Long-term Motor and Cognitive Outcome of Acute Encephalitis

WHAT’S KNOWN ON THIS SUBJECT: Encephalitis in children can cause significant neurologic sequelae, such as motor and cognitive impairment. Previous reported data are based mostly on questionnaires and clinical assessments.

WHAT THIS STUDY ADDS: Significant cognitive impairment, attention-deficit/hyperactivity disorder, and learning disabilities are common after childhood encephalitis. Even children who were considered fully recovered may be significantly affected. Identifiable pathogens, abnormal neuroimaging, and abnormal neurologic examination on discharge are risk factors of poor outcome.

abstract

OBJECTIVES: To examine the long-term motor and neurocognitive outcome of children with acute encephalitis and to look at possible prognostic factors.

METHODS: Children who were treated for acute encephalitis in 2000–2010 were reevaluated. All children and their parents were interviewed by using structured questionnaires, and the children underwent full neurologic examinations, along with comprehensive neurocognitive, attention, and behavioral assessments.

RESULTS: Of the 47 children enrolled, 1 died and 29 had neurologic sequelae, including motor impairment, mental retardation, epilepsy, and attention and learning disorders. Children with encephalitis had a significantly higher prevalence of attention-deficit/hyperactivity disorder (50%) and learning disabilities (20%) compared with the reported rate (5%–10%) in the general population of Israel ($P < .05$) and lower IQ scores. Lower intelligence scores and significantly impaired attention and learning were found even in children who were considered fully recovered at the time of discharge. Risk factors for long-term severe neurologic sequelae were focal signs in the neurologic examination and abnormal neuroimaging on admission, confirmed infectious cause, and long hospital stay.

CONCLUSIONS: Encephalitis in children may be associated with significant long-term neurologic sequelae. Significant cognitive impairment, attention-deficit/hyperactivity disorder, and learning disabilities are common, and even children who were considered fully recovered at discharge may be significantly affected. Neuropsychological testing should be recommended for survivors of childhood encephalitis.

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KEY WORDS attention-deficit, encephalitis, intelligence, sequelae

ABBREVIATIONS ADHD—attention-deficit/hyperactivity disorder

CI—confidence interval

CNS—central nervous system

HSV—herpes simplex virus

OR—odds ratio

Dr Michaeli conducted the initial analyses and drafted the initial manuscript; Dr Kassis conceptualized and designed the study, and reviewed and revised the manuscript; Dr Shachor-Meyouhas conceptualized the study, and reviewed and revised the manuscript; Dr Shahar designed the data collection questionnaires and reviewed and revised the manuscript; and Dr Ravid conceptualized and designed the study, conducted the initial analyses and examinations, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted.

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Encephalitis is the presence of an inflammatory process in the brain parenchyma associated with clinical evidence of brain dysfunction. Diagnosis requires evidence of neurologic dysfunction and central nervous system (CNS) inflammation. Viruses are the most frequently diagnosed infectious cause of encephalitis; bacteria, fungi, and parasites are less common. The frequency and distribution of viruses or other infectious agents causing encephalitis vary according to geographical region. In Asia, the major identified cause of acute encephalitis is the Japanese encephalitis virus. Tick-borne encephalitis virus and enterovirus are common in the Western world. Data on long-term neurologic outcomes in children with encephalitis are limited and vary depending on the different geographic areas and endemic agents. In the majority of studies, data were determined by using clinical follow-up assessments at outpatient clinics and structured questionnaires; only a few studies used standardized cognitive and behavioral tests. Previously reported neurologic sequelae include developmental delay, motor deficits, epilepsy, and learning and behavioral problems.

Information regarding prognostic factors of acute encephalitis in children is sparse, and data vary between studies. Several factors have been suggested as indicative of poor outcome, such as young age, deteriorating electroencephalography (EEG) findings, focal neurologic signs at discharge, low Glasgow Coma Scale score on admission, and abnormal neuroimaging results. The aim of the present study was to evaluate the long-term sequelae of acute encephalitis in children and to look for predictors of long-term morbidity. Although most previous studies were based on clinical assessments or questionnaires, this study is distinctive because it provides an objective neurocognitive performance assessment. This information can help in offering guidance in anticipatory counseling, as well as emphasizing important aspects for future follow-up.

METHODS

Study Population
Medical records of children and adolescents, aged 1 month to 18 years, admitted to Meyer Children’s Hospital in Haifa, Israel, during the years 2000 to 2010 with a final diagnosis of acute encephalitis were reviewed. The hospital is the main tertiary center in the north of Israel and serves a population of 280,000 children. Inclusion criteria included: (1) at least 1 symptom or sign of cerebral dysfunction, such as altered mental status, motor or sensory deficits, or seizures; and (2) at least 1 of the following signs of inflammation: fever (>38°C), white blood cell count >15 × 10^9 cells/µL, C-reactive protein level >10 mg/L, and cerebrospinal fluid cell count >6 cells/µL. Children with meningoencephalitis, demyelinating disease, or any underlying neurologic, systemic, or metabolic disease were excluded from the study. All eligible patients were contacted, by letter and then by telephone, to ask whether they would be willing to be followed up. Fifty-eight patients fulfilled the inclusion criteria. Of those, 1 died during the acute phase, 8 declined to be assessed, and 3 could not be located. There was no difference between those children regarding age at onset, gender, and presenting symptoms.

Written informed consent was obtained from the parents during the follow-up visit. The study was approved by the institutional review board.

Data Collection
A structured form was used to obtain data from patients’ hospital records regarding presenting symptoms and signs, laboratory examinations, EEG and neuroimaging studies, and clinical findings at discharge.

The causative organisms were identified according to serum virus antibody titers (West Nile virus, mycoplasma, Coxiella burnetii, and Bartonella species), and cerebrospinal fluid polymerase chain reaction (herpes simplex virus [HSV], herpesvirus 6, and enterovirus).

Outcome at discharge was classified for all survivors as good, moderate, or poor. Good outcome was defined as having no neurologic sequelae. Moderate outcome was defined as having minor to moderate sequelae, including altered behavior or clinical signs not affecting functions. Poor outcome was defined as having severe neurologic sequelae that impair everyday functions.

Clinical, Motor, and Neurocognitive Assessment
All the children were interviewed and underwent thorough neurologic examination by a pediatric neurologist during the follow-up visit. A structured questionnaire was used to obtain information from parents regarding comorbid illnesses, medications, behavioral problems, school performance, and ability to perform daily activities. The Kaufman Brief Intelligence Test was used to assess intelligence. This standardized, individually administered test yields 3 scores: verbal, nonverbal, and the overall score, known as the IQ composite. The mean ± 1SD age-based standard score for each test is 100 ± 15. Scores lower than 2 SDs from the mean were considered as retardation. Scores between 1 and 2 SDs from the mean were considered as borderline intelligence.

The diagnosis of attention-deficit/hyperactivity disorder (ADHD) was based on the criteria of the Diagnostic and...
Clinical Presentation, EEG, and Neuroimaging Studies

The most common presenting symptoms were fever (73%) and altered mental status (69%). Hemiparesis was found in 13 (28%) patients and ataxia in 6 (13%) patients. Eighteen (39%) patients had seizures.

An etiologic agent was identified in 23 (50%) patients. The most common pathogen was enterovirus (9 patients), followed by HSV (6 patients).

EEG was performed on 31 patients; results were normal in only 3 (10%). Abnormal results on neuroimaging studies were found in 39% of the patients (Table 1).

At discharge, neurologic examination was normal in 27 (58%) patients; 53% of patients showed focal motor deficits, and 15% of patients had various levels of cognitive impairment.

Long-term Motor and Cognitive Outcome

Persisting symptoms were reported by parents of 23 (50%) children. The most common residual symptoms were behavioral problems (52%), recurrent headaches (22%), tic disorder (22%), and sleeping problems (19%). Five (11%) children developed long-standing epilepsy, which was intractable in 4 (80%). Only 4 (9%) children had residual motor deficits. Those children suffered from spastic hemiparesis and were diagnosed with herpes encephalitis. On the Kaufman Brief Intelligence Test, full-scale IQ >85 was found in only 69% of patients, compared with 84% in the general population, and 22% of patients had a full-scale IQ ≤70, compared with 2.2% in the general population (Fig 1).

Twenty-three (50%) patients fulfilled the criteria for ADHD. This rate is significantly higher than the reported rate (5%–10%) in the general population of Israel19 (P < .05). A substantial number of patients had learning disorders (20%) compared with the reported rate (10%) in the general population of Israel20 (P < .05), and 8 (17%) were placed in special education classes.

Overall, full recovery was found in only 17 (37%) patients. Moderate outcome was found in 35% of children, and 13 (28%) children suffered from poor outcome (Table 2).

Association Between Pathogen and Long-term Neurologic Outcome

Of 23 patients with verified pathogens, patients with HSV had the highest rate of neurologic sequelae, including significant motor deficit (66%), mental retardation (50%), ADHD (66%), and epilepsy (50%). However, patients with herpes encephalitis were not the only ones with an adversely affected prognosis. Of the 40 patients excluding those with HSV, ADHD was found in 18 (45%) patients and mental retardation in 7 (17%) (Table 3). Overall, having a confirmed etiologic agent was significantly associated with being at risk for poor long-term outcome (OR: 3.67 [95% CI: 1.1–15.68]; P = .04).

### Statistical Analysis

Data were summarized as proportions or means ± SDs. \( \chi^2 \) analysis was used to test for qualitative variables, and Student’s \( t \) test was used for quantitative variables.

Multivariate analyses of the associations between clinical presentation, pathogen, EEG and neuroimaging studies, and long-term outcome were conducted by using logistic regressions with odds ratios (ORs) and 95% confidence intervals (CIs). Analyses for the total sample were adjusted for age and gender. For all comparisons and analyses, a \( P \) value of <.05 was used as the cutoff point of statistical significance.

### RESULTS

A total of 48 patients (28 boys and 18 girls) were enrolled in our study. Mean age at disease onset was 5 ± 4.88 years (range: 1–17 years), and mean time to follow-up was 5.8 ± 3.08 years (range: 1–11 years).

### TABLE 1 Initial Clinical Presentation, EEG, and Neuroimaging Studies in Patients With Encephalitis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>5 ± 4.88</td>
</tr>
<tr>
<td>Focal neurologic signs</td>
<td></td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>13 (28)</td>
</tr>
<tr>
<td>Ataxia</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Cranial nerves</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Coma</td>
<td>7 (15)</td>
</tr>
<tr>
<td>Seizures</td>
<td>18 (39)</td>
</tr>
<tr>
<td>Confirmed pathogen</td>
<td>23 (50)</td>
</tr>
<tr>
<td>EEG (( n = 31 )) Normal</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Generalized δ waves</td>
<td>24 (77)</td>
</tr>
<tr>
<td>Focal spikes or slow waves</td>
<td>6 (19)</td>
</tr>
<tr>
<td>Neuroimaging (( n = 33 ))</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>25 (68)</td>
</tr>
<tr>
<td>Leptomeningeal enhancement</td>
<td>9 (24)</td>
</tr>
<tr>
<td>Cortical hyperdensity</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Brain edema</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

Data are \( N \)%; unless otherwise noted.
Association Between Clinical Presentation, EEG, and Neuroimaging Studies and Long-term Outcome

Predictors of poor long-term outcome are summarized in Table 4. The strongest predictors included long hospital stay (P = .004), abnormal neurologic examination results at discharge (P = .03), abnormal results on neuroimaging studies (P = .04), and confirmed pathogen (P = .04). Although patients with seizures, abnormal neuroimaging findings, and focal neurologic signs at presentation displayed a tendency toward increased risk for epilepsy, the number of patients was too small to give reasonable interpretations.

Association Between Outcome at Hospital Discharge and Long-term Outcome

Figure 2 shows the distribution of outcome at hospital discharge and at the long-term follow-up visit. At hospital discharge, 27 (59%) patients had apparently made a full recovery, whereas 6 (13%) had moderate neurologic sequelae and 13 (28%) had severe neurologic sequelae. Of the 13 children with severe sequelae, 6 improved (46%) and 3 (3%) fully recovered. Conversely, of the 27 children who were considered to have made a full recovery at time of discharge, only 13 had a good long-term outcome. Four (15%) had mental retardation, 4 (15%) had learning disabilities, and 11 (41%) had ADHD.

DISCUSSION

The major findings of the present study are that encephalitis in children can lead to significant long-term neurologic sequelae, mainly reduced neurocognitive performance, behavioral problems, ADHD, and learning disabilities. Overall, 50% of our patients suffered from ADHD and 20% from learning disabilities. These values are significantly higher than the recent estimates of ADHD (5%–10%) and learning disability (10%) rates in Israel (P < .05). Only 37% of the survivors had fully recovered, and 28% of the children were left with severe neurologic disabilities that impaired everyday functions, such as motor deficits, mental retardation, and intractable seizures. Similar studies that investigate the long-term outcome of encephalitis are sparse, and the results of long-term neurologic sequelae vary with geographic location and type of infectious pathogen. A similar incidence of severe neurologic sequelae was previously reported by Wang et al,9 who found 25% significant morbidity, such as epilepsy, mental retardation, and focal neurologic signs, in children who experienced acute encephalitis. In a study by Clarke et al,11 7 (35%) of 20 children who survived acute encephalitis experienced moderate to severe neurologic impairment. In contrast, an older study by Rautonen et al8 found that only 6.7% of children with encephalitis suffered from severe damage and 90.5% were cured with no or only minor sequelae. This study, however, included only clinical follow-up visits up to 6 months after discharge and may therefore have underestimated neurocognitive sequelae that could manifest at a later stage.

As noted earlier, the most common sequelae in our study was ADHD, which was found in 50% of patients. None of our patients was diagnosed with ADHD before the onset of disease, although most were too young at disease onset to manifest the characteristic clinical symptoms. Because all patients were healthy before the disease, we assumed the same incidence of the disorder in our study as in the general population. Although the association between ADHD and other brain insults, such as head trauma,21,22 bacterial meningitis,23 and
Brain tumor was previously reported, little is known about its association with infectious encephalitis. Behavioral anomalies similar to ADHD were first described as a complication of encephalitis after the influenza epidemic of 1918. In their study on patients recovering from CNS infections due to enterovirus 71, Gau et al reported a 20% incidence of ADHD, compared with 3% in the control group. They suggested that the infection may involve the prefronto-striatum-subcortical area of the brain that relates to the core symptoms of ADHD. After tick-borne encephalitis, children had lower scores than control subjects and relative impairment on several attention/concentration tests. Impaired memory function and reduced ability to concentrate was reported by Fowler et al in children who survived encephalitis. When assessed by using computerized cognitive tests, these children had slower reaction times but no differences in working memory compared with control subjects. This association is important, because ADHD symptoms may influence school performance as well as peer and family relationships. Early diagnosis of ADHD symptoms will allow early educational intervention and treatment if necessary. Another important finding of our study was the significantly lower intelligence scores in children after acute encephalitis. A full-scale IQ of 85 was found in only 69% of patients, compared with 84% in the general population, whereas 22% of patients had a full-scale IQ of ≤70, compared with 2.2% in the general population. There is little information regarding cognitive function after viral encephalitis in children. Similar significantly lower IQ evaluations were previously reported by Chang et al in children who contracted enterovirus 71 encephalitis. In contrast, in a study from Germany, no significant difference was found in intelligence or neuropsychological evaluations between children who experienced tick-borne encephalitis and control subjects. Lower intelligence scores and impaired attention and learning were found in our study even in children who were considered as fully recovered at the time of discharge. 4

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>N</th>
<th>Neurologic Sequelae (n)</th>
<th>Total N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterovirus</td>
<td>9</td>
<td>Mental retardation (3), ADHD (5), tic disorder (3), sleep disturbances (2), learning disabilities (1), epilepsy (1)</td>
<td>7 (78)</td>
</tr>
<tr>
<td>HSV</td>
<td>6</td>
<td>Mental retardation (3), ADHD (4), motor deficit (4), tic disorder (3), sleep disturbances (3), epilepsy (3)</td>
<td>5 (83)</td>
</tr>
<tr>
<td>West Nile virus</td>
<td>3</td>
<td>ADHD (1), headaches (1)</td>
<td>1 (53)</td>
</tr>
<tr>
<td>Human herpesvirus 6</td>
<td>1</td>
<td>None</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Mycoplasma pneumonia</td>
<td>1</td>
<td>ADHD (1), tic disorder (1)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Coxella burnetti</td>
<td>1</td>
<td>ADHD and learning disabilities (1), headaches (1), sleep disturbances (1)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Bartonella henselae</td>
<td>1</td>
<td>None</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>1</td>
<td>None</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

* Percentage of subjects with neurologic sequelae.

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>0.49 (0.13–1.8)</td>
<td>.39</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>0.89 (0.75–1.05)</td>
<td>.15</td>
</tr>
<tr>
<td>Focal neurologic signs at presentation</td>
<td>1.8 (0.5–6.32)</td>
<td>.35</td>
</tr>
<tr>
<td>Coma at presentation</td>
<td>1.67 (0.37–7.6)</td>
<td>.51</td>
</tr>
<tr>
<td>Admission to ICU</td>
<td>1.25 (0.33–4.73)</td>
<td>.74</td>
</tr>
<tr>
<td>Seizures</td>
<td>2.33 (0.63–8.64)</td>
<td>.2</td>
</tr>
<tr>
<td>Confirmed pathogen</td>
<td>3.67 (1.1–15.8)</td>
<td>.04*</td>
</tr>
<tr>
<td>Abnormal EEG</td>
<td>2.75 (0.52–14.63)</td>
<td>.24</td>
</tr>
<tr>
<td>Abnormal neuroimaging results</td>
<td>3.56 (0.91–15.94)</td>
<td>.04*</td>
</tr>
<tr>
<td>Abnormal neurologic examination results at discharge</td>
<td>3.11 (1.07–12.89)</td>
<td>.03*</td>
</tr>
<tr>
<td>Hospital stay</td>
<td>1.18 (1.05–1.32)</td>
<td>.004*</td>
</tr>
</tbody>
</table>

* P < .05.
(15%) had mental retardation, 11 (41%) had ADHD, and 4 (15%) had severe learning disability. A possible explanation for these findings is that cognitive recovery at discharge, especially in young children, is usually based on level of consciousness, attention, and orientation. Neurocognitive parameters, such as memory, attention, or comprehension, are not assessed, and future neuropsychological sequelae that interfere with intelligence and learning may thus be underestimated. In addition, cognitive deficits at discharge may not be evident until the demands increase during school years. Similar late-onset cognitive sequelae were also seen in other studies. 14,28,29

Epilepsy is a known sequela of CNS infections. Furthermore, between 1% and 5% of epilepsy causes have been presumed to be due to CNS infections. 30 Recurrent seizures, status epilepticus, and multifocal spikes on EEG were previously reported as risk factors for postencephalitic epilepsy in children. 31,32 In our study, 5 children (11%) developed long-term epilepsy; the condition was intractable in 4 children (80%). Seizures, abnormal neuroimaging findings, and focal neurologic signs at presentation displayed a tendency toward increased risk for epilepsy, but the number of patients was too small to make a meaningful interpretation.

Potential risk factors for a poor neurologic outcome in our study were identifiable pathogens, abnormal imaging, abnormal neurologic examination at discharge, and longer hospital stay. The cause of encephalitis was found in 50% of our patients. This finding is consistent with previous studies, in which an etiologic diagnosis was made in 31% to 75% of cases. 8,9,11,14,15 The most common pathogens in our study were enterovirus, HSV, and West Nile virus. Children with HSV encephalitis had the worst outcome. One patient died, and 5 of 6 survivors had severe neurologic sequelae. These results are in line with other recent studies that found a high incidence of neurologic sequelae in children with HSV encephalitis 33–35; these sequelae were probably secondary to cortical necrosis and infarction. However, all agents, even those previously considered benign, such as enterovirus, 9,14 caused major neurologic sequelae. Some 78% of our patients with enterovirus encephalitis experienced long-term neurologic sequelae, such as mental retardation (33%) and ADHD (55%). Enterovirus 71, a distinctive species of enterovirus that is common in the Asia-Pacific region but not in our region, has also been reported as being associated with ADHD and reduced cognitive functioning. 12,26

Several studies, as well as our study, have shown the predictive value of abnormal neuroimaging on both short-term 7,36 and long-term 9,10,37 outcomes of childhood encephalitis. This finding may be explained by irreversible parenchymal damage. Severe brain lesions may also cause focal neurologic signs and correlate with abnormal neurologic examinations at discharge, which independently was found to be a predictor for long-term neurologic sequelae. 9

Long hospital stay was also associated with poor prognosis in the present study and most likely reflects the severity of the disease. Other factors that reflect severity of disease, such as low Glasgow Coma Scale score on admission, 15,28,37 deep coma, 28 and ICU admission, 14 were previously found as poor prognostic factors in other studies (although not in the present study). Several authors have suggested that young age is associated with a poor long-term prognosis in children with encephalitis. 8,11,38 We did not observe this correlation in our study.

Although the strength of our study is the clinical examination and neuropsychological evaluations of the patients, it did have several limitations. As a retrospective study, it is limited by the quality of information regarding symptoms and signs, laboratory evaluation, and treatment during admission available in hospital charts. Furthermore, because medications were not given according to a standardized protocol, the impact of certain treatments, such as steroids and intravenous immunoglobulin, could not be assessed. Similarly, because the diagnostic methods for causative organisms and antibodies for autoimmune encephalitis have evolved during the last decade, higher rates of causative organisms might be found if those children were being evaluated today. Nevertheless, the cause of encephalitis was found in 50% of our patients, which is consistent with previous studies. 9,11,14,15 In addition, the study was also limited by the highly variable follow-up period. However, because attention and cognitive deficits may first be evident years after disease onset, their prevalence could be even higher. Another limitation of our study is the lack of a control group. Because all patients were healthy before the disease, we compared the incidence of cognitive impairment, learning disabilities, and ADHD with the incidence of the general population, but it is not fully controlled for age and socioeconomic status.

CONCLUSIONS

Encephalitis in children may be associated with significant long-term neurologic sequelae. Significant cognitive impairment, ADHD, and learning disabilities are common, and even children who were considered fully recovered at discharge may be significantly affected. Neuropsychological testing should be recommended for survivors of childhood encephalitis. Patients with identifiable pathogens, abnormal imaging, abnormal neurologic examinations on discharge, and long hospital stay have an increased risk of a poor outcome.
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