Encephalitis in US Children

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KEYWORDS

• Encephalitis • Meningoencephalitis • Myelitis • Herpes simplex virus • Enterovirus • Anti-NMDA • Arbovirus

KEY POINTS

- Encephalitis is an uncommon and potentially devastating condition of neurologic dysfunction due to brain parenchymal inflammation.
- In the absence of brain biopsy, presence of encephalopathy with clinical findings suggestive of central nervous system inflammation infers a diagnosis of encephalitis.
- Viruses, including herpes simplex viruses and enteroviruses, are the most common causes in children in the United States, although immune-mediated etiologic factors are increasingly recognized and may respond to immune modulation.
- Given the broad differential diagnosis, a staged diagnostic approach can be initially targeted toward common, treatable, and at-risk etiologic factors, followed by broader, more invasive testing for unexplained persistent or severe disease.
- Supportive care with empiric therapy toward bacteria and herpes simplex viruses should be administered during diagnostic evaluation with definitive therapy ultimately tailored toward identified treatable etiologic factors.

INTRODUCTION

Encephalitis is a rare but serious condition of neurologic dysfunction due to inflammation of the brain parenchyma. A wide variety of infectious and noninfectious etiologies are associated with encephalitis, though the cause in more than half of cases remains unexplained despite extensive testing. Given the heterogeneous and wide differential

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diagnosis, epidemiologic, clinical, laboratory, and radiographic factors are necessary to guide the diagnostic evaluation and treatment. This article focuses on the most common causes of acute encephalitis in previously healthy children in the United States and introduces a practical approach to prioritizing diagnostic evaluation and treatment.

CASE DEFINITION

Brain parenchymal inflammation associated with neurologic dysfunction is the strict definition of confirmed encephalitis.[1] However, due to the rarity of premortem brain biopsy specimens available for histopathologic confirmation (particularly in children), clinical correlates are used to infer evidence of probable brain inflammation. Wide variability in criteria used and emphasized by pediatric neurologists and infectious diseases subspecialists was previously used to infer a clinical diagnosis of encephalitis.[2] In 2013, the International Encephalitis Consortium (IEC) created simplified consensus diagnostic criteria for a standardized case definition of encephalitis and encephalopathy of a presumed infectious or autoimmune etiology.[3] Altered mental status for more than 24 hours without an alternative cause is required as evidence of neurologic dysfunction. In addition, supplemental minor criteria must be present (2 for possible, $\geq$3 for probable or confirmed): fever greater than or equal to 38°C within 72 hours, seizures, new focal neurologic findings, cerebrospinal fluid (CSF) pleocytosis ($\geq$5 white blood cells/μL), neuroimaging with brain parenchymal changes, or electroencephalogram (EEG) consistent with encephalitis (**Fig. 1**). Confirmed cases require pathologic confirmation on brain biopsy, evidence of infection with a microorganism associated with encephalitis, or laboratory evidence of an autoimmune condition associated with encephalitis.

The IEC case definition combines previously distinct categories of encephalopathy and encephalitis without differentiating infectious from postinfectious or noninfectious processes, which may have important therapeutic implications. In cases with altered mental status greater than or equal to 24 hours without signs of an inflammatory response (fever, CSF pleocytosis, parenchymal changes on neuroimaging), a clinical diagnosis of encephalopathy, rather than encephalitis, is appropriate. In cases meeting encephalitis criteria with CSF pleocytosis, meningeal signs, or leptomeningeal enhancement, a clinical diagnosis of meningoencephalitis may be more descriptive.[4]

Several factors should be considered when applying the IEC case definition to pediatric patients. Simple and complex febrile seizures are common occurrences in young children and, in isolation, do not necessitate pursuing a workup for encephalitis if the child has returned to baseline mental status. Normal CSF white blood cell (WBC) counts in infants are higher than those cited for adults and a 95th percentile cutoff of less than or equal to 19 WBCs/μL for infants less than or equal to 1 month and less than or equal to 9 WBCs/μL for infants 1 to 2 months are more commonly used to define pleocytosis in these age groups.[5] Young infants are more likely to have infectious encephalitis without pleocytosis, particularly with enterovirus (EV; ~50%) or human parechovirus (HPeV; pleocytosis uncommon).[6–8] Therefore, as the IEC criteria suggest, CSF pleocytosis is a supportive but not necessary criterion for encephalitis, particularly in young infants.

EPIDEMIOLOGY

Overall, there were 7.3 encephalitis cases per 100,000 person years in the United States during 2000 to 2010,[9] with peak incidence in infants less than 1 year (13.5 per 100,000) and lowest in children ages 10 to 14 years (4.1 per 100,000).[9] Hospital