Cognitive and Executive Function 12 Years after Childhood Bacterial Meningitis: Effect of Acute Neurologic Complications and Age of Onset

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Objectives This study investigated long-term neurobehavioral outcome from childhood bacterial meningitis, with particular focus on the influence of acute neurologic complications and age at illness. Methods This prospective, longitudinal study compared survivors of childhood bacterial meningitis (n = 109) with grade- and gender-matched controls (n = 96) selected from the target children’s schools 12 years post-illness, in order to identify residual deficits in intellectual, academic, and executive ability. Results Results showed that at 12 years post-illness, children with a history of meningitis were at greater risk of impairment in each of these domains. However, development was shown to keep pace with that exhibited by healthy controls, suggesting no deterioration in function with time since illness. While prediagnosis symptom duration and acute neurologic complications were not predictors of 12-year outcome, meningitis before 12 months of age was significantly related to poorer performance on tasks requiring language and executive skills. Conclusions These findings suggest that while the overall impact of meningitis may be relatively general and mild, younger age at illness is predictive of neurobehavioral outcome. There was no evidence of progressive deterioration postmeningitis, with comparison of results from 7 to 12 years post-illness demonstrating significant “catch-up” in aspects of executive function.

Key words childhood meningitis; executive function; cognitive ability.

Bacterial meningitis is a severe and potentially life-threatening illness most commonly affecting infants and young children (Davies & Rudd, 1994; Feigin & Pearlman, 1998). Before antibiotics, survival rates were less than 10%. Antibiotic treatments, combined with improved critical care management, have led to a dramatic increase in these survival rates. More recently, Haemophilus influenzae type b (Hib) meningitis immunizations have virtually eliminated this pathogen from North America, northern Europe, Australia, and New Zealand (Peltola, Kilpi, & Anttila, 1992; Robbins, Schneerson, Anderson, & Smith, 1996). The recent licensing of a conjugated pneumococcal vaccine may have a similar impact upon the numbers of children with pneumococcal meningitis (Whitney, 2002). Nevertheless, recurring epidemics of meningococcal disease, antibiotic resistance, and failure of vaccines to reach many developing countries means that bacterial meningitis remains a serious world health issue (Booy & Kroll, 1998; Schuchat, Robinson, & Wenger, 1997).

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Bacterial meningitis results from invasion of the central nervous system (CNS) by bacteria which overcome the host defense mechanisms, causing disruption to cerebrovascular and cerebrospinal fluid dynamics. By the time of diagnosis, cerebral vasculitis may be developing, associated with vascular occlusion, cranial nerve inflammation, and hypoxic injury from regional alterations of cerebral perfusion. Biochemical changes also occur, and can result in focal and diffuse cortical insults (Dodge & Schwartz, 1965). Decreased concentration of glucose in cerebrospinal fluid (in association with cerebrovascular disruption), cellular electrolyte imbalance, and inappropriate secretion of antidiuretic hormone accompany meningitis and have been documented as risk factors for residual impairments (Feigin & Pearlman, 1998; Taylor et al., 1990). Morbidity and mortality result from compression and herniation of cerebral tissue or focal ischemia, caused by altered cerebral blood flow (Anderson et al., 1997; Herson & Todd, 1977; Klein, Feigin, & McCracken, 1986; Snyder, Stovring, Cushing, Davis, & Hardy, 1981; Stovring & Snyder, 1980).

Cerebral pathology and clinical symptoms are mostly transient and subside within weeks for most children surviving meningitis (Feigin & Pearlman, 1998; Vienny et al., 1984). However, for some the impact of these disruptions is fatal or leads to severe residual impairment, including sensorineural hearing loss and other cranial nerve dysfunction, seizure disorders, hemiplegia, ataxia, hydrocephalus, and visual problems (Claesson, Trollfors, Jodol, & Rosenhall, 1984; Dodge et al., 1984; Feldman et al., 1982; Jadavji, Biggar, Gold, & Prober, 1986; Klein et al., 1986; Stovring & Snyder, 1980; Thomas & Hopkins, 1972). In a meta-analysis involving 19 prospective studies and a total of 1602 children, Baraff, Lee, and Schriger (1993) reported that 4.5% of children died in the acute stages of illness, with 16.4% of survivors displaying at least one major adverse outcome (deafness, intellectual disability, epilepsy, physical impairment).

Neurobehavioral sequelae have been identified in many survivors; however, the reported frequency and nature of deficits varies across studies. Some early researchers documented pervasive impairments in cognitive functions and academic achievement in postmeningitis subjects (Kresky, Buchbinder, & Greenberg, 1962; Sell, Merrill, Doyne, & Zimsky, 1972; Sell, Webb, Pate, & Doyne, 1972; Spores, Azerrad, Williamson, & Merrill, 1969). Other, more recent reports document a favorable disease prognosis, possibly reflecting improvements in medical care in later studies, or more representative sampling techniques (Feldman & Michaels, 1988; Fellick et al., 2001; Taylor et al., 1990). Subtle deficits in visuomotor coordination, auditory perception, and language functions are also reported. Our own study (Anderson et al., 1997) showed that, 7 years post-illness, survivors performed more poorly than peers with respect to intellectual functions, particularly verbal ability, motor skills, and educational progress.

Deficits in executive skills, including attentional control, planning, and reasoning, have rarely been assessed, with such skills argued to be immature and difficult to access in young children (Anderson, 1998). Recent research suggests that executive impairments may be common following early brain insult, due to their developing status and the immature state of associated brain regions (Dennis, Barnes, Donnelly, Wilkinson, & Humphreys, 1996; Levin et al., 1991) at time of illness. Such impairments often escape detection in early childhood, becoming apparent only when children are older and are required to think and reason independently (Grimwood, Anderson, Anderson, Tan, & Nolan, 2000). The critical importance of these executive skills for normal development, and their potential vulnerability during infancy and early childhood (Anderson & Taylor, 1999; Anderson, Northam, Hendy, & Wrennall, 2001), suggests they should be carefully evaluated in meningitis survivors.

Few studies have addressed specific risk factors or long-term consequences of childhood bacterial meningitis. Taylor and colleagues (1990) followed 97 Hib meningitis survivors and found that acute neurologic complications were predictive of poorer school performance and increased behavioral disturbance. Similar results have been suggested by other researchers (Grimwood et al., 1995; Emmett, Jeffery, Chandler, & Dugdale, 1980), indicating that the more severe the brain insult, the greater the impact on cognition and behavior.

Age at illness has also been proposed as a predictor of outcome. Bacterial meningitis provides a unique opportunity to study the effects of early neurologic insults in children who are neurologically normal prior to disease onset. Follow-up of disease survivors allows researchers to test hypotheses regarding neural plasticity, to study the relative contributions of biologic and environmental influences on outcomes, and to explore the significance of transient neurologic abnormalities for later development. Recent research has emphasized the
vulnerability of the immature CNS to generalized insult, such as cerebral infection, with a number of studies reporting substantial and permanent deficits in neurobehavioral function following such events (Anderson & Moore, 1995; Ewing-Cobbs, Miner, Fletcher, & Levin, 1989). Further, Bedford et al. (2001) have recently reported on a questionnaire survey of 1717 children, aged 5 years, who had suffered meningitis in infancy. They demonstrated a 10-fold increase in risk for severe or moderate disabilities at age 5, compared with children from a healthy control group. Disabilities extended across health, developmental, and behavioral domains, but with greatest deficits in neuromotor function, memory, and learning. They noted that most severe impairment was observed where illness occurred in the first month of life.

Previously, our group (Anderson et al., 1997; Grimwood et al., 1995, 1996) reported a prospective, 7-year follow-up study of 130 school-aged survivors (mean age = 8.4 years) and age-matched controls. Delays in diagnosis, acute neurologic complications, and illness before age 12 months were identified as risks contributing to poorer outcome. Results showed that children with a history of bacterial meningitis, while generally achieving results within the normal range, performed more poorly than age-matched controls in a number of domains including general intelligence, academic ability, memory, and language. While there was a suggestion of impaired higher-order cognitive skills, the age of the cohort at time of assessment precluded detailed assessment of these skills.

The present study aimed to reevaluate this cohort 12 years postmeningitis, with the assumption that cognitive and cerebral development would be largely complete by this age. We were interested in determining the presence and nature of any persisting deficits which would reflect permanent impairment or, alternatively, delayed skill acquisition and the role of acute neurologic complications and age at illness on outcome. Further, the older age of the cohort enabled additional testing of executive skills, including attentional control, goal setting, and concept formation/abstraction. We predicted that children with meningitis would exhibit deficits in these skills, with impairments being greater when risk factors of early illness and neurologic complications were present. Finally, we hypothesized that since the previous evaluation, executive functions would have demonstrated slower development in meningitis survivors than in healthy controls.

Method
Participants

A prospective cohort of all children aged between 3 months and 14 years admitted to the Royal Children’s Hospital (RCH), 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. All children received a standardized treatment protocol, including penicillin and chloramphenicol until the pathogen was identified, whereupon a single antibiotic was administered according to susceptibility testing. Fluid restriction was enforced for the first 24–48 hours postadmission. Steroids were not routinely administered.

One hundred and eighty-one children were initially enrolled in the study. Children with documented preexisting neurologic and developmental deficits, immunodeficiency states, previous CNS surgery, or meningitis secondary to cranial trauma or shunt infections (n = 15) were later excluded. Eight children died during the course of their illness, leaving a sample of 158 survivors. The median age at illness was 18 months (range = 3 months to 14 years), and 60 children (38%) suffered their illness before 12 months of age.

A 7-year follow-up assessment was conducted between 1991 and 1993, and 130 (82%) of the original 158 survivors were evaluated. The remaining 28 cases were unable to be found (n = 26), refused to participate (n = 1), or had died from unrelated causes (n = 1). A comparison group (n = 130) was also introduced into the study at this time point. Grade- and sex-matched controls were recruited from the classroom of each child with meningitis by selecting the next same-sex student on the class roll. Where parents refused permission to approach the school (n = 1), a control was selected in a similar fashion from a neighboring school to ensure equivalent socioeconomic background. For meningitis survivors attending special schools for disabled children (n = 7), controls were recruited from another school in the same region. Children included in the comparison group had no previous history of meningitis. Results from this follow-up have been previously reported (Anderson et al., 1997; Grimwood et al., 1995, 1996).

During 1996 and 1997 children who had participated in the 7-year follow-up study were again approached to participate in the present study. At this 12-year review, 109 children postmeningitis (84% of the 7-year study, 69% of the original cohort) were
reassessed, at a mean of 11.5 (SD = 0.9) years post-illness. Of the remainder, 9 had moved out of state, 11 were unable to be contacted, and 1 declined to participate. For controls, 96 (74%) were reevaluated, with 5 having moved, 24 unable to be contacted, and 5 declining to participate. The age range of the follow-up sample was 10–18 years (M = 12.7, SD = 1.6). The demographic and clinical characteristics of the sample are provided in Tables 1 and 2.

No statistically significant differences were found between the follow-up sample and the group lost to follow-up on any of the demographic variables, medical measures, or full-scale IQ.

**Measures**

**Socioeconomic Status (SES)**

SES characteristics at the time of assessment were measured using two variables: highest level of education attained by the mother and occupational status. Occupational status was coded using the Daniel 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 highest-ranking parental occupation was used. Ethnicity was also noted, with language other than English spoken at home as the marker.

**Illness Variables**

A prospective questionnaire for presenting history, examination findings, laboratory and treatment details, and clinical course was completed during hospitalization and at the discharge neurologic examination. Several neurologic variables were investigated as possible risk factors for long-term outcome. These were based on findings from previous research (Grimwood et al., 1996; Herson & Todd, 1977) and included seizures, obtundation or coma, hydrocephalus, hemiparesis, persistent hypotonia, visual loss, ataxia, and sensorineural deafness. Age at illness was dichotomized (≤ 12, > 12 months of age), in accordance with literature suggesting a period of brain plasticity within the first 12 months of life (Dennis, 1980; Kolb, Gibb, & Gorny, 2000; Woods & Carey, 1979).

**Severity Index**

A severity rating system (Pentland, Anderson, & Wrennall, 2000) was developed and a score was derived for each child in the meningitis sample, following similar guidelines to those employed by Herson and Todd (1977). The rating score was determined from the standardized treatment and recovery protocols employed during each child’s hospital admission. A weighted value was assigned to each acute complication, which Grimwood et al. (1996) had identified as being associated with adverse outcome, based on the strength of predictive power. The overall severity rating represented the sum of these weighted scores. This scoring procedure is shown in Table 3.

**General Performance Variables**

Intellectual and academic measures were administered to provide a detailed description of the cognitive functioning of the sample. Wechsler Intelligence Scale for Children–III (WISC-III; Wechsler, 1992) was administered to all children 16 years and younger. Children aged 17 and 18 years (n = 7) were administered the Wechsler Adult Intelligence Scale–III. The Full Scale Intellectual Quotient (FSIQ) was used to measure general intelligence, while three index scores (verbal comprehension [VC], perceptual...
organization [PO], and freedom from distractibility) were utilized to assess more specific cognitive domains. Each score had a mean of 100 and a standard deviation of 15.

Wide Range Achievement Test–3 (Wilkinson, 1993). This test provides measures of reading (word decoding), spelling, and arithmetic ability. Scores are age standardized with a mean of 100 and a standard deviation of 15.

Executive Function Measures

Measures of executive function were chosen based on the following criteria: (1) adequate normative data for the age group under investigation, (2) appropriateness of the measure to the age group, (3) availability of reliability/validity data, and (4) documentation of the measure to evaluate aspects of executive function under examination.

Attentional Control

- Code Transmission Test (Manly, Robertson, Anderson, & Nimmo-Smith, 1999). This is a measure of auditory sustained attention normed for children 6–16 years. Children listen to a tape recording consisting of a recitation of 360 digits (40 targets) presented at regular intervals. The tasks are to identify when two 5s occur together and to respond with the digit which preceded the two 5s on the tape. Performance measures include the total number of correctly identified targets (Codes–total correct) and number of errors (Codes–total errors).

- Contingency Naming Test (CNT; Anderson, Anderson, Northam, & Taylor, 2000; Taylor et al., 1990). This task taps cognitive flexibility and is normed for children 6–16 years. It includes four subtests, each of increasing difficulty. The child is presented with a card on which are printed three rows of shapes of different colors (pink, blue, or green). Within each “outside” shape, a second, “inside” shape is drawn. Above some of the stimuli, a reverse arrow is drawn. For subtest 1, the child is required to name the color of each stimulus, while for the second subtest the aim is to name the outside shapes. The third and fourth subtests involve a “shift” in attention. For Trial 3, the child is provided with two rules to determine the correct response. If both the inside shape and the outside shape are the same, the child must name the color of the stimulus. If the inside and outside shapes are different, the correct response is the name of the outside shape. On the fourth subtest, the child is instructed to follow the same rules as for Trial 3, except when there is a reverse arrow above the stimulus. Where an arrow is present, the child is directed to reverse the rules from Trial 3 (i.e., where the shapes are the same, the correct response is the shape of the stimulus). Completion times in seconds (CNT-time) and errors (CNT-errors) were recorded.

Goal Setting

- Tower of London (TOL; Shallice, 1982; Anderson, Anderson, & Lajoie, 1996). This nonverbal task measures problem-solving ability. It makes use of three colored balls, which can be placed onto three pegs of different heights. Children are required to match a pattern, presented on a stimulus card, in a prescribed number of moves while adhering to a number of specified rules. There are a total of 12 problems. If a child fails to complete an item correctly, balls are replaced in their original configurations and the child has the opportunity to try again, within a time limit of 60 seconds. Administration and scoring were according to Anderson et al. (1996) and generated the following measures: number of items correct (TOL–trials correct), number of failed attempts (TOL–extra attempts), and total time to completion (TOL–time).

- Complex Figure of Rey (CFR; Rey, 1964). This visually based task assesses planning and organizational abilities. Children are asked to copy a complex geometric design using a series of color pencils, the order of which was noted.

Table III. Severity Rating System

<table>
<thead>
<tr>
<th>Complication</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prediagnosis symptom duration &gt; 24 hours</td>
<td>1</td>
</tr>
<tr>
<td>Focal neurologic signs</td>
<td>1</td>
</tr>
<tr>
<td>Tertiary referral</td>
<td>2</td>
</tr>
<tr>
<td>Failure to return to normal consciousness within 72 hours</td>
<td>2</td>
</tr>
<tr>
<td>Seizures in hospital</td>
<td>3</td>
</tr>
<tr>
<td>Seizures &gt;72 hours after admission</td>
<td>3</td>
</tr>
<tr>
<td>Deterioration of consciousness in hospital</td>
<td>3</td>
</tr>
<tr>
<td>Laboratory parameters</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus pneumoniae</td>
<td>2</td>
</tr>
<tr>
<td>Cerebro spinal fluid leukocytes &lt; 1000/mm³</td>
<td>2</td>
</tr>
<tr>
<td>Serum sodium &lt; 130 mEq/L</td>
<td>2</td>
</tr>
</tbody>
</table>
Accuracy (CFR-accuracy) was scored according to Lezak (1993). An organizational strategy score (CFR-strategy) was derived (Anderson, Anderson, & Garth, 2001) and provided a strategy rating between 1 (unrecognizable) and 7 (excellent organization).

Concept Formation/Abstraction
- The Controlled Oral Word Association Test (COWAT; adapted from Gaddes & Crockett, 1975; Anderson, Lajoie, & Bell, 1995) assesses verbal fluency/concept formation. Children are asked to generate words according to a particular letter category. They are instructed that they have 60 seconds to think of all the words they can beginning with each letter, are not to use words beginning with capital letters (e.g., people's names), and must say different words every time. Three trials are administered (F, A, and S). Number of words generated (COWAT–total words) and errors/rule breaks (COWAT–total errors) were recorded.
- Twenty Questions Test (TQT; Mosher & Hornsby, 1966; Garth, Anderson, & Wrennall, 1997). This task assesses abstract thinking. Children are presented with a sheet of 42 color pictures and are told that the examiner is thinking of one of the pictures. The child must identify the target by asking up to 20 questions which each have a yes or no answer. Each child is given five trials with a different target item for each trial. Questions are categorized as “constraint seeking” (eliminating two or more alternatives), “hypothesis seeking” (referring to a single picture only), or “pseudo-constraint seeking” (similar to a hypothesis-seeking question in that it refers to only one picture, but it is phrased like a constraint-seeking question). Measures included: number of trials solved (TQT–trials solved), proportion of constraint seeking (TQT–constraint seeking), and total time for the five trials (TQT–total time).
- Making Inferences (Wiig & Secord, 1989). This test assesses higher-order receptive language skills. Two statements, segments of a short story, are read aloud by the examiner and printed on a card placed in front of the child. Four options are read to the child, who selects the two options that best explain the story. The test consists of 12 items, for each of which 3 points are awarded when two plausible inferences are identified, 1 point if only one plausible inference is identified. The total score is the sum of the points for the 12 items (Making Inferences–total score).

Procedure
Approval for the study was obtained from the RCH ethics committee, and enrollment in the study was by written parental consent. Children were evaluated from 1996 to 1997. Examiners were blinded to the medical history of the children. In addition to neuropsychologic evaluation, all children underwent physical, neurologic, and audiologic investigation, in fixed order. Assessments were all performed on the same day, with short breaks between sessions to avoid fatigue.

Neuropsychologic assessment took place over three 1-hour sessions. The WISC-III was administered in the first session, with the remainder of the tasks administered in set order during the second and third sessions. Two children in the meningitis group did not complete testing, due to severe intellectual and physical disability. These children did not contribute to the group results for general performance or executive function measures.

Development of intellectual, educational, and executive functions was examined by comparing results from data at the 7-year follow-up (Grimwood et al., 1995) with the current results of FSIQ scores and the two measures common to both protocols, COWAT and CFR.

Data Analysis
Data comparisons were performed using SPSS for Windows, version 11.0.0. (SPSS Inc., Chicago, Illinois). Gender and SES at testing were treated as covariates for all univariate analyses of covariance (ANCOVA) and multivariate analyses of covariance (MANCOVA). Age at testing was also used as a covariate when age-standardized scores were not available. For MANCOVA analyses, \( p < .05 \) was considered statistically significant; however, for ANCOVA analyses, \( p < .01 \) was reported as statistically significant to allow for multiple comparisons.

Between-Group Analyses (Meningitis versus Controls)
ANCOVAs were performed to examine the group difference for FSIQ. Separate MANCOVAs were used to assess the group differences for the WISC-III index scores and academic achievement. MANCOVAs were also performed to determine group differences for the
executive domains, namely attentional control, goal setting, and concept formation.

Medical Predictors

Two-way multivariate and univariate analyses were undertaken to examine the impact of neurologic complications. Neurologic complications included seizures, obtundation or coma, hydrocephalus, hemiparesis, persistent hypotonia, visual loss, ataxia, and sensorineural deafness. Further examination of the impact of illness severity was conducted using correlations of the severity rating and test scores within the meningitis survivor group.

To assess the impact of age at illness, the meningitis sample was divided into children experiencing meningitis before 12 months of age (n = 38) and after 12 months of age (n = 69). In this study, age at illness is confounded by age at testing; that is, the early age at illness group is significantly younger (M = 11.6, SE = 0.1) than the later age at illness group (M = 13.4, SE = 0.2). Given the relationship between age at testing and age at illness, it was inappropriate to covary for age at testing when examining the contribution of this risk factor. To overcome this problem, we compared the two age-at-illness groups with age-matched controls and examined the Group (meningitis vs. control) × Age at Illness (≤ 12 months, > 12 months) interaction.

Longitudinal Analyses

Finally, repeated-measures ANCOVAs were employed to investigate changes in performance for cognitive variables that were available for both the 7- and 12-year follow-up (FSIQ, COWAT–total words, COWAT–total errors, and CFR–accuracy).

Results

Meningitis versus Controls

General Performance

Data for intellectual and academic measures are presented in Table 4. While mean scores for the meningitis group were consistently within the average range, the group tended to perform more poorly than healthy controls on all measures. Mean FSIQ for the meningitis group was significantly below that of the control group, F(1, 199) = 6.83, p = .01. A significant “group” main effect was identified for the WISC-III index scores (Pillai’s = .041, p < .05), with univariate analyses revealing that the meningitis group performed significantly more poorly than controls on VC, F(1, 194) = 6.89, p < .01. The meningitis group also tended to score below controls on perceptual organization, although this group difference failed to reach statistical significance, F(1, 194) = 4.86, p = .03. The MANCOVA for academic achievement revealed a significant “group” main effect (Pillai’s = .049, p = .02), and univariate analyses found significant group differences in reading, F(1, 198) = 7.38, p < .01, and spelling, F(1, 199) = 10.06, p < .01. Twenty-nine (27%) of the meningitis group required special educational assistance, while only 12 (12.5%) controls needed such additional support, χ²(1) = 6.52, p = .011.

Executive Functions

MANCOVAs identified significant “group” main effects for goal setting (Pillai’s = 0.076, p < .01) and concept formation/abstraction (Pillai’s = 0.091, p < .01), while no group difference was found for attentional control (Pillai’s = 0.016, p > .05). In goal setting, univariate
analyses revealed that the meningitis group was less accurate than controls when copying, CFR-accuracy: $F(1, 198) = 8.70, p = .004$, and its organizational strategies were less efficient, CFR-strategy: $F(1, 198) = 8.46, p = .004$. Although the group difference failed to reach significance, the meningitis group tended to be less planful on the TOL and made more errors than the control group, TOL-extra attempts: $F(1,198) = 5.40, p > .05$). In concept formation/abstraction, the meningitis group tended to score lower than controls across all variables, but MakingInferences was the only variable to reach statistical significance, $F(1, 198) = 9.67, p < .01$ (see Table 5).

Medical Predictors

Acute Neurologic Complications

Meningitis survivors with complicated ($n = 47$) and uncomplicated ($n = 60$) illness histories were compared on the general performance and executive function domains. There were no group differences with respect to age and SES. The complications group did not differ in terms of FSIQ, $F(1, 100) = 2.31, p > .05$, while the complications main effects for the WISC-III index scores (Pillai's = 0.032, $p > .05$) and academic achievement (Pillai's = 0.037, $p > .05$) were not significant. Although no group differences were observed, the complications group scored lower than the no-complications group on all intellectual and academic variables. The complications main effects for attentional control (Pillai's = 0.021, $p > .05$), goal setting (Pillai's = 0.036, $p > .05$), and concept formation/abstraction (Pillai's = 0.038, $p > .05$) failed to reach significance.

Further analysis of the impact of complications was conducted using the severity rating score, described in Table 3. In keeping with ANCOVA results, correlations between the severity rating score and executive function measures detected no statistically significant relationship and no consistent trends for the complications group to perform more poorly than the no-complications group.

Age at Illness

The two meningitis age-at-illness groups ($\leq 12$ months, $> 12$ months) were similar with respect to presence of acute neurologic complications, including abnormal neurologic signs, duration of prediagnostic symptoms, seizures, or coma. When compared with age-matched controls, children in the early age at illness group exhibited significant neuropsychologic deficits, while children in the late age at illness group performed
similarly to age-matched peers (see Table 6). The Group \( \times \) Age at Illness interaction was significant for FSIQ, \( F(1, 197) = 5.21, p < .05 \), with children in the early age at illness group scoring significantly below age peers. The MANCOVA for the WISC-III index scores failed to reach significance (Pillai’s \( F(1, 192) = 5.25, p = .05 \)), although the early age at illness group tended to perform below age-matched controls on VC, \( F(1, 196) = 5.25, p = .05 \). The MANCOVA for academic achievement revealed a significant Group \( \times \) Age at Illness interaction: attention control (Pillai’s \( F(1, 196) = 12.47, p = .001 \), tended to score below peers in the spelling domain, \( F(1, 197) = 4.85, p < .05 \). For each executive function domain, the Group \( \times \) Age at Illness interaction was significant: attention control (Pillai’s \( F(1, 197) = 5.21, p = .05 \), goal setting (Pillai’s \( F(1, 192) = 2.5, p < .05 \), concept formation/abstraction (Pillai’s \( F(1, 196) = 4.85, p < .05 \). Children in the early age at illness group made more errors on the Code Transmission Test, needed more time on the CNT, required more attempts on the TOL, were less accurate on the CFR, generated fewer words on the COWAT, and displayed poorer listening comprehension (Making Inferences).

### Table VI. Age at Illness and Neuropsychological Functioning Following Bacterial Meningitis

<table>
<thead>
<tr>
<th>Age at Illness(^a)</th>
<th>(&lt; 12 \text{ months} (n = 38)) Mean (95% CI)</th>
<th>Matched controls ((n = 31)) Mean (95% CI)</th>
<th>(&gt; 12 \text{ months} (n = 69)) Mean (95% CI)</th>
<th>Matched controls ((n = 65)) Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intellectual ability</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full Scale IQ</td>
<td>95.3 (91.6, 99.0)</td>
<td>04.9 (100.7, 109.0)</td>
<td>98.3 (95.5, 101.1)</td>
<td>100.0 (97.1, 102.8)</td>
</tr>
<tr>
<td>Verbal comprehension</td>
<td>92.4 (88.7, 96.0)</td>
<td>101.8 (97.8, 105.9)</td>
<td>96.5 (93.7, 99.3)</td>
<td>98.1 (95.2, 101.0)</td>
</tr>
<tr>
<td>Perceptual organization</td>
<td>99.0 (94.8, 103.2)</td>
<td>101.8 (102.0, 111.3)</td>
<td>99.7 (96.5, 102.9)</td>
<td>102.1 (98.8, 105.3)</td>
</tr>
<tr>
<td>Freedom from distractibility</td>
<td>97.7 (93.2, 102.1)</td>
<td>103.5 (98.5, 108.5)</td>
<td>97.8 (94.4, 101.2)</td>
<td>97.9 (94.4, 101.4)</td>
</tr>
<tr>
<td><strong>Academic ability</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reading</td>
<td>94.4 (90.1, 98.7)</td>
<td>108.9 (104.2, 113.6)</td>
<td>101.5 (98.4, 104.7)</td>
<td>102.0 (98.8, 105.3)</td>
</tr>
<tr>
<td>Spelling</td>
<td>93.9 (98.8, 98.0)</td>
<td>105.4 (100.8, 110.0)</td>
<td>96.3 (93.2, 99.4)</td>
<td>99.4 (96.2, 102.5)</td>
</tr>
<tr>
<td>Arithmetic</td>
<td>97.2 (93.5, 100.9)</td>
<td>101.2 (97.0, 105.4)</td>
<td>93.7 (90.9, 96.5)</td>
<td>95.7 (92.8, 98.5)</td>
</tr>
<tr>
<td><strong>Attentional control</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Codes–total correct</td>
<td>35.4 (34.4, 36.3)</td>
<td>37.7 (36.7, 38.8)</td>
<td>37.9 (37.2, 38.6)</td>
<td>37.8 (37.1, 38.6)</td>
</tr>
<tr>
<td>Codes–total errors</td>
<td>5.4 (4.0, 6.8)</td>
<td>2.5 (1.5, 3.6)</td>
<td>2.3 (0.8, 3.9)</td>
<td>2.5 (1.5, 3.6)</td>
</tr>
<tr>
<td>CNT–time (seconds)</td>
<td>167.9 (158.3, 177.5)</td>
<td>147.3 (136.7, 157.9)</td>
<td>140.4 (133.4, 147.5)</td>
<td>139.9 (132.6, 147.2)</td>
</tr>
<tr>
<td>CNT–errors</td>
<td>3.1 (2.1, 4.1)</td>
<td>2.6 (1.5, 3.7)</td>
<td>2.3 (1.6, 3.0)</td>
<td>2.4 (1.6, 3.1)</td>
</tr>
<tr>
<td><strong>Goal setting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOL–trials correct</td>
<td>10.7 (10.4, 11.0)</td>
<td>11.3 (11.0, 11.7)</td>
<td>11.1 (10.9, 11.4)</td>
<td>11.1 (10.9, 11.4)</td>
</tr>
<tr>
<td>TOL–extra attempts</td>
<td>7.8 (6.8, 8.7)</td>
<td>5.6 (4.5, 6.6)</td>
<td>6.4 (5.7, 7.1)</td>
<td>5.9 (5.2, 6.6)</td>
</tr>
<tr>
<td>TOL–time</td>
<td>264.4 (243.1, 285.7)</td>
<td>226.1 (202.4, 249.9)</td>
<td>239.8 (223.9, 255.7)</td>
<td>229.6 (213.3, 246.0)</td>
</tr>
<tr>
<td>CFR–accuracy</td>
<td>29.4 (28.4, 30.5)</td>
<td>32.7 (31.5, 33.9)</td>
<td>32.8 (32.0, 33.6)</td>
<td>33.4 (32.6, 34.2)</td>
</tr>
<tr>
<td>CFR–strategy</td>
<td>4.3 (4.0, 4.7)</td>
<td>4.8 (4.5, 5.2)</td>
<td>4.9 (4.6, 5.1)</td>
<td>5.3 (5.0, 5.5)</td>
</tr>
<tr>
<td><strong>Concept formation/abstract</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>COWAT–total words</td>
<td>22.1 (19.5, 24.8)</td>
<td>29.2 (26.3, 32.1)</td>
<td>27.7 (25.7, 29.7)</td>
<td>27.7 (25.7, 29.8)</td>
</tr>
<tr>
<td>COWAT–total errors</td>
<td>1.3 (0.9, 1.7)</td>
<td>0.7 (0.3, 1.2)</td>
<td>1.0 (0.7, 1.3)</td>
<td>0.8 (0.5, 1.1)</td>
</tr>
<tr>
<td>TQT–trials solved</td>
<td>6.3 (5.8, 6.8)</td>
<td>5.8 (5.2, 6.4)</td>
<td>5.9 (5.5, 6.3)</td>
<td>5.4 (5.0, 5.8)</td>
</tr>
<tr>
<td>TQT–constraint-seeking Qs</td>
<td>29.6 (27.0, 32.2)</td>
<td>32.3 (29.4, 35.2)</td>
<td>30.7 (28.7, 32.6)</td>
<td>32.8 (30.8, 34.8)</td>
</tr>
<tr>
<td>TQT–total time</td>
<td>570.1 (491.7, 648.4)</td>
<td>571.9 (485.6, 658.2)</td>
<td>519.9 (462.5, 577.4)</td>
<td>483.0 (423.6, 542.3)</td>
</tr>
<tr>
<td>Making Inferences–total</td>
<td>23.7 (22.2, 25.2)</td>
<td>29.2 (27.5, 30.9)</td>
<td>28.1 (27.0, 29.2)</td>
<td>28.7 (27.6, 29.9)</td>
</tr>
</tbody>
</table>

Codes = Code Transmission Test; CNT = Contingency Naming Test; TOL = Tower of London; CFR = Complex Figure of Rey; COWAT = Controlled Oral Word Association Test; TQT = Twenty Questions Test.

\(^a\) Group means adjusted for age, gender, and socioeconomic status.

Longitudinal Comparison

Repeated-measures ANCOVAs (7- and 12-year follow-up) were conducted for FSIQ, CFR, and COWAT to examine developmental trajectories in intellectual and executive function, respectively, using scores from the...
7-year follow-up and current assessment (Table 7). No Group × Time interaction differences were identified for IQ, indicating similar developmental trajectories for meningitis survivors and controls over time. For the CFR, the analysis identified a significant “time” main effect, $F(1, 198) = 58.18, p < .001$, indicating expected developmental progress. In addition, a significant interaction was found for Group × Time, $F(1, 198) = 5.74, p = .02$, with meningitis survivors recording greater improvements over time (meningitis: 8.17 points; controls: 6.08 points), suggesting some “catch-up” in these skills. Significant development over time was also noted for the COWAT, $F(1, 198) = 38.74, p < .001$, with both groups showing similar rates of improvement with time. Longitudinal comparisons of meningitis survivors according to age at illness detected no significant effects.

**DISCUSSION**

The aim of the present study was to examine long-term outcome from childhood bacterial meningitis in a school-aged population and to investigate the relative contribution of acute neurologic complications as a marker of brain injury, and age at illness as an indicator of the vulnerability of the young brain. The study employed a prospective, longitudinal design and compared postmeningitis children to age- and grade-matched controls in the domains of general performance (IQ, educational skills) and executive functions. Possible confounding effects of gender and psychosocial factors, such as geographic region, parental education, and occupation were controlled by sampling and statistical methods.

Results suggest that even 12 years post-illness, children with a history of meningitis experience neurobehavioral sequelae. However, impairments were not generally severe in our study. Mean group scores fell within the average range, with a consistent decrement of approximately one third of a standard deviation for meningitis survivors across IQ and educational measures. Further, there was a greater representation of children postmeningitis in lower IQ ranges (48–136), with nine children achieving FSIQs < 80 in comparison with the three controls (78–135) in this range. Similarly, children postmeningitis were more than twice as likely as controls to require special educational assistance (27.0 vs. 12.5%), suggesting that the impact of performance differences is of clinical significance. Across the domains of executive functions, children with a history of meningitis were consistently less efficient than their peers. They took longer to complete tasks, made more errors, were less organized, and struggled with problem-solving situations within both verbal and spatial domains. Again, while performances were not severely impaired, they fell below developmental expectations.

In our previous investigations of this cohort, we observed a changing pattern of impairments, which led us to consider whether we were identifying permanent cognitive deficits or a developmental lag associated with a transient insult to the developing CNS. At an initial evaluation, 12 months post-illness, children were noted to be more likely than expected to have delayed expressive language development (Anderson, Leaper, & Judd, 1987). Of note, at that evaluation (mean age at assessment = 23 months), language skills could be argued to be in a state of rapid development (Gardner, 1979; Gleason, 1985), with the possibility that a delay in language acquisition may explain the poorer performance of children following meningitis. At 7 years post-illness (mean age at testing = 8.4 years, $SD = 1.6$) (Anderson et al., 1997; Grimwood et al., 1995), expressive language skills had developed and no child required language intervention. However, the cohort now demonstrated substantial deficits in reading, being four times more likely than controls to be unable to read at all, and with almost double the risk of achieving a reading age of 2 years below chronological age, and

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### Table VII. Adjusted Group Means and Standard Errors for Measures Used at Both the 7-Year and 12-Year Follow-Up Assessments

<table>
<thead>
<tr>
<th>Measure</th>
<th>Meningitis (n = 107)</th>
<th>Controls (n = 96)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7-Year Follow-Up</td>
<td>12-Year Follow-Up</td>
</tr>
<tr>
<td></td>
<td>Adjusted M (SE)</td>
<td>Adjusted M (SE)</td>
</tr>
<tr>
<td>Full-scale IQe</td>
<td>100.3 (1.2)</td>
<td>97.2 (1.1)</td>
</tr>
<tr>
<td>CFR-accuracy</td>
<td>23.5 (0.7)</td>
<td>31.7 (0.3)</td>
</tr>
<tr>
<td>COWAT-total wordsc</td>
<td>17.7 (0.6)</td>
<td>25.8 (0.8)</td>
</tr>
</tbody>
</table>

*a Two postmeningitis children were unable to complete these tests.
*b Group means adjusted for gender and socioeconomic status.
*c Group means adjusted for age, gender, and socioeconomic status.
thus eligible for a diagnosis of specific reading disability. Again, it could be argued, given the age of the sample, that these literacy skills were in a state of development and may simply be lagging behind rather than permanently impaired. We predicted that identified deficits in memory and learning may be impeding normal skill acquisition in areas such as literacy and verbal knowledge, with a hint that potential executive deficits may further impact on cognitive development.

On this occasion, results may be argued to be consistent with that expected for a 12-year follow-up period. Differences, however, continue to exist for intellectual measures, but there is no apparent deterioration in skills, with the gap between meningitis survivors and controls remaining stable over time. For literacy skills, a significant group difference was identified, but overall performance was at expected levels, implying substantial improvements in this domain since previous follow-up.

The suggestion of executive deficits identified at the 7-year evaluation was now thoroughly evaluated and global deficits were identified, encompassing attentional control, goal setting, and concept formation/abstract thought. While meningitis survivors continued to perform more poorly than controls, longitudinal analyses identified some specific gains in goal-setting skills in the meningitis group over time, with group mean scores increasing by more than two standard deviations from 7- to 12-year follow-up. This may reflect that these skills, which are in an ongoing state of development into adolescence, continue to show some catch-up with respect to normal levels of development. In contrast, more language-based executive abilities showed no such catch-up. These skills are thought to mature earlier, around age 10 years, with more gradual improvement after that time (Anderson, 1998; Levin et al., 1991; Welsh, Pennington, & Groisser, 1991). If true, it could be argued that these skills should be mostly developed in the current cohort, and identified deficits may reflect a more permanent set of higher-level language deficits. The presence of such deficits might be consistent with the mild, but significant, discrepancies across groups identified at each level. That is, less efficient conceptualization and abstraction skills may subtly reduce development in a range of cognitive and language domains through middle childhood. Of note, moving into adolescence, when the child needs to function independently, executive difficulties may have increasing impact. This possibility is supported by research examining survivors of meningitis and other generalized cerebral insults in adulthood (Anderson et al., 1994; Dennis, 1989; Gronwall, Wrightson, & McGinn, 1997; Hugosson et al., 1997), when ongoing deficits are identified in these higher-level skills.

**Acute Neurologic Complications**

The present data do not provide evidence for a sustained adverse effect due to acute neurologic complications. No differences were identified between children with and without complications, and no consistent trends for lower performances were evident, with the two groups performing similarly across all domains. This is at odds with results from the longitudinal study of Taylor and colleagues (1990, 1996), who identify complications as a major predictive factor in their sample. A number of explanations may be considered to account for our findings. It may be that, with time since illness, the impact of neurologic complications on cognition becomes less substantial, with psychosocial factors being more relevant. Such a pattern has been reported in other samples of children with early brain injury, where social disadvantage and limited access to rehabilitation have been found to be more predictive of outcome with increasing time since injury (Kinsella et al., 1997; Yeates et al., 1997). It should be noted that in an earlier report of this sample (Grimwood et al., 1996), when children who died as a result of illness were included in assessment of outcome, the impact of complications, not surprisingly, became more marked. Finally, the requirements for task participation increase with older cohorts, and it has been noted that two children in the meningitis sample were unable to complete tasks due to meningitis-related sequelae (e.g., intellectual impairment, blindness, hearing impairments).

These considerations may reflect a tendency for permanent neurologic complications to be more predictive of severe functional deficits. In contrast, where complications are more transient and no obvious residual physical, sensory, or neurologic deficits are sustained, ongoing development may be relatively unaffected by these early symptoms.

**Age at Illness**

As was the case for our 7-year follow-up, age at illness continues to be important for long-term outcome. For intellectual and academic scores, those contracting meningitis prior to 12 months of age performed more poorly, with greatest difficulties in VC and reading ability. For executive functions, younger age at illness was associated with poorer attentional control and less
efficient higher-level language skills, less accurate performances, slower generation of verbal responses, poorer interpretation of complex verbal and visual materials, and reduced goal-setting abilities. These results suggest that while the overall impact of meningitis may be relatively general and mild, age at illness appears to be particularly relevant for linguistic and executive functions, which are developing rapidly in infancy and early childhood. The implication of these findings is that contrary to neural plasticity theories, generalized cerebral insult may have a greater impact on the less mature CNS.

The specific vulnerability of the language system, consistently identified within this cohort, albeit via different symptoms at different developmental stages, would support an interpretation that language skills, which are emerging but not functional and are in a very rapid stage of development at the time of illness, are differentially impaired, with a delay in onset and mastery of skills and a possible shortfall in eventual level of skill (Dennis, 1989). The observation of more intact non-verbal skills, and our understanding that these skills are more stable during this period, is supportive of such an explanation. Further research is required to follow children with early brain injury, such as bacterial meningitis, into adulthood to establish persisting versus transient deficits in neurobehavioral function.

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