

# Encephalitis in Previously Healthy Children

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## PRACTICE GAP

Children experience a variety of outcomes after encephalitis, with 42% of all patients having incomplete neurologic and functional recovery. The most common pediatric encephalitides are reviewed herein, including key components of their diagnostic evaluation, appropriate empirical treatments, and anticipated long-term sequelae.

## OBJECTIVES *After completing this article, readers should be able to:*

1. Recognize the most common infectious and autoimmune pediatric encephalitides.
2. Describe an initial approach to a diagnostic evaluation when there is clinical concern for encephalitis, including laboratory data and imaging.
3. Understand agents used in empirical antimicrobial treatment and immunomodulating therapy for infectious and autoimmune encephalitides, respectively.
4. Appreciate the variable long-term outcomes seen in encephalitis.

## ABSTRACT

Encephalitis is defined as altered mental status for more than 24 hours accompanied by 2 or more findings concerning for inflammation of the brain parenchyma: fever, seizures or other focal neurologic disorders, cerebrospinal fluid pleocytosis, and abnormal neuroimaging and electroencephalographic findings. Herpes simplex virus causes the most severe form of virus-induced encephalitis; the early administration of acyclovir can improve the prognosis of this disease. The rising interest in autoimmune causes of encephalitis, most notably anti-*N*-methyl-D-aspartate receptor, should prompt the clinician to consider immunomodulatory treatments, which may improve outcomes. A broad testing panel may be necessary to detect the etiologic agent; a few published pediatric cases suggest that infectious and autoimmune causes may occur concurrently in the same patient with encephalitis. More than 40% of children diagnosed as having encephalitis will not return to their previous level of neurologic function after resolution of their disease, although outcomes are highly variable depending on the etiologic agent.

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### ABBREVIATIONS

CSF	cerebrospinal fluid
EEG	electroencephalogram
EV	enterovirus
FDA	Food and Drug Administration
HSV	herpes simplex virus
IVIG	intravenous immunoglobulin
MRI	magnetic resonance imaging
NGS	next-generation sequencing
NMDAR	<i>N</i> -methyl-D-aspartate receptor
PCR	polymerase chain reaction
WNV	West Nile virus

## DEFINITION AND PATHOPHYSIOLOGY

Encephalitis is defined as inflammation of the brain with resultant neurologic dysfunction, often a consequence of direct infection (eg, virus) or a noninfectious process (eg, an autoimmune cause). (1)(2) A consensus statement by the International Encephalitis Consortium outlines diagnostic criteria for possible and probable/confirmed encephalitis. (2) A requirement for this disease is altered mental status for >24 hours without an alternative diagnosis. Additional criteria to support the diagnosis of encephalitis include 2 or more of the following: fever (>100°F [ $>38^{\circ}\text{C}$ ]) within 72 hours, seizures (new onset or different than preexisting seizure history), new focal neurologic findings, cerebrospinal fluid (CSF) pleocytosis (white blood cell count,  $>5/\mu\text{L}$  [ $>0.01 \times 10^9/\text{L}$ ]), abnormal neuroimaging findings consistent with encephalitis, and/or abnormal electroencephalogram (EEG) readings consistent with encephalitis. (2)

Pediatric encephalitides can be categorized as infectious or autoimmune. Historically, infectious agents accounted for most documented etiologies of encephalitis. Before the use of vaccines, measles, mumps, varicella, and polio were among the top causes. With the widespread use of vaccinations, other viral etiologies, such as herpes simplex virus (HSV) and enterovirus (EV), rose to the top of the infectious etiologies. (3)(4) The pathophysiology of infectious encephalitis is usually by hematogenous spread of the pathogen into the CSF after systemic infection. (5)

Autoimmune encephalitides are recently described medical phenomena. Their pathogenesis is attributed to the body's immune response to a preceding antigenic stimulus. (1) The prototype of these diseases is anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis. Anti-NMDAR arises when a patient develops antibodies against the NR1 subunit of the NMDAR. Increased interest in autoimmune encephalitis has driven the discovery of other antibodies that may be attributed as possible causative agents for encephalitis.

The incidence of pediatric encephalitis is unclear given the diverse etiologies, inconsistent definitions of encephalitis, and denominator populations across studies. Recent reports note that cases of pediatric encephalitis may be increasing, (6) due in part to recognition of autoimmune etiologies of these causes (1)(7)(8)(9)(10) and improvements in describing abnormalities in brain parenchyma through the use of magnetic resonance imaging (MRI). A large proportion (ie, up to 30%) have an undiagnosed etiology. (8) This review focuses on encephalitis in the healthy, immunocompetent pediatric patient.

## SPECIFIC ETIOLOGIES

### Herpes Simplex Virus

HSV should be considered in all children suspected of having encephalitis given the severe morbidity associated with delayed or incorrect treatment of this potentially devastating viral encephalitis. (1) It is among the most common infectious causes of pediatric encephalitis in the postvaccine era, (3) although exact numbers are unclear given that it is not a nationally reportable infection. Beyond the neonatal period, the serotype is almost exclusively HSV-1. Pediatric HSV encephalitis may be a manifestation of either primary disease (when virus from an actively shedding individual contacts the oral mucosa or abraded skin of the child) or reactivation (when the virus emerges from latency in the trigeminal ganglia). The virus has a predilection for the temporal lobes of the brain, as found on brain imaging or EEG monitoring. Given its sporadic nature, there is no seasonality to HSV encephalitis.

### Enterovirus

EV is among the top causes of encephalitis in children, most frequently occurring in the first year of life. (11) Incidence rates are difficult to elicit, again (similar to HSV) because EV is not nationally reportable. EV is spread through fecal-oral and respiratory transmission, and subsequent replication and viremia then seed end organs such as the central nervous system. Seasonality does factor into diagnostic suspicion, given that EV incidence peaks in the summer and fall.

### West Nile Virus

West Nile virus (WNV) is the most common arbovirus in North America causing neuroinvasive disease (including encephalitis). It is so named due to being first discovered in the West Nile area of Uganda in 1937. Analysis of all cases of WNV-associated neuroinvasive disease shows that less than 4% involve children younger than 18 years, (12) but sheer overall numbers of WNV in the population-at-large still renders a high case number of pediatric WNV infections annually. Encephalitis composes approximately half of all pediatric WNV neuroinvasive disease. (13) Compared with other arboviruses, WNV does not have a clear geographic specificity, having been reported throughout the United States (except Hawaii and Alaska). WNV is transmitted through the bite of infected *Culex* mosquitos. Seasonality is important in diagnostic suspicion given that summer is the major time for its responsible mosquito vector.

## La Crosse Virus

La Crosse virus is the second most common arbovirus to cause neuroinvasive disease in North America, and it is so named due to it being first discovered and isolated from a child who died from fatal meningoencephalitis in La Crosse, Wisconsin. Although sheer numbers from the general population lag behind WNV, 88% of all encephalitis attributed to La Crosse virus occurs in children younger than 18 years. (13) There is a clear geographic specificity, with most cases originating from the Appalachian and Midwestern region of the United States. (13)(14)(15) La Crosse virus is transmitted through the bite of infected *Aedes* mosquitoes. Similar to WNV, there is a seasonality (late spring through early fall) to this viral disease given its arboviral vector.

## Zika Virus

Zika virus is so named due to discovery of this virus in the Zika forest of Uganda in 1947. This pathogen has captured the attention of clinicians due to its causation of infant microcephaly and neurologic deficits after prenatal exposure. However, children (older than 1 month) may also acquire Zika virus encephalitis. Transmission occurs from the bite of infected *Aedes* mosquitoes (*Aedes aegypti* and less commonly *Aedes albopictus*). The major risk factor is residence in or travel to areas in which these mosquitoes are present and there are identified ongoing outbreaks. The seasonality of Zika virus should place it in the differential of a patient with encephalitis presenting in the summer and early fall.

## AUTOIMMUNE ENCEPHALITIS

*Autoimmune encephalitis* is a collective term for a variety of diseases that occur when there is an aberrant response of the immune system against neuronal cells. These diseases may be organized roughly into 4 groups: those that are neurologic manifestations of systemic autoimmune diseases (such as systemic lupus erythematosus), those that are paraneoplastic manifestations of primary cancers, those with antibodies against intracellular proteins, and those with antibodies against cell surface proteins (such as anti-NMDAR). (16) The oncologic association with the latter 2 autoimmune groups is not entirely correlated, although anti-NMDAR encephalitis was first described in association with ovarian teratomas in young women. (17)(18) Case numbers of autoimmune encephalitis may, ultimately, if not already, outnumber those of viral encephalitides. At minimum, the incidence of NMDAR encephalitis seems to exceed the rate for a single viral etiology in pediatric patients in the United States. (19)

Autoimmune causes of encephalitides have less clear epidemiologic patterns and identifiable risk factors compared with

infectious etiologies. Interestingly, infection itself can be a risk factor for autoimmune encephalitis because up to 20% of patients with HSV develop anti-NMDAR antibodies. (20) There are 2 published cases of children with anti-NMDAR encephalitis attributed as a complication from active HSV and tuberculosis disease (each with 1 patient). (21)

Congenital immune-mediated encephalitis may be of particular interest to pediatricians. Several publications have described cases of infants developing signs from transplacental transfer of autoantibodies from both symptomatic and asymptomatic mothers. (22) These signs may include neurologic manifestations, poor feeding, poor respiratory effort, and lethargy at birth. Duration of illness is usually transient because the antibodies are eliminated by the infant, although at least 1 fatality has occurred in a symptomatic infant. (22)

## PRESENTATION

There is considerable overlap in symptoms between infectious and autoimmune encephalitis. As mentioned earlier, altered mental status for longer than 24 hours is necessary. A variety of accompanying clinical features include fever (67%–80%), seizure (33%–78%), headache (43%), weakness or pyramidal signs (36%–78%), agitation (34%), or decreased consciousness (47%). (8)(23) Viral encephalitis is more likely to cause fever compared with autoimmune encephalitis. The presentation for autoimmune encephalitis tends to be more chronic, with delayed diagnosis up to several weeks. (5)

Although neurologic deficits are part of the classical presentation, physical examination findings other than those involving the central nervous system should be sought because other findings potentially provide diagnostic clues for infectious causes. For example, cutaneous lesions involving the hands, feet, and mouth may suggest EV infection, whereas vesicular lesions on an erythematous base may suggest HSV or varicella as an etiology. (7)

## DIAGNOSTIC TESTING

In considering infectious etiologies, a careful history of signs, symptoms, and epidemiologic risk factors is of utmost importance to narrow the differential diagnosis. Important items to identify include geographic areas of travel or residence, recreational and occupational exposures, insect or animal contact (such as ticks or mosquitoes), and seasonality. Autoimmune encephalitides should be considered in a patient who presents with mood, behavior, or personality changes that resemble acute psychosis.

Diagnostic evaluation of a child with suspected encephalitis always includes CSF studies, which may be accompanied by

serum serological testing and neuroimaging. The Table guides the clinician to organize testing in a tiered manner, focusing on treatable or common conditions, followed by other tests if the patient does not improve and initial testing is unrevealing for the etiologic agent. These latter tests should be prioritized by risk factors (eg, patient age, seasonality of presentation, arbovirus exposure, geography and travel history, and non-adherence to the childhood vaccine schedule).

In encephalitis, CSF studies often reflect a lymphocytic pleocytosis with elevated protein levels and normal glucose levels. (5)(6) Autoimmune encephalitis tends to have a lower level of CSF pleocytosis, (24) followed by higher levels in infectious encephalitis. HSV encephalitis was historically reported to have elevated levels of red blood cells given the hemorrhagic nature of brain parenchymal lesions; hemorrhagic fluid has become rare, however, given that diagnosis is made earlier and, hence, the intracranial lesions have not evolved to the point of hemorrhaging. (25) If hemorrhagic fluid is found, it is generally attributed to the lumbar puncture technique.

Evaluation of any case of pediatric encephalitis should include polymerase chain reaction (PCR) of the CSF against HSV, given the availability of treatment to ameliorate the poor prognosis. PCR has become the gold standard to diagnose HSV and EV. Targeted PCR can be developed at individual institutions rather than using commercially available PCR kits that involve sending samples to outside laboratories, which would prolong the time to results. Although “homegrown” PCR testing offers the advantages of low cost or rapid turnaround time, providers should understand the sensitivity and specificity of their own laboratory’s test, how the test is validated, and how quality control is performed to feel confident in using the test result to direct clinical management.

Multiplex syndromic PCR panels (such as those developed for diarrheal, respiratory, or meningitis/encephalitis presentations) have gained popularity in recent years given their effect on turnaround time (4–24 hours for PCR compared with days for microbiologic cultures) and broad spectrum of pathogen detection. These panels may test for bacterial, viral, and/or fungal etiologies. Although these multiplex PCR panels, compared with microbiologic cultures, may provide a timely diagnosis, decreased length of hospital stay, and less need for invasive diagnostic procedures and may help direct antimicrobial therapy, they are not without limitations. Limitations include decreased sensitivity compared with targeted PCR assays and confusion about whether positive results for latent viruses in an immunocompetent patient (eg, cytomegalovirus, Epstein-Barr virus, human herpesvirus-6) represent true disease or viral reactivation in a time of stress.

For arboviral diagnosis, the clinician needs to rely on virus-specific immunoglobulin M antibodies in the CSF because there is usually no PCR method for common arboviruses. (13)

A promising addition to diagnostic testing for encephalitis is metagenomic next-generation sequencing (NGS) of CSF. A published study of 204 patients (~20% being <18 years of age) showed that in 58 cases of meningitis and encephalitis attributed to infectious etiologies, 22% (n = 13) were detected solely by NGS. (26) Of those detected by NGS alone, 7 of these results guided clinical management. Further refinement to address concerns about false-negative results, as well as optimal timing and appropriate patients for testing, are needed before Food and Drug Administration (FDA) approval and widespread commercial use. (26)

When autoimmune encephalitis is suspected, autoantibodies in the serum and CSF are sought through indirect immunofluorescence assay and confirmatory Western blot analysis. These tests are available in reference laboratories, usually as part of a panel for autoimmune testing. Autoimmune evaluation is usually conducted simultaneously with an infectious evaluation, in the event that any identified infections may have a treatment that, when implemented, may speed the recovery of the autoimmune disease.

MRI of the brain with and without intravenous contrast is the first-line imaging test for pediatric patients presenting with suspected intracranial infection. This test is designated as “usually appropriate” according to the American College of Radiology Appropriateness Criteria® imaging guidelines. (27) For pediatric patients presenting with suspected autoimmune encephalitis, a dedicated epilepsy protocol MRI with and without intravenous contrast is recommended because this study is tailored for evaluation of the hippocampi, which are most commonly affected in the autoimmune encephalitides. Computed tomography of the head without intravenous contrast is recommended as a first-line study in pediatric patients presenting with acute mental status change and suspected intracranial infection because this test can rapidly and accurately exclude all acute neurosurgical emergencies. (27) However, computed tomography is not recommended in the evaluation of pediatric encephalitis (without acute mental status change) because it has lower diagnostic accuracy than MRI and requires patient exposure to ionizing radiation. Patterns seen on neuroimaging may be helpful to differentiate between infectious and autoimmune encephalitis; (5) these patterns are by no means universal, however, and should always be interpreted within the clinical context of the patient’s presentation. MRI patterns include autoimmune etiologies localizing to the limbic system (can be unilateral or bilateral) and HSV encephalitis unilaterally affecting the medial

temporal lobe. (28)(29)(30) Figure 1 depicts a typical case of HSV encephalitis from our institution. Unfortunately for diagnostic purposes, most infectious causes of encephalitis are not associated with a typical imaging pattern.

Initial experience with anti-NMDAR encephalitis indicated a strong association of ovarian teratoma in almost 60% of affected young women. (31)(32) Increasing diagnosis of this disorder, in males as well as females, showed that younger female patients (aged <18 years) had a lower incidence (31%) of associated tumors. (18) Despite a likely low yield, abdominal/pelvic ultrasonography may allow resection of a tumor to alleviate the encephalitis. (33) Figure 2 depicts a typical case of anti-NMDAR encephalitis associated with an ovarian tumor.

The role of EEG in the evaluation of encephalitis is controversial. The Infectious Diseases Society of America guidelines recommend obtaining EEGs in all encephalitic patients. (1) In contrast, the consensus guidelines from of the United Kingdom do not routinely recommend EEGs because most patients with encephalitis will have abnormal results. (7)(34) Consultation with experts in pediatric neurology is indicated to evaluate the utility of EEG for a particular patient. If EEG is performed, most patients with autoimmune encephalitis demonstrate interictal and background abnormalities. (30) EEG abnormalities are often nonspecific, although generalized or focal slowing may be seen, particularly in anti-NMDAR encephalitis. (20)

The provider should recognize that a large proportion of pediatric cases of encephalitis (up to 30%) have no identifiable etiology. (8) The decision to aggressively pursue an etiology depends on the clinical status of the child. In cases of static or worsening symptoms, continued diagnostic testing may provide a tangible answer that would be reassuring to both patients and medical providers. Close attention to new historical details and evolving physical examination findings may guide additional testing, although

diagnostic evaluation should always be in concert with ongoing supportive measures. In addition, continued evaluation should be weighed against risks of invasive procedures and financial costs of additional testing.

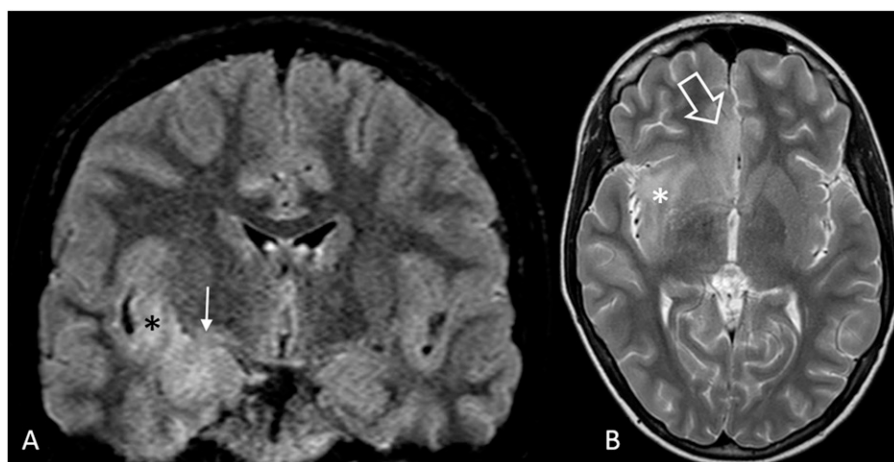
## DIFFERENTIAL DIAGNOSIS

Encephalitis can be difficult to distinguish from meningitis because the two often present with the overlapping signs of fever, headache, and altered mental status. (1) It is unsurprising, then, that the term *meningoencephalitis* may often be used to describe a child's presentation. (35) It can be helpful, in guiding initial diagnostics and therapeutics, to differentiate encephalitic or meningitic symptoms based on whether there is evidence of brain parenchymal dysfunction (eg, seizures, weakness, focal deficits) or meningeal irritation (eg, nuchal rigidity), respectively. (35)

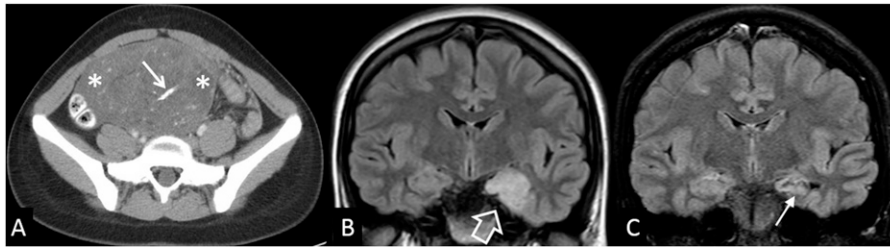
Because seizures, headaches, and focal neurologic deficits are common presentations for intracranial processes, space-occupying lesions such as tumors and abscesses should be promptly ruled out given vastly different treatment ventures. Likewise, ischemic and hemorrhagic strokes should be considered in the differential diagnosis given the need for prompt intervention.

Care should be taken to distinguish encephalitis from encephalopathy as well. Encephalopathy is a disease state characterized by disruption of brain function in the absence of inflammation of brain parenchyma (1)(2)(7) that lacks the additional criteria outlined by the International Encephalitis Consortium. (2) Encephalopathy can occur in the setting of metabolic disturbances, hypoxia, ischemia, intoxication, medications, organ dysfunction, or even systemic infection and is treated quite differently from encephalitis. (1)

Acute disseminated encephalomyelitis should be included in the differential diagnosis. Acute disseminated



**Figure 1.** Magnetic resonance images of herpes simplex virus (HSV) encephalitis. This 12-year-old boy presented in status epilepticus after 1 week of fever, headache, and vomiting. A. Coronal fluid-attenuated inversion recovery image depicts abnormal increased signal in the right amygdala (thin arrow) and right anterior insula (black asterisk). B. Axial T2-weighted image depicts abnormal increased signal in the right insula (white asterisk) and olfactory portions of the right frontal lobe (wide arrow). The asymmetrical distribution of signal abnormality in the limbic structures seen here is typical of HSV encephalitis. Cerebrospinal fluid qualitative polymerase chain reaction detected HSV-1.



**Figure 2.** Computed tomography (CT) scan and magnetic resonance images (MRIs) of ovarian tumor-associated anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis. A large pelvic mass was discovered in this 17-year-old female during a routine annual clinic visit. A. CT scan of the pelvis shows a large pelvic mass (asterisks) with internal coarse calcifications (thin arrow). During treatment planning for the tumor, the patient developed a severe headache of several days' duration followed by seizure. B. MRI of the brain was performed and revealed asymmetrical swelling and increased fluid-attenuated inversion recovery signal in the left amygdala (wide arrow) and left hippocampus. The ovarian tumor, which was a teratoma, was resected. An elevated cerebrospinal fluid NMDA titer (1:2,560) was found, consistent with anti-NMDAR encephalitis. C. Follow-up MRI 6 months later shows atrophy of the left amygdala (thin arrow) and hippocampus.

encephalomyelitis is due to postinfectious demyelination. It is often preceded by a prodromal illness, which is postulated to lead to the development of autoantibodies, causing a multifocal demyelinating process in the central nervous system. (36)

## TREATMENT

### Empirical Antimicrobial Coverage

Given that HSV is the leading cause of severe encephalitis, is more frequently associated with poor outcomes than other viral causes, and is treatable, acyclovir therapy should be quickly initiated in all encephalitic patients until HSV is ruled out. (1)(7)

Antibacterial agents are frequently started given the clinical overlap with acute bacterial meningitis because there are improved outcomes after swift empirical treatment for bacterial meningitis. Vancomycin and a third-generation cephalosporin (eg, ceftriaxone) are typically used to cover *Streptococcus pneumoniae*, *Haemophilus influenzae* serotype b, and *Neisseria meningitidis*. Providers may consider empirical use of ampicillin for coverage of *Listeria monocytogenes* if there is concern for consumption of contaminated food (eg, deli meats or raw dairy products). Antibacterial agents are typically discontinued once bacterial cultures from CSF and blood are negative.

A potential role for mycoplasma in pediatric encephalitis has intrigued scientists. Confirming the role of mycoplasma has been hampered by difficulty in interpreting various microbiologic tests (serological tests may indicate active or previous infection; antigen may be detected in the respiratory tract long after the acute respiratory infection has resolved). It is unclear whether antimicrobial treatment affects recovery of encephalitis attributed to mycoplasma. There is no evidence suggesting that antimicrobial treatment affects the disease process, even with PCR detection of mycoplasma in the CSF. (37) It is difficult to recommend empirical therapy

of a disease without a definitive diagnostic test or therapeutic end point.

In otherwise healthy, immunocompetent children, CSF tested with a PCR multiplex panel may detect cytomegalovirus, Epstein-Barr virus, or human herpesvirus-6. This may not be clinically significant, but merely reflect bystander reactivation in the setting of stress. Therefore, these patients would not require antiviral therapy.

### Immunomodulators for Infectious and Autoimmune Etiologies

Corticosteroids may play a role in the treatment of encephalitis. Among the viral encephalitides, corticosteroids are more commonly used in varicella zoster encephalitis given the vasculitic nature of this infection and may be used in HSV encephalitis if there is concern for cerebral edema. (35)

In autoimmune encephalitis such as anti-NMDAR, the therapeutic goal is inhibition of the immune response. First-line therapies include intravenous high-dose corticosteroids, intravenous immunoglobulin (IVIG), and plasma exchange. The mechanism of action from corticosteroids is a non-specific damping of the immune system. IVIG seems to act, in part, by decreasing the overall burden of the offending autoantibody by dilution. (38) Plasma exchange may be used in autoimmune encephalitis for its potential to remove the disease-causing antibodies. It is difficult to tease out the individual contributions of these 3 agents in assessing therapeutic outcomes because some combination is usually used. (21)(39) A recent systematic review found that plasma exchange tends to be performed if anti-NMDAR encephalitis is refractory to corticosteroids and IVIG. (40)

If there is a poor patient response to first-line therapies, other aspects of the immune system (eg, B cells and cytokines) may be targeted. (38)(40) Rituximab is a commonly used second-line agent in autoimmune encephalitis and

**Table.** Diagnostic Evaluation of Pediatric Encephalitis

COMMON AND/OR TREATABLE CONDITIONS		CSF STUDIES	RISK FACTORS OR IF PATIENT IS NOT IMPROVING
Lumbar puncture			Autoimmune panel (name and components listed by commercial laboratory)
Opening pressure			Meningoencephalitis multiplex PCR panel
Cell count (white blood cell count + differential count, red blood cell count)			CSF immunoglobulin M for specific arboviruses (West Nile virus, La Crosse virus)
Protein			Extra CSF to freeze (eg, for metagenomic next-generation sequencing)
Glucose			
Gram-stain and bacterial culture			
HSV PCR			
Enterovirus PCR			

COMMON AND/OR TREATABLE CONDITIONS		NON-CSF STUDIES	RISK FACTORS OR IF PATIENT IS NOT IMPROVING
Complete blood cell count with differential count			Autoimmune panel (name and components listed by commercial laboratory)
Complete metabolic panel			Respiratory pathogen PCR panel
Blood culture			Abdominal/pelvic ultrasonography to evaluate for potentially resectable tumors
HSV serum PCR			Extra red-top serum tube to freeze (eg, for pre-IVIG serological tests, if IVIG is subsequently used)
Enterovirus serum PCR			

NEUROIMAGING	
Magnetic resonance imaging of the brain	

The tests are arranged in order of preference for treatable or common conditions, followed by other tests if the patient does not improve and initial testing is unrevealing for the etiologic agent. CSF=cerebrospinal fluid, HSV=herpes simplex virus, IVIG=intravenous immunoglobulin, PCR=polymerase chain reaction.

exerts its effect by binding CD20, thus depleting B cells and halting the production of antibodies. (41) The published literature highlights the variability in timing of administration during the disease process, making causality between treatment and outcomes difficult. (20)(41) In a multicenter, retrospective study of 144 children with autoimmune and inflammatory central nervous system conditions, initiation of rituximab ranged from 3 weeks to 9.5 years after diagnosis. (41) Rituximab was found to cause infusion reactions, anaphylaxis, and infectious complications (including need for hospitalization and intravenous antibiotics). (41) Given the potential for morbidity associated with rituximab treatment, consultation with a pediatric neurologist is recommended.

### REHABILITATION INTERVENTIONS

Data on the impact of rehabilitation after encephalitis are sparse. (42)(43) Cognitive therapy, behavioral therapy, and/or physical therapy seem to have a positive effect on long-term functional

outcomes, although it is difficult to separate the natural course of the encephalitic disease from possible benefit from rehabilitation. Enlisting the expertise of therapists in cases of encephalitis may be encouraged, although optimal timing from onset of symptoms to initiation of rehabilitation is not clear.

### OUTCOMES

Outcomes are highly variable among the various encephalitides and depend on the etiologic agent. A retrospective study involving 164 children performed in Australia demonstrated that many children, after being diagnosed as having either infectious or autoimmune encephalitis, experience an “abnormal” outcome, including difficulties in learning (28%), behavior (24%), and speech (17%). (8) Seventeen percent of children ultimately were diagnosed as having epilepsy. (8) One meta-analysis examining outcomes in patients with infectious encephalitis demonstrated that 42% experience incomplete recovery, 6.7% demonstrate severe sequelae, and 17.5%

eventually demonstrate a decrease in their intelligence quotient more than 1 SD below the mean. (44)

Of patients with infectious encephalitis, those with HSV encephalitis tend to be the most severely affected, with up to 64% experiencing late effects; a broad range of deficits, including neuropsychological dysfunction, developmental delay, and focal motor deficits, have been reported. (25)(45) Children with EV encephalitis, on the other hand, have fared better in the long-term. In a prospective study of a large Taiwanese outbreak of EV-71 (a well-known neuroinvasive EV serotype), 51 of 63 children (81%) had no deficits at mean follow-up of 2.8 years (range, 1.4–4.9 years). (45) Longitudinal epidemiologic studies of acquired Zika virus infection are needed to better understand neurodevelopmental sequelae, (46) although subtle long-term neurologic defects have been reported years after resolution of primary infection.

Of patients with autoimmune encephalitis, approximately one-third demonstrate full recovery, one-third demonstrate partial recovery, and one-third show limited recovery with severe deficits. This has been demonstrated in both observational studies in single institutions and systematic reviews of patients diagnosed as having anti-NMDAR encephalitis. (18)(47)(48) Time to recovery may be prolonged, with one observational study citing at least a 6-week interval between presentation and signs of initial improvement. (18) Use of immunotherapy generally correlates with improved outcomes, (48) although optimal timing for initiation of these therapies is unclear. (41)

Several studies have suggested predictors of poor outcomes of encephalitis, including status epilepticus, ICU admission, presence of a movement disorder, and (with autoimmune encephalitis) a delay of immunotherapy (although what constitutes a delay is unclear). (8)(48) The presence of diffusion restriction on MRI, usually representing cytotoxic edema and irreversible cell death, is also a poor prognostic indicator in pediatric patients. (8)

Disease relapse may be seen. Of an Australian cohort of 164 pediatric patients with encephalitis (either infectious or autoimmune), 8 (5%) relapsed. (8) Even higher rates have been reported in HSV encephalitis and anti-NMDAR encephalitis, with up to 30% and 25% of children, respectively, experiencing relapse. (25)(48)

## CONCLUSION

A diagnosis of encephalitis in children has the potential to negatively impact their trajectory of health, development, and quality of life, although outcomes are highly variable. Swift recognition, diagnostic evaluation, and treatment is imperative to cover potentially treatable causes within the wide sphere of infectious and autoimmune encephalitides. Prompt

administration of acyclovir may decrease morbidity and mortality associated with HSV encephalitis.

## Summary

- Based on consensus, the general pediatrician should recognize enterovirus and herpes simplex virus (HSV) as causes of the most frequent and the most severe forms of infectious encephalitis. Likewise, medical providers should appreciate anti-N-methyl-D-aspartate receptor as the most widely known cause of autoimmune encephalitis.
- Based on consensus, the initial evaluation of encephalitis should focus on the most common and treatable causes, guided by epidemiologic factors such as age, geography, and seasonality.
- Based on strong evidence, randomized controlled trials have consistently shown that early administration of acyclovir is imperative in decreasing the morbidity and mortality associated with HSV encephalitis. (1)
- Based on strong evidence, prospective studies and meta-analyses have demonstrated that long-term outcomes are highly variable in both infectious and noninfectious encephalitis, with children infected with HSV experiencing worse outcomes. (44)(45)

**To view teaching slides that accompany this article, visit <http://pedsinreview.aappublications.org/content/42/2/68>.**

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QUIZ

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1. A pediatric resident in Colorado performs a retrospective study on the epidemiology and etiology of encephalitis in immunocompetent children older than six weeks of age over the past 15 years. Which of the following is the most likely conclusion of the study?
  - A. Approximately 30% had an undiagnosed etiology.
  - B. *Borrelia burgdorferi* was the most common overall etiology.
  - C. Herpes simplex virus 2 was the most common viral etiology.
  - D. Powassan virus was the most common arbovirus causing encephalitis.
  - E. Subjects with enterovirus had the worst prognosis.
2. A previously healthy 17-year-old girl is brought to the emergency department by her parents with a 4-day history of worsening headaches and confusion. Over the past day she has become much more agitated and seems to be having visual hallucinations. Her parents think she felt warm yesterday but there is no documented fever. Her vital signs are normal. Other than altered mental status the only finding on physical examination is a left lower abdominal/pelvic mass. A computerized tomography (CT) scan of the head is done and is normal. Lumbar puncture is performed, and cerebrospinal fluid (CSF) cell count shows 11 red blood cells (RBC) and 52 white blood cells (WBC) (81% lymphocytes, 11% monocytes, 8% neutrophils). CSF glucose is 66 mg/dl and protein 42 mg/dl. Gram stain of the CSF shows no organisms. Magnetic resonance imaging of the brain shows increased FLAIR signal in the left amygdala and hippocampus. Pelvic sonography shows a 10 cm cystic ovarian mass on the left. Which of the following is the most likely etiology for her current symptoms?
  - A. Herpes simplex virus 2 (HSV-2).
  - B. Human herpes virus 6 (HHV-6).
  - C. Parechovirus.
  - D. N-methyl-D-aspartate receptor (NMDAR) antibody.
  - E. *Rickettsia rickettsii*.
3. A previously healthy and fully immunized 11-year-old boy is brought to the emergency department (ED) by his parents with a 3-day history of worsening headache and intermittent fever. Over the past day he is much sleepier and seems confused and agitated at times. While in the ED he had a brief generalized tonic-clonic seizure. His temperature is 38.3°C; other vital signs are normal. He is difficult to arouse and does not respond to questions. The remainder of his examination including fundoscopic examination is normal. Which of the following is the most appropriate next step in diagnosis?
  - A. Chest radiography.
  - B. CT scan of his head and neck.
  - C. Electroencephalogram.
  - D. Lumbar puncture.
  - E. Nasopharyngeal swab for respiratory pathogen multiplex PCR.

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4. For the patient in question 3, which of the following is the most appropriate initial empiric antimicrobial therapy?
- A. Acyclovir, ampicillin, and doxycycline.
  - B. Acyclovir, ceftriaxone, and vancomycin.
  - C. Ampicillin, gentamicin, and doxycycline.
  - D. Ampicillin, gentamicin, and vancomycin.
  - E. Ceftriaxone, doxycycline, and vancomycin.
5. A previously healthy 16-month-old girl is admitted to the hospital with a 2-day history of fever, some fussiness, and mild nasal congestion. One hour prior she had a 2-3 minute generalized tonic-clonic seizure. She is sleeping but does wake up with stimulation and recognizes her parents. Her temperature is 39.1°C. She has no focal findings on physical examination. Lumbar puncture is performed. CSF cell count shows 0 RBC, 3 WBC, glucose 62 mg/dl, and protein 23 mg/dl. CSF gram stain shows no organisms. A CSF multiplex PCR panel is only positive for human herpes virus 6 (HHV-6). Which of the following is the most appropriate antiviral therapy?
- A. Acyclovir.
  - B. Cidofovir.
  - C. Foscarnet.
  - D. Ganciclovir.
  - E. No antiviral therapy.

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