Pediatric Neurology 53 (2015) 65–72

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Original Article

Epilepsy After Resolution of Presumed Childhood Encephalitis

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ABSTRACT

OBJECTIVE: To evaluate factors associated with the development of epilepsy after resolution of presumed childhood encephalitis. **METHODS:** A total of 217 patients with suspected encephalitis who met criteria for the California Encephalitis Project were identified. Evaluable outcome information was available for 99 patients (40 girls, 59 boys, ages 2 months to 17 years) without preexisting neurological conditions, including prior seizures or abnormal brain magnetic resonance imaging scans. We identified factors correlated with the development of epilepsy after resolution of the acute illness. **RESULTS:** Development of epilepsy was correlated with the initial presenting sign of seizure ($P < 0.001$). With each additional antiepileptic drug used to control seizures, the odds ratio of developing epilepsy was increased twofold ($P < 0.001$). An abnormal electroencephalograph ($P < 0.05$) and longer hospital duration (median of 8 versus 21 days) also correlated with development of epilepsy ($P < 0.01$). The need for medically induced coma was associated with epilepsy ($P < 0.001$). Seizures in those patients were particularly refractory, often requiring longer than 24 hours to obtain seizure control. Individuals who required antiepileptic drugs at discharge ($P < 0.001$) or were readmitted after their acute illness ($P < 0.001$) were more likely to develop epilepsy. Of our patients who were able to wean antiepileptic drugs after being started during hospitalization, 42% were successfully tapered off within 6 months. **CONCLUSIONS:** Limited data are available on the risk of developing epilepsy after childhood encephalitis. This is the first study that not only identifies risk factors for the development of epilepsy, but also provides data regarding the success rate of discontinuing antiepileptic medication after resolution of encephalitis.

Keywords: Epilepsy, childhood, encephalitis, seizures

Pediatr Neurol 2015; 53: 65-72

Introduction

Encephalitis is potentially devastating, particularly in children. The annual incidence worldwide ranges from 3.5 to 7.4 per 100,000 and increases to 16 per 100,000 in children.[1] Presenting signs and symptoms can be nonspecific and subtle or quite dramatic. Some children present only with low-grade fever, headache, or nausea, whereas others present with profound encephalopathy, vomiting, seizures, and/or focal neurological deficits.[2-5] Those children who present with subtle signs can also unexpectedly worsen and later develop seizures and other severe neurological sequelae.[5]

Encephalitis can result in greater morbidity and mortality in children than in adults. In one study of 1570 patients in California, 62 had intractable seizures during the acute illness, with children comprising 69% of these

Article History:
Received February 4, 2015; Accepted in final form March 14, 2015
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0887-8994/$ – see front matter © 2015 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pediatrneurol.2015.03.016

patients.[3] Another study of 148 patients in India demonstrated that 61% of children had seizures during encephalitis in comparison to 37% of the adults.[6] Seizures reportedly are more likely to occur with specific viral infections, with herpes virus (HSV) (75% of patients with HSV) more commonly associated with seizures than Japanese encephalitis (54%), followed by nonspecific encephalitis (43%).[6] The postinfectious long-term complications of encephalitis include dystonia, spasticity, epilepsy, and neurocognitive problems.[4] In fact, despite treatment with acyclovir in cases of herpes encephalitis, two-thirds of patients experienced significant neurological impairment.[7] Unfortunately, literature on long-term outcome and prognosis following encephalitis is limited, but studies on HSV encephalitis quote long-term morbidity rates as 30% in adults and up to 67% in children, with seizures occurring in 44% of these patients in one prospective study in Toronto, Canada.[8,9]

In the general population, seizures are a common neurological problem, with up to 10% of the population having a seizure in their lifetime and up to 3% of the adult population developing epilepsy.[10,11] Central nervous system (CNS) injuries such as stroke, viral infection, trauma, febrile seizure, and status epilepticus are considered common risk factors for developing epilepsy.[12,13] A group in Texas reported the 20-year risk of developing an unprovoked seizure after encephalitis or meningitis to be 6.8%, noting that patients with a prior CNS infection had a sevenfold increase in unprovoked seizures compared with the general population.[14] CNS injuries are reported to account for 30%-49% of all unprovoked seizures and epilepsies. Long-term follow up studies conducted in Seattle of individuals with a history of brain injury reveal that after a single late seizure, the risk for recurrent seizure is typically greater than 80%.[15] The risk of epilepsy was increased by 16 times with viral encephalitis when compared to the general population and this risk remained elevated up to 15 years postinfection.[12]

A correlation between encephalitis and later development of epilepsy has been shown; however, these studies were often limited by follow-up data, etiology of encephalitis, low patient number, or lack of assessment of other potential contributing factors that resulted in epilepsy. To identify factors potentially contributing to the development of epilepsy, we studied a large cohort of patients longitudinally at a single institution who were enrolled in the California Encephalitis Project (CEP).

Methods

A cohort of 217 patients who met diagnostic criteria for inclusion in the CEP at Rady Children's Hospital San Diego between 2004 and 2011 were studied.[16] To be included in the CEP, children had to be hospitalized with encephalopathy lasting 24 hours and meet at least one of the criteria: fever, seizure, cerebrospinal fluid pleocytosis, focal neurological signs, or with neuroimaging or electroencephalograph (EEG) evidence of encephalitis.[3] Details of the CEP and the standardized testing associated with CEP have previously been described.[2,3,16] This retrospective study was granted approval under the multi-institutional protocol established by the State of California for the CEP and a waiver of consent was granted. Patients were excluded from our study if they had prior neurological abnormalities, tumor, or were found to have other medical conditions causing these similar encephalitic signs and symptoms. Patients who were lost to follow-up or died during hospitalization were also excluded, resulting in 99 patients remaining in the study. Fig 1 summarizes these excluded patients.

In this study, factors from initial presentation, hospital course, and discharge that might predispose a patient to epilepsy were assessed. The electronic medical record was reviewed including emergency room encounters, hospital admission course, medication administrations, all prior and subsequent clinic visits, laboratory results, neuroimaging studies, and EEG results.[16] Details of neuroimaging and EEG acquisition are described in a prior publication.[16] In this study, the term "epilepsy" was defined as any patient with at least one unprovoked seizure after resolution of the patient's acute CNS insult. This is now an internationally accepted alternative definition of epilepsy in comparison to the traditional definition of requiring two unprovoked seizures.[17,18] For our assessment, "difficult to control seizures" was defined as patients who required medically induced coma and more than three antiepileptic drugs (AEDs) for seizure control.

Continuous variables were reported as medians and interquartile ranges, and categorical data as counts and percentages. The Fisher exact test was used to conduct group comparisons between categorical variables (development of epilepsy, discharge on AEDs, etc.), and the Mann-Whitney *U* test to compare continuous variables (hospital duration). A logistic regression was used to assess the impact of the number of AEDs given with the odds of developing epilepsy. *P*-values less than 0.05 were considered a statistically significant result. All data analyses are conducted using the R statistical programming language.[19]

Results

Within our cohort of 217 patients, follow-up information was available for a total of 99 patients who had met the inclusion criteria (Fig 1). Our study cohort comprised 40 females and 59 males, with a mean age at presentation of 9 years old (range of 2 months to 17 years). Of the 99 patients in this study, 24 later developed epilepsy.

Presenting features associated with developing epilepsy

According to our demographic analysis, race seemed to be correlated with later development of epilepsy, although this had borderline statistical significance (Table 1, $P = 0.049$). This relationship seems to be largely driven by a much higher proportion of Caucasian subjects in the non-epileptic group (n = 18, 24%) compared with the proportion of Caucasian subjects in the epileptic group (n = 1, 4.2%). Because of this discrepancy between the number of individuals in each of the Caucasian groups, race has a statically significant correlation with development with epilepsy, but these data suggest that being Caucasian decreases likelihood of developing epilepsy rather than a particular race increasing likelihood of epilepsy. A seizure at presentation showed a positive correlation with the later development of epilepsy ($P < 0.001$). There was not a significant relationship between presenting symptoms of fever, headache, or altered mental status and the subsequent development of epilepsy in this study.

Elements of hospital stay associated with developing epilepsy

One major factor found to be important in the development of epilepsy was the number of AEDs used to obtain seizure control. These AEDs included maintenance and abortive seizure medications given en route to the hospital, in the emergency room, or during the hospitalization as well as any continuous infusions needed to control seizures