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Original Article

Neurological Outcomes After Presumed Childhood Encephalitis

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ABSTRACT

OBJECTIVE: To evaluate factors during acute presumed childhood encephalitis that are associated with development of long-term neurological sequelae. **METHODS:** A total of 217 patients from Rady Children's Hospital San Diego with suspected encephalitis who met criteria for the California Encephalitis Project were identified. A cohort of 99 patients (40 females, 59 males, age 2 months-17 years) without preexisting neurological conditions, including prior seizures or abnormal brain magnetic resonance imaging scans was studied. Mean duration of follow-up was 29 months. Factors that had a relationship with the development of neurological sequelae (defined as developmental delay, learning difficulties, behavioral problems, or focal neurological findings) after acute encephalitis were identified. **RESULTS:** Neurological sequelae at follow-up was associated with younger age (6.56 versus 9.22 years) at presentation ($P = 0.04$) as well as an initial presenting sign of seizure ($P = 0.03$). Duration of hospital stay (median of 7 versus 15.5 days; $P = 0.02$) was associated with neurological sequelae. Of the patients with neurological sequelae, a longer hospital stay was associated with patients of an older age ($P = 0.04$). Abnormalities on neuroimaging ($P = 1.00$) or spinal fluid analysis ($P = 1.00$) were not uniquely associated with neurological sequelae. Children who were readmitted after their acute illness ($P = 0.04$) were more likely to develop neurological sequelae. There was a strong relationship between the patients who later developed epilepsy and those who developed neurological sequelae ($P = 0.02$). **SIGNIFICANCE:** Limited data are available on the long-term neurological outcomes of childhood encephalitis. Almost half of our patients were found to have neurological sequelae at follow-up, indicating the importance of earlier therapies to improve neurological outcome.

Keywords: childhood, encephalitis, neurologic, sequelae, outcomes

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Introduction

Encephalitis can be a severe and devastating neurological condition, particularly in children. This inflammatory process can be secondary to noninfectious or infectious causes, such as bacterial, viral, fungal, or parasitic.[1,2] The presentation of encephalitis can vary including headaches, fever, vomiting, nausea, seizures, focal neurological signs, or altered consciousness.[3,4] Long-term complications include dystonia, spasticity, epilepsy, ataxia, neurocognitive, and behavioral problems, some of which are not recognized until after the acute illness.[2] In cases of herpes encephalitis, two-thirds of patients developed significant neurological impairment despite treatment with acyclovir.[5] Unfortunately, literature on long-term outcomes and prognosis following encephalitis is limited. These limited studies include data on herpes simplex virus encephalitis, which quote long-term morbidity rates as 30% in adults and up to 67% in children.[6]

Neurological sequelae have been previously reported as an outcome after encephalitis; however, prior studies had

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limited information on longitudinal follow-up or factors that were associated with the development of neurological sequelae. Neurological sequelae after encephalitis reported in prior studies include evidence of cognitive, emotional, or behavioral problems as well as focal neurological abnormalities or epilepsy; however, many of these studies were limited by small patient numbers, lack of follow-up, or lack of data regarding associated factors.[7-10] This current study is the fourth part of a series of studies on a cohort of patients with childhood encephalitis that address all the limitations of small patient number, follow-up, and associating factors during acute illness. The first paper in the series from our cohort of patients enrolled in the California Encephalitis Project demonstrated the importance of continuous electroencephalograph monitoring during acute management of encephalitis patients.[11] The second paper describes types of neuroimaging findings during the acute illness as well as an association with hospital duration.[12] The third manuscript evaluates factors of presentation and hospital course that relate to the later development of epilepsy.[13] This current study is focused on identifying factors of childhood encephalitis that are associated with the development of nonepileptic neurological sequelae, providing relevant prognostic information and enhancing our understanding and management of childhood encephalitis outcomes.

Methods

Details of this cohort of patients with inclusion and exclusion criteria are described in our prior study.[13] In brief, 99 patients were selected from the original cohort of 217 patients from these criteria. All these patients were enrolled in the California Encephalitis Project at Rady Children's Hospital San Diego between 2004 and 2011. Criteria for the California Encephalitis Project included patient being hospitalized with encephalopathy for 24 hours and having at least one of the following: fever, focal neurological signs, seizure, cerebrospinal fluid pleocytosis, or neuroimaging or electroencephalograph evidence of concerning to the treating physician of encephalitis.[3,11,13] Details of the standardized testing associated with the California Encephalitis Project have previously been described.[1,3,11] All patients within this cohort were neurologically normal before the onset of acute encephalitis. The mean duration to the last follow-up after discharge of all 99 patients was 29 months (range 0.5-109 months). Of the 48 patients who later developed neurological sequelae, the mean duration of follow-up was 35.6 months (range 0.5-109 months).

In this study, factors from initial presentation, hospital course, and discharge that might predispose a patient to development of neurological abnormalities were assessed. The medical record was reviewed including emergency room encounters, hospital admission course, medication administrations, all prior and subsequent clinic visits, laboratory results, neuroimaging studies, and electroencephalograph results.[11,13] Details of neuroimaging and electroencephalography acquisition are described in a prior publication.[11] For our assessment, "difficult-to-control seizures" was defined as patients who required medically induced coma as well as more than three antiepileptic drugs (AEDs) for seizure control. In this study, the term "neurological sequelae" at follow-up was defined as any new aspects of developmental delay, learning difficulties, behavioral problems, or focal neurological findings. Epilepsy was not included as a "neurological sequelae" for the purposes of this report and was assessed as a separate outcome measure.[13]

Continuous variables were reported as means or medians with standard deviations or ranges, and categorical data as counts and percentages. Fisher's exact test was used to conduct group comparisons between categorical variables (e.g., readmission, discharge on AEDs), whereas Student t test and the Mann-Whitney U test were used to compare continuous variables (age and hospital duration, respectively). Pearson's correlation coefficient was used in assessing hospital duration as a function of age in our neurological sequelae group. Throughout, we used the Benjamini-Hochberg method to control the family-wise false discovery rate and report the adjusted P-values. Adjusted P-values less than 0.05 were considered a statistically significant result. All data analyses are conducted using the R statistical programming language.[14]

Results

Within our cohort of 217 patients, we had follow-up information on a total of 99 patients who had met the inclusion criteria for this study. Details of excluded patients are previously described.[13] Our study cohort comprises 40 girls and 59 boys, with a mean age at presentation of 9 years old (range of 2 months-17 years). Of the 99 patients in this study, 48 later had neurological sequelae.

Types of neurological sequelae

To identify patients with neurological sequelae after acute encephalitis, follow-up visits were assessed for any deficits that were noted on examination or in the history documented. Forty-eight of the 99 patients were noted to have development of neurological sequelae, with a mean duration of follow-up of 35.6 months (Table 1; range 0.5-109 months). Of the patients who had neurological sequelae, 23 (47.9%) were noted to have learning problems by school assessment or comprehensive clinical evaluation. The next most common finding in our cohort was developmental delays (39.6%), which encompasses gross motor, fine motor, social, or language delays. In this study, global developmental delay is listed as a subset of developmental delay. Ten of our patients had behavioral problems noted in follow-up assessments, including emotional lability, difficulty with impulse control, hyperactivity, and anger outbursts. There was one patient with a small visual field deficit, one who was deaf, and one with bladder spasticity.

TABLE 1.
Findings of Patients With Neurological Sequelae

Neurological Sequelae Noted at Follow-up	Number of Patients	% Neurological Sequelae (of 48 Patients)
Learning problems	23	47.9
Developmental delay (global developmental delay)	19 (7)	39.6 (14.6)
Behavioral problems	10	20.8
Motor deficit	2	4.2
Visual abnormality	1	2.1
Hearing abnormality	1	2.1
Bladder spasticity	1	2.1