestingly, the two studies have employed similar designs including large samples, adequate control groups with participants enrolled during similar time periods, and equivalent test procedures.

There were, however, some methodological differences that may help explain the discrepant results. First, Taylor et al. (1990) used a retrospective design, which may have influenced the representative nature of their sample and the accuracy of medical information used to describe it. It is worthy of note that the mean FSIQ score for the Taylor et al. study was higher than the test mean (sibling controls: FSIQ = 110; postmeningitic sample: FSIQ = 108), even taking into account a possible inflation of test scores over time. In contrast, scores for the present study were closer to test expectations (controls: FSIQ = 104; postmeningitic sample: FSIQ = 99). This difference may reflect a sample bias, with higher SES, high-functioning families agreeing to participate, thus inflating the overall scores.

In addition, their study employed sibling controls, who were on average 2 years older, and perhaps adversely affected by the presence of a child with an earlier life-threatening illness within the family. Treatment of missing data also varied for the studies, with Taylor et al. (1990) excluding test scores for children unable to complete tests. While this is an important procedural discrepancy, our results remain significant if these children are excluded. Finally, while the age range of the samples are similar, mean age is slightly older for the Taylor et al. study (9.6 *vs*. 8.4 years). If postmeningitic children were experiencing a developmental delay, rather than a fixed deficit, it could be that an older sample would present with fewer deficits. As the effects reported are generally small, these methodological differences may account for the discrepancies between the two studies. Regardless, it is evident that further research, preferably longitudinal in design, is necessary before it is determined that children who survive meningitis without any neurological deficits have a favorable prognosis.

Acute Medical Complications and Neuropsychological Outcome

Within the postmeningitic group, although a disease severity response was observed for most neuropsychological measures, this only reached statistical significance for VIQ, with children experiencing acute neurological complications exhibiting poorer scores. When data from all enrolled children, including those who died from their illness, were analyzed using neurological, audiological, neuropsychological and behavioral summary measures as endpoints, medical complications were more clearly associated with adverse outcome (Grimwood et al., 1995).

Age at Illness and Neuropsychological Outcome

In contrast, early age at illness was identified as a significant risk factor, with children suffering meningitis before

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age 12 months performing more poorly than children suffering meningitis later in infancy and childhood, and age-matched controls, on measures of language and reading skills. While it was found that these younger children were more likely to experience a period of coma associated with their illness, the small disadvantage with respect to acute neurological complications is not sufficient to explain the more substantial deficits associated with age at illness. Age at illness was also found to be an independent risk factor for other adverse outcomes from meningitis (Grimwood & Keir, 1996). Thus our data would support an early vulnerability model, rather than arguing for functional plasticity of the immature CNS. Interestingly this is in keeping with studies which identify neonatal meningitis as particularly detrimental to later outcome (Baraff et al., 1993).

Within this context, the importance of language development is of particular interest. The postmeningitic group as a whole exhibited poor performances on language-based tasks, with children suffering the disease before age 12 months achieving lower VIQ, and performing more poorly on language and reading measures, and on complex learning tasks. While language deficits following bacterial meningitis in childhood have been previously reported they are generally attributed to auditory impairments commonly associated with bacterial meningitis (Lieberth, 1985; Lutsar et al., 1995). However, the presence of severe auditory impairment in a subset of the sample is insufficient to explain the current data. No overall differences were detected between post-meningitic individuals and controls for auditory acuity, impedance, or auditory span. However, the ability of the postmeningitic group to discriminate speech in a noisy environment was poorer than expected, possibly reflecting a central auditory processing difficulty that may interfere with language acquisition and the development of reading skills within a noisy classroom environment.

The present results may be interpreted using both developmental psychology and neuropsychological paradigms. The importance of language in this group may be associated, not simply with localized cerebral pathology or specific auditory deficits, but also with the developmental stage at which the disease occurs. For example, it is well documented that during the first 12 months of life, language is in a critical period of development, with skills only just beginning to emerge (Gardner, 1979; Gleason, 1985). The experience of a disease such as bacterial meningitis may serve to interrupt this development, thus leading to a delay, or possibly a deficit in ongoing development. Therefore the present results may represent an interaction between level of skill development (i.e., critical period) and time of illness. The greater magnitude of language deficits in children experiencing meningitis at an earlier age provides initial support for such a suggestion.

In contrast to impairments in verbal skills, age at illness was not associated with poorer nonverbal abilities or short-term memory capacity. These results appear contrary to previous research describing deficits in nonverbal abilities and/or information processing deficits following early brain insult or disease (Rourke, 1989). However, while this contradictory evidence relates to preschool children, their samples were generally older at time of insult, usually in the 2- to 5-year range, perhaps reflecting a later critical period for development of nonverbal and information-processing skills.

An alternative or parallel explanation may encompass the strategic and organizational difficulties exhibited by the post-meningitic sample as well as their language deficits. It may be that the generalized CNS disturbance associated with the acute phase of bacterial meningitis disrupts ongoing cerebral maturation. In particular, frontal lobe development and myelination are critical in the first few years of life. Interruption of this process has been related to neuropsychological deficits, including slowed information processing and poor development of executive functioning (Ewing-Cobbs et al., 1989; Kriel et al., 1989; Rourke, 1989; Wrightson et al., 1995; Anderson & Moore, 1995). Such difficulties may not be detectable in the preschool years, only becoming evident as the child is required to think and reason independently.

Future research needs to employ a developmental approach when determining children at risk for neuropsychological sequelae following childhood brain disease or insult. Several factors, including age at illness, skills in a critical stage of development, presence of medical complications, and psychosocial factors all may have implications for ongoing development.

CONCLUSIONS

This study has found that, while meningitis survivors achieve scores within the average range on measures of intelligence, linguistic ability, and learning capacity, these scores are consistently below those of control children. While the magnitude of these findings may be modest, greater deficits in functional skills, such as educational competence, may indicate the significance of even mild-to-moderate deficits. Further, within the postmeningitic group, children who had meningitis before age 12 months exhibited greater deficits than older children or controls. These results emphasize the importance of ongoing review following bacterial meningitis, with the aim being early identification and intervention of neuropsychological problems that may become evident only as the child reaches school age.

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