Encephalitis in the Pediatric Population

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Educational Gap

Management of encephalitis, which can be fatal, requires understanding of a broad range of causative agents, pathophysiologic mechanisms, clinical syndromes, and outcomes.

Objectives

After completing this article, readers should be able to:

1. **Know the many causes of encephalitis, including infectious, parainfectious, and noninfectious disorders.**
2. **Recognize the clinical features of encephalitis.**
3. **Be able to conduct a diagnostic investigation of a patient with encephalitis by using clinical and laboratory criteria.**
4. **Know the anticipated clinical course of different types of encephalitis.**
5. **Be familiar with the modalities used to treat encephalitis.**
6. **Understand the factors that influence the outcome in a patient who has encephalitis.**

Introduction

The broad definition of the term "encephalitis," that is, *inflammation of the brain*, necessitates acknowledgment of the enormous inclusivity of the topic. The most common interpretation of the term implies a direct invasion of the brain by an infectious pathogen, most commonly, viral, fungal, or parasitic. The topic also includes examples of meningitis mediated by bacteria or other agents, which can produce extrameningeal symptoms such as lethargy or seizures, in which case, the combined term "meningoencephalitis" is used.

There are also many examples of encephalitis not due to direct central nervous system (CNS) infections. Inflammatory processes due to an acute or chronic illness can result in an acute immune-mediated encephalitis, such as acute disseminated encephalomyelitis (ADEM), lupus cerebritis, and paraneoplastic syndromes. Agents or conditions that produce slowly progressive CNS symptoms, such as tertiary syphilis or "slow viruses" (the prion protein encephalopathies), also are considered examples of encephalitis. Table 1 lists only a limited number of the many pathogens and pathologic conditions that can cause either acute or subacute encephalitis. In this discussion, we will mainly address examples of acute encephalitis related to direct CNS infection and para-infectious processes involving the CNS. These examples embrace the major portion of the spectrum of disease presentation, course, and recovery, as well as mechanisms of cerebral injury.

In addition to the taxonomic classification in Table 1, causes of infectious encephalitis often are grouped according to the most common methods of transmission. "Arboviruses" are those spread by insect vectors, such as West Nile virus (WNV) and the equine encephalitis group (both by mosquitoes). Zoonotic causes of encephalitis not spread by intermediary insect vectors include many of the parasitic infections (larva migrans) and rabies. Community-acquired encephalitides, such as enterovirus, adenovirus, and late-childhood herpesvirus infections, generally are spread by person-to-person contact. Vertically transmitted pathogens include neonatal herpes simplex (HSV), rubella virus,

Abbreviations

ADEM: acute disseminated encephalomyelitis
CEP: California Encephalitis Project
CNS: central nervous system
CPP: cerebral perfusion pressure
CSF: cerebrospinal fluid
HSV: herpes simplex virus
IVIG: intravenous immune globulin
MS: multiple sclerosis
PCR: polymerase chain reaction
WNV: West Nile virus

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Table 1. Potential Causes of Acute Encephalitis

Agent	Subcategory	Specific Examples
Virus	Herpesviruses	Herpes simplex 1
		Herpes simplex 2
		Human herpes virus 6
		Varicella-zoster
		Cytomegalovirus
	Picornaviruses (Enteroviruses)	Coxsackievirus A
		Coxsackievirus B
		Echovirus
		Enterovirus 70
		Enterovirus 71
	Adenoviruses	Various subtypes
	Alphaviruses	Eastern equine encephalitis
		Western equine encephalitis
		Venezuelan equine encephalitis
	Flaviviruses	St Louis encephalitis
		West Nile virus
		Japanese encephalitis
		Tick-borne encephalitis
		Powassan encephalitis
	Bunyaviruses	California encephalitis
	Myxoviruses	Mumps encephalomyelitis
	Rhabdoviruses	Rabies
	Togaviruses	Rubella
	Retroviruses	Human immunodeficiency virus I and II
	Influenza viruses	Influenza A
		Influenza B
	Metapneumoviruses	Human metapneumovirus
Bacterium	Specific encephalitis syndromes	*Listeria monocytogenes*
		Francisella tularensis
		Rickettsia species
		Mycoplasma pneumoniae
		Chlamydia pneumoniae
	Other causes of bacterial meningitis	"Meningoencephalitis" when necrosis and direct brain invasion or inflammation occur
Fungus		*Cryptococcus neoformans*
		Blastomyces dermatitidis
		Histoplasma capsulatum
		Paracoccidioides brasiliensis
Parasitic infection	Primary amebic meningoencephalitis	*Naegleria fowleri*
		Balamuthia mandrillaris
	Raccoon roundworm encephalitis	*Baylisascaris procyonis*
	Neural larva migrans	*Toxocara canis*
		Angiostrongylus cantonensis (Asia)
Parainfectious immune-mediated response		Acute disseminated encephalomyelitis
		Acute hemorrhagic leukoencephalitis
		Bickerstaff brainstem encephalitis
		Post-infectious cerebellitis
		Mycoplasma encephalitis
Systemic inflammatory diseases		Systemic lupus erythematosus
Malignancies	Paraneoplastic syndromes	Antineuronal antibodies producing specific encephalitic syndromes

and cytomegalovirus, and likely many other viral agents. Vertical, symptomatic transmission of WNV has been well documented. Finally, sexual transmission is the major mechanism of infection for adult herpes simplex type 2 virus and HIV (which can produce an acute, often transient, meningoencephalitis in the absence of opportunistic infection).

Iconic examples of parainfectious encephalitis in children include ADEM and acute cerebellar ataxia. Variants of these conditions, such as acute hemorrhagic leukoencephalitis and Bickerstaff brainstem encephalitis, are reported primarily in adult and older adult populations. Parainfectious syndromes are differentiated in practice from acute infectious encephalitis based upon clinical history and a lack of supporting evidence for direct CNS invasion. In the case of ADEM, there is usually an antecedent illness or immunization, followed 2 to 30 days later by various focal neurologic symptoms, possibly accompanied by signs of meningeal irritation. The early presentation may be confused with acute infectious encephalitis, and some instances of each phenomenon may be categorized incorrectly. Lumbar puncture findings can be variable, ranging from normal to a mild or moderate lymphocytic pleocytosis with an elevated protein concentration. Acute cerebellar ataxia follows a similar course of antecedent illness, but with symptoms limited to the cerebellum (ataxia, nystagmus, and cerebellar dysarthria).

Infectious, parainfectious, and primary inflammatory causes of encephalitis are typically considered mutually exclusive. However, the example of *Mycoplasma*-related encephalitis illustrates some difficulty in differentiating direct versus indirect mechanisms of CNS disease, and the magnitude of the topic. Although widely regarded as a parainfectious phenomenon with variable pathology, up to 2% of these patients have *Mycoplasma* polymerase chain reaction (PCR)-positive cerebrospinal fluid (CSF), which might indicate some direct CNS invasion. *Mycoplasma* is a prevalent pediatric illness and cause of encephalitis. One hundred and eleven of 1988 patients referred to the California Encephalitis Project (CEP) tested positive for *Mycoplasma pneumoniae*; 76% of those affected were pediatric patients. (1)(2)

Epidemiology

Epidemiological data on encephalitis is organized according to identified agent. The CEP was initiated in 1998 for the collection of epidemiological data and is the most comprehensive database to date. It includes all referred immunocompetent individuals over 6 months of age and all clinical presentations, including chronic and slowly progressive encephalitis. Criteria for inclusion include encephalopathy or ataxia, plus at least one clinical finding (fever, seizures, focal neurologic deficits, CSF pleocytosis, abnormal neuroimaging, or abnormal EEG). By using a combination of CSF PCR, nasopharyngeal/throat specimen viral isolation, and acute and convalescent paired sera, all patients receive testing for herpesviruses, arboviruses, enteroviruses, respiratory viruses, measles virus, *Chlamydia* species, and *M pneumoniae*. Between 1998 and 2005, 1,570 patients were enrolled. A confirmed or probable causative agent was identified in only 16% of cases. Of identifiable causes, 69% were viral, 20% bacterial, 8% noninfectious (ie, autoimmune disease), 7% prion protein, 3% parasitic, and 1% fungal. Extensive testing procedures still revealed no identifiable cause in 63% of patients. (3) Among the more prominent causes of viral encephalitis, HSV accounted for only 2.5% of the CEP cases; in contrast, HSV was identified in 5% of 322 pediatric patients with acute encephalitis seen in one series between 1994 and 2005. (4)

Epidemics of infectious encephalitis have always attracted much media attention, such as the WNV outbreak first seen in the United States in New York City in 1999. Between 1999 and 2007, 1,478 pediatric cases of confirmed WNV infection occurred in the United States, of which 443 (30%) had neurologic involvement. Of those with neurologic symptoms, there were three fatalities. Overall, children accounted for only 4% of reported WNV infection cases, with an estimated median annual incidence of 0.07 per 100,000. The pediatric fatality rate contrasts favorably with the 12% mortality rate from the 1999 epidemic, in which the majority of symptomatic cases were elderly people. WNV is now an epidemiological risk factor throughout the contiguous United States and the Caribbean. (5) Although WNV remains the most commonly encountered arboviral encephalitis agent, California encephalitis viruses have the greatest proportion of pediatric symptomatic infections (88% of cases), and eastern equine encephalitis has the highest overall mortality rate of 42%.

The importance of local epidemiological information and seasonality cannot be ignored. Many cases of viral encephalitis either occur in epidemics, display a clear seasonal predilection, or both. For example, enteroviruses are most often seen in spring and summer; arthropod-borne illnesses, in the summer and fall. Respiratory virus-mediated cases often are specific to fall and winter. These elements of conventional epidemiological wisdom, however, should be subordinate to locally observed trends, such as cases of H1N1 influenza encephalitis observed during an out-of-season epidemic.

In contrast, ADEM tends to be more sporadically observed than many infectious causes, although population data in the United States have supported a winter-spring predilection for the condition. Recent data from Canada, however, failed to show this seasonality. (6) The inclusion criteria for ADEM strongly influences reported incidence, producing wide variations, with a range of 0.2 to 0.8 per 100,000 children in the United States and Canada, and 0.07 per 100,000 in Germany. Antecedent infectious illness or vaccination typically is identified in 50% to 75% of patients. Presenting symptoms are highly variable, as the range of reported incidences of any one neurologic symptom in pooled study data suggest. Outcomes statistics are similarly scattered, with a 57% to 89% reported rate of full recovery.

Mechanisms of Cerebral Injury

Infectious agents and parainfectious processes are presumed to mediate their acute symptoms through any combination of postulated mechanisms listed in Table 2. Evidence is best for the causes of fatal cases, in which wholesale parenchymal destruction is usually identifiable at necropsy, including direct neuronal and glial invasion with apoptosis, neuronophagia, vascular occlusion leading to infarction, and secondary effects of cerebral edema.

Evidence supporting largely immune-mediated mechanisms of injury (cytotoxic antibodies, cytokine effects, etc) is less direct, and more evident in parainfectious/inflammatory causes of encephalitis. In ADEM fatalities, perivenular lymphocytic infiltration with local myelinolysis is a hallmark finding on pathology specimens. (12) Evidence supporting the concept of antibody-mediated mechanisms derives mainly from the clinical efficacy of intravenous immune globulin (IVIG) and plasmapheresis in the treatment of ADEM. Demonstration of antibody targeting precise CNS molecules in human ADEM and other demyelinating disease cases is scarce, with poor concordance, even between individuals who have similar syndromes. Existing knowledge of autoantibodies targeting specific CNS molecules is derived mainly from experience with paraneoplastic syndromes in adults, eg, anti-Yo, anti-Hu, and anti-Purkinje cell antibodies. These mechanisms, however, produce subacute encephalitis or cerebellitis distinct from typical pediatric ADEM. Even in children with classic postinfectious cerebellitis, fewer than half display anti-Purkinje cell antibodies.

The lack of routinely detectable autoantibody in parainfectious CNS disease is likely attributable to both the large number of causative infectious agents and the multiplicity of possible targeting mechanisms. The latter may include both molecular mimicry and abnormal handling of normally occurring cellular antigens. For example, an invading virus may manufacture proteins that share epitopes with normal human myelin (mimicry), or may produce enzymes that cleave or misfold normal host proteins into immunologically unrecognized forms. For example, vaccinia virus core protein kinase cleaves myelin basic protein.

Even more difficult is the isolation of cytokine effects in producing CNS injury. Interleukins 6 and 8, interferon γ, and tumor necrosis factor α seem to be among those cytokines most commonly identified as correlating with

Table 2. Proposed Mechanisms of CNS Injury in Encephalitis and Myelitis[a]

Pathogen-mediated cell death
Direct neuronal invasion and cell lysis
Direct glial cell invasion and cell lysis
Mechanical and vascular injury
Cerebral edema with impairment of capillary integrity
Cerebral edema leading to herniation syndromes
Decreased cerebral perfusion pressure leading to ischemia
Vascular occlusion and infarction
Immune-mediated disease
Cytokine effects, including apoptosis
Cytotoxic antibody causing impaired neuronal function or apoptosis
Demyelination
Immune activation, including microglial cells, with neuronophagia
Neurotransmitter and neurophysiologic disturbances
Alterations in neuronal function leading to seizures and secondary apoptosis (eg, altered membrane potentials, balance of excitatory and inhibitory neurotransmitters)

[a]Italicized items are also proposed mechanisms in parainfectious processes.

severity of disease course or outcomes across multiple causes of encephalitis, both infectious and noninfectious (eg, lupus cerebritis), but with high variability between specific agents. High concentrations of interleukins 6 and 8 can be found in the CSF of patients with *Mycoplasma* encephalitis and Japanese encephalitis. Higher titers in a small number of Japanese encephalitis patients seemingly correlated with a lower survival rate. It is unclear if cytokines are causative of further CNS injury or are active markers of disease severity.

Presentation and Evaluation

The typical presentation of acute encephalitis consists of any combination of altered mental status, seizures, other behavioral changes, weakness, sensory disturbances, or nonepileptic movement disorders, in the absence of an identifiable external cause, such as intoxication, traumatic brain injury, or psychosocial stressors. In the younger child or infant, symptoms may be even less distinct, and can include uncharacteristic somnolence, disinterest in feeding, weak suck, irritability, loss of head control, or abnormal eye movements. Further clinical clues may include the presence of fever (either acutely or in the 1–4 week interval before the onset of symptoms), or meningeal irritation (Table 3). However, these supporting clues may not be apparent upon first presentation. Because the clinical symptoms of encephalitis include a very broad range in both scope and severity, suspicion should be high in the approach to any child presenting with uncharacteristic behavior that is persistent and disproportionate to environmental and situational factors.

Upon identification of a suspected case of encephalitis, a relatively short but critical series of steps should be executed, as summarized in Table 4. Additional facts to consider in the initial evaluation of the patient include seasonal presentation, history of immunosuppression, travel history, recent local epidemiological information, and presence of focal neurologic symptoms or deficits. Table 5 lists additional specific testing that should be routinely considered based upon protocols developed for the CEP and specific clinical settings. Table 6 lists, according to clinical clues, other viral causes of encephalitis that would require agent-specific testing if suspected.

In patients in whom a parainfectious process is suspected, acute testing for demyelinating inflammatory conditions is increasingly popular. This testing is motivated by the increasing recognition of pediatric multiple sclerosis (MS) and other demyelinating conditions, eg, neuromyelitis optica (Devic disease), which may be mistaken initially for ADEM. Signs that increase suspicion for MS-related conditions include the presence of exclusively white matter abnormalities on MRI (especially if monolesional), optic neuritis, isolated myelitis, a recurrent or polyphasic disease course, or postadolescent age. In these cases, standard lumbar puncture studies also include myelin basic protein assay and measurement of CSF immunoglobulins with oligoclonal banding, and concomitant serum protein electrophoresis. Although the presence of disproportionate oligoclonal antibody production within the CSF is more suggestive of idiopathic demyelination (eg, MS), this finding is not sufficiently specific to prove a diagnosis of MS because ADEM and other CNS inflammatory conditions, including CNS infection, can produce similar results. The neuromyelitis optica antibody often is present in cases having optic neuritis associated with spinal cord symptoms. Documented neuromyelitis optica antibody-positive patients also have presented with optic neuritis only.

In following the standard evaluation of patients with symptoms of encephalitis, the diagnostic testing results most commonly encountered include either unremarkable or variable leukocytosis or lymphocytosis. Comprehensive metabolic panels often fail to demonstrate specific abnormalities. Some enteroviral infections can produce a sepsislike syndrome with more remarkable hematologic abnormalities. Neonatal HSV infections sometimes produce hepatic function abnormalities and disseminated intravascular coagulation. Inappropriate secretion of antidiuretic hormone can be seen in almost any encephalitic process, but is reported more commonly in St Louis encephalitis (primarily a disease of the elderly population) and WNV infections.

Understanding clinical-anatomic correlations may be helpful in refining the differential diagnosis, because some causes of encephalitis display tropism for specific CNS tissues. Table 3 describes the cardinal symptoms of infection or inflammation in major anatomic subdivisions, as well as commonly used clinical terms. Although the anatomic localization is an important part of initial symptom recognition, neuroimaging plays an indispensable role, whether or not localizing clinical symptoms are present. In the very young child, clinically based neuroanatomic localization also can be notoriously difficult. Table 7 describes some classically cited agent-specific localization-related findings, identifiable by symptoms, neuroimaging, or both. However, a high degree of variability in clinical presentations mandates that the search for an etiologic agent cannot be confined strictly to those agents classically injurious to specific CNS locations.

Neuroimaging, including MRI, early in the course of disease may sometimes yield false-negative results.

Table 3. Localization of CNS Lesions and Associated Terminology and Symptoms

Common Clinical Term	Anatomic Region	Acute Symptoms
Limbic encephalitis	Limbic system	Agitation, confusion, delirium, seizures, autonomic changes
Rhombencephalitis	Brainstem and/or cerebellum	Eye movement and gaze deficits, nystagmus, facial palsies, ataxia, auditory disturbances, autonomic disturbances, upper-motor-neuron weakness, sensory disturbances, hyporeflexia, dysphagia, dysarthria, lethargy, coma, respiratory failure
"Cerebritis" or "encephalitis" (generically applied)	Cerebral hemispheres (cortex, subcortical white matter, or both)	Seizures, upper-motor-neuron weakness, sensory disturbances, lethargy, coma
	Basal ganglia	Weakness, hyperkinetic (dystonia, choreoathetosis) or parkinsonian movement abnormalities, apathetic or disinhibited behavior
	Hypothalamus (diencephalon)	Salt and water disturbances (eg, syndrome of inappropriate antidiuretic hormone, diabetes insipidus), adrenal and thyroid failure, paroxysmal autonomic dysfunction
	Thalamus (diencephalon)	Sensory disturbances, postural abnormalities, lethargy, coma
Panencephalitis	Two or more distinct regions	Symptomatic involvement of two or more distinct regions
Meningitis	Meninges	Headache, stiff neck, fever, neck or back pain, malaise but not formal disturbances of arousal
Meningoencephalitis	Meninges *plus* brain parenchyma	Symptoms of meningitis paired with those of *any* anatomic subdivision of brain
Myelitis	Anterior horn cells *or* long tracts on the spinal cord	Poliomyelitis (flaccid paralysis and hyporeflexia with preserved sensation), transverse myelitis (long-tract symptoms including sensory disturbance below the affected region), or both
Encephalomyelitis	Any spinal cord plus any cerebral region	Spinal symptoms may be inapparent in contrast to cortical or brainstem symptoms
Cranial neuritis	Cranial nerves I-XII	Impairment of any of the modalities of cranial nerve function attributed to dysfunction of the extra-axial course of the nerves involved and *not* damage to brain parenchyma or cranial nerve nuclei. Can be indistinguishable from nuclear involvement.

For purposes other than identifying substantial cerebral edema, midline shift or hemorrhage, computed tomography imaging generally is not sufficient for the diagnostic workup of encephalitis.

The lumbar puncture is the single most utilized test for the diagnosis of encephalitis. The primary results, however, generally lack specificity, and can be normal early in the course of the disease. In those patients displaying abnormal CSF results, the most characteristic findings are increased opening pressure, normal or elevated protein concentration, normal glucose level, and pleocytosis, which often begins with polymorphonuclear leukocytes and then converts to lymphocytic, or sometimes monocytic, predominance with progression of the disease. Although there are reported variations on this theme with certain etiologic agents, such as hemorrhagic pleocytosis with HSV, atypical lymphocytes with Epstein-Barr virus, or mononuclear leukocytes with echovirus or varicella-zoster infection, there are no pathognomonic CSF findings that help to differentiate infectious cases of encephalitis.

The ability to obtain PCR amplification of viral DNA fortunately has added new usefulness to the lumbar puncture in encephalitis. This modality, however, requires clinical suspicion of a specific diagnostic entity, and is not available as a broad "battery" of testing. Additionally, viral DNA often is not recovered in certain stages of illness. For example, 5% to 10% of adult cases of HSV

Table 4. **Initial Evaluation**

1. Clinically stabilize	Address symptoms of autonomic instability or septic shock, seizures/status epilepticus
2. Standard laboratory studies	Complete blood count, comprehensive metabolic panel, urinalysis
3. Neuroimaging	MRI with and without contrast preferable; emergent computed tomography if signs/symptoms of critically increased intracranial pressure[a] *before* lumbar puncture
4. Lumbar puncture	Opening pressure, cell count, glucose, protein, viral and bacterial culture, polymerase chain reaction testing for enterovirus, herpes simplex; other specific studies based upon clinical history (see Table 3 and Table 5)
5. Acute empiric treatment	Acyclovir if any suspicion of herpes simplex infection; anticonvulsant prophylaxis if any suspicion of clinical seizures, or if risk for seizures deemed high
6. Electroencephalography	Used to evaluate for clinically relevant lateralized findings (periodic lateralized epileptiform discharges), to monitor for occult seizures or subclinical status epilepticus

[a]Signs of acute increased intracranial pressure include vomiting and lethargy, bulging fontanel, pupillary asymmetry or lack of reactivity, gaze palsies, intermittent or fixed involuntary downward gaze ("sun-setting eyes"), or irregular respirations.

meningitis have negative PCR results upon the first lumber puncture. Furthermore, results often are not immediately available, and can take from 1 to 7 days or longer to be available. Hence, the decision to use specific antibiotic or antiviral treatments, such as acyclovir for suspected HSV meningitis, is still largely predicated upon clinical suspicion.

Parainfectious encephalitis such as ADEM or acute cerebellar ataxia may manifest many of the same CSF findings as infectious encephalitis. However, pleocytosis tends to be less dramatic in most, but not all, parainfectious cases. When pathogen genomic material can be isolated from the CSF, the likelihood of a parainfectious or purely inflammatory etiology becomes remote.

The most reliable standard for demonstrating causation of acute infectious encephalitis remains the pairing of acute and convalescent serum titers. A fourfold rise in titer, especially immune globulin M, against a suspected agent is most often considered diagnostic. This method is limited by the adequacy of follow-up and the accuracy of testing selection. Many patients are discharged and lost to close follow-up long before convalescent titers are obtainable. Of those tested, the causative agent may be missed by clinical suspicion-guided testing targeting other organisms erroneously.

Clinical Course and Treatment

The priority in the treatment of acute encephalitis is the duality of clinical stabilization and containment of potentially damaging inflammatory processes. Because many patients present with any combination of seizures, delirium, autonomic instability, and respiratory irregularities, treatment of these acute symptoms often takes priority. This stabilization should not, however, delay addressing the suspicion of either an infectious or parainfectious condition and initiating appropriate treatment. Commonly, such patients are empirically treated with intravenous acyclovir while waiting for lumbar puncture, or while waiting for laboratory results, including HSV PCR. Either because of delays in obtaining these results, or because of the known false-negative rate of PCR testing of acute CSF specimens, many will complete the required 21-day course of acyclovir without a firmly established laboratory diagnosis.

The emphasis on prompt treatment of possible HSV encephalitis should not overshadow a thorough search for clues to other causative agents. Table 5 lists some alternative considerations in the diagnosis of acute infectious encephalitis that might affect treatment options.

Beyond the primary infectious considerations, ADEM ranks as the most likely cause of an acute encephalitis. The constellation of a temporally separate infectious illness or an immunization before the onset of symptoms, multiple encephalitic symptoms, and multifocal MRI abnormalities in both gray and white matter are highly suggestive (but not pathognomonic) for the diagnosis of ADEM. Treatment varies substantially from the approach to acute infectious encephalitis in that high-dose corticosteroids are a first-line treatment, followed by IVIG or plasmapheresis in cases refractory to corticosteroid treatment. The use of both IVIG and plasmapheresis remains unsupported by clinical trials; but IVIG has

Table 5. Additional Testing in Encephalitis, Modeled Upon the California Encephalitis Project

Source	Method	Specific Agent	Added Criteria
Cerebrospinal fluid	Polymerase chain reaction (PCR)	Herpes simplex virus 1 Herpes simplex virus 2 Enterovirus Human herpes virus 6 Varicella-zoster virus	Immunosuppressed patients[a]
	Antibody assay	Measles antibody	
	Fungal culture; India-ink microscopy	Cryptococcus; other fungal agents	
Nasopharyngeal/throat Swab	PCR + virus isolation	*Mycoplasma pneumoniae* Enterovirus (Human metapneumovirus)[b] Adenovirus Respiratory syncytial virus Influenza A Influenza B	Routinely tested October-March, if respiratory symptoms present, or based upon local epidemiology
Acute phase serum	Serology	*Mycoplasma pneumoniae* Epstein-Barr virus Parvovirus B19 Measles St. Louis encephalitis Western equine encephalitis Eastern equine encephalitis West Nile virus	As indicated by season
Convalescent phase serum	Serology	*Mycoplasma pneumoniae* Epstein-Barr virus Parvovirus B19 Measles Influenza A Influenza B Adenovirus West Nile virus Systemic lupus erythematosus Western equine encephalitis	As indicated by season and local epidemiology
		Varicella zoster virus Herpes simplex virus *(Chlamydia pneumoniae)*	As indicated by clinical presentation and PCR results
Other agent-specific testing	Various	See Table 1	Based upon clinical presentation and epidemiological factors as described in Table 6

[a]The predilection for some agents to affect primarily immunosuppressed patients does not wholly exclude the possibility of CNS disease in otherwise immunocompetent individuals.
[b]Items in parentheses are part of the CEP protocol, but generally not found to be major causes of encephalitis nationwide.

received wider acceptance as an alternative treatment at this time.

The use of corticosteroids in the setting of nonherpetic infectious encephalitis remains controversial. Outside of single case reports, the only available supportive evidence for their use derives from the treatment of progressive multifocal leukoencephalopathy, a subacute/chronic encephalitis caused by polyomavirus JC that occurs primarily in severely immunocompromised HIV-positive patients.

The maintenance of adequate cerebral perfusion pressure (CPP) (generally accepted as 70 mm Hg or higher over 2 years of age) is a critical issue in treating infectious encephalitis. Increased intracranial pressure is a variable finding in encephalitis. Preserving CPP by managing intracranial pressure is an important element of treatment. In

Table 6. **Alternative Considerations in the Diagnosis of (Viral) Encephalitis**

Suggestive Findings	Diagnostic Consideration
History of recent nonfebrile cough, serous otitis, community epidemic of "walking pneumonia"	*Mycoplasma pneumoniae*
History of arthritis, serositis, uveitis, nephritis, or other inflammatory conditions	Lupus or other autoimmune cerebritis/vasculitis
History of recent unexplained weight loss, anemia, slow-onset encephalitis symptoms, limbic encephalitis	Paraneoplastic syndrome
Fever, chest x-ray or hepatic abnormalities, subacute onset of encephalitis, multiple enhancing lesions on MRI, meningeal enhancement, mixed CSF pleocytosis	Fungal infection
Fever, chest x-ray or hepatic abnormalities, subacute onset of encephalitis/rhombencephalitis, basilar meningeal enhancement, hypoglycorrachia with mixed pleocytosis	Tuberculous meningitis
Fever, heart murmur, history of congenital or rheumatic heart disease, multifocal enhancing lesions on MRI	Mycotic emboli
Antecedent infectious illness with complete recovery before onset of neurologic symptoms, or immunization within the previous 30 days	Acute disseminated encephalomyelitis
Neonate with extramedullary hematopoiesis ("blueberry muffin baby")	Rubella
Neonate with symptoms of acute encephalitis	Toxoplasmosis, rubella, cytomegalovirus, HSV, parvovirus B19
Tick or biting arthropod exposure	*Borrelia burgdorferi* *Rickettsia* species *Ehrlichia* species *Coxiella burnetii*
Age <4–5 years, peripheral and/or CSF eosinophilia, discrete MRI lesions with enhancement, pica or extensive exposure to soil/locations frequented by animals	Neural larva migrans, including baylisascariasis (Raccoon encephalitis), toxocariasis (dogs), angiostrongylosis (rodents),
Rhombencephalitis with hemorrhagic pleocytosis, HSV PCR negative, elevated CSF lactate (not routinely tested in encephalitis)	*Listeria monocytogenes*
Fever, exposure to cats, local adenopathy	*Bartonella henselae*
Animal bite, or close exposure to wild animals behaving abnormally (including bats), rapidly deteriorating course	Rabies

a series of 20 children with meningitis or meningoencephalitis, 4 of 4 patients with CPP <50 mm Hg died, whereas 3 of 16 with CPP maintained at >50 mm Hg survived. (7)

When symptomatic intracranial hypertension exists, conservative measures (head elevation, hyperventilation, and fluid restriction) are the most accepted strategies. Mannitol is used on a limited basis, as individual case reports and small series attest. However, the duration of use is limited by the dynamics of inflammation-related intracranial hypertension, with eventual breakdown of the blood-brain barrier and the possible passage of osmotically active agents into the extravascular space. This outcome may result in the ultimate worsening of cerebral edema. If more conservative strategies fail and mannitol is unsuccessful also, isolated reports and small series (3–4 patients) attest to the successful use of craniectomy for decompression.

The treatment of symptomatic seizures often becomes a focus of management in patients with encephalitis. In the CEP, 42% of patients manifested seizures. Of these, 62 patients eventually developed intractable seizures requiring barbiturate coma or anesthesia. This group of patients experienced a 32% mortality rate, compared with an 11% overall mortality rate for the entire cohort. Nearly every anticonvulsant agent known has been used in the treatment of patients with encephalitis-related acute symptomatic seizures. Those agents most easily administered are available in intravenous formulations and include benzodiazepines (midazolam, lorazepam, diazepam), barbiturates (phenobarbital, pentobarbital), anesthetic agents (propofol, ketamine, inhalant anesthesia), phenytoin, fosphenytoin, divalproex sodium, and levetiracetam. The typical approach begins with benzodiazepines upon recognition of either recurrent or prolonged seizure activity, followed

Table 7. **Examples of Agent-Specific Findings in Infectious Encephalitis**

Agent	Location	Other Specific Details
HSV I	Basal frontal and mesial temporal lobes with prominent lesions on MRI in older children and adults; tropism not as reliable in neonates	Hemorrhagic meningoencephalitis; >50% of cases in individuals >20 y; causes up to 30% of neonatal meningoencephalitis
HSV II	Neonatal panencephalitis; Adult aseptic meningitis; Rhombencephalitis or ascending myelitis in immunocompromised adults	
Enterovirus 71	Brainstem encephalitis; Poliomyelitis syndrome	A cause of epidemic hand, foot and mouth disease; also, epidemics of encephalomyelitis in Taiwan; acute pulmonary edema
Eastern equine encephalitis	50% of affected patients with MRI lesions in basal ganglia, thalamus, and brainstem	Summer-fall seasonality; Atlantic and Gulf coasts; Great Lakes region
West Nile virus	Brainstem encephalitis; myelitis in 10% of cases; basal ganglia less commonly involved	Only 4% of cases are pediatric; summer-fall seasonality
Mumps	Ependymal cells (choroid plexus and lining of ventricles); secondary neuronal destruction and perivascular demyelination	Late winter-early spring; most patients have only aseptic meningitis symptoms

by loading of a more sustainable anticonvulsant, with intent to maintain. Fosphenytoin, phenobarbital, and, in some locations, phenytoin are still most commonly used anticonvulsants, but newer agents such as divalproex or levetiracetam are gaining acceptance.

If either high therapeutic levels or apparently adequate dosing fail to achieve cessation of seizure activity, sedative or anesthetic agent infusions emerge as the next most likely treatment, including the use of midazolam, pentobarbital, propofol, or ketamine drips. During this phase of treatment, bedside EEG monitoring usually is obtained, motivated both by the prevalence of otherwise undetectable subclinical seizures in the comatose patient and the desire to achieve a burst-suppression EEG pattern as a measure of the adequacy of dosing.

Often, other anticonvulsants are added to the treatment regimen, either as intravenous formulations or via nasogastric or other direct enteral route, during the escalation of the therapy with sedative-hypnotic and anesthetic agents. The use of polypharmacy is intended to achieve both more rapid seizure cessation as well as a more stable anticonvulsant configuration, facilitating the successful withdrawal of the anesthetic agent without seizure relapse. However, metabolic interactions can frustrate attempts to obtain therapeutic levels of any or all agents simultaneously in use.

Inhalant anesthetics often are used as a treatment of last resort. Isolated use of ketosis or vagus nerve stimulation has produced limited results as well. In general, the longer the list of unsuccessful anticonvulsant interventions, the poorer the prognosis for full recovery and survival.

Outcomes

Clinical outcomes of both infectious and inflammatory encephalitis range from full recovery to death. The accurate prediction of clinical outcome remains elusive. Nonetheless, several factors can be identified that strongly influence the potential for recovery: nature of the infectious agent or process, age of the patient, extent of primary cerebral and spinal cord involvement, presence of complicated cerebral edema, extent of cerebral perfusion and vascular injury, presence of other organ system disease and complications, and response to treatment modalities. The importance of the nonneurologic aspects of infectious disease in affecting outcome should not be underestimated. This association is especially true in neonatal encephalitis accompanied by sepsislike syndromes, infectious pneumonitis, or hepatitis, which may produce mortality rates >50%. Even among older children, pulmonary disease especially affects outcome, as in the Taiwanese enterovirus 71 epidemics, in which the worst survival rate was among those experiencing pulmonary edema in the acute phase of illness. (8)

The question of future functional capacity is paramount for families of encephalitis survivors. In response to this question, much depends upon the causative agent. As a general principle, agents that produce more extensive cerebral necrosis (especially if bilateral hemispheric or

brainstem injury is abundant) or vascular disease have worse functional outcomes.

Otherwise, available statistics offer little guidance in anticipatory counseling. The specific etiologic agent does play some role; for example, >60% of patients who have HSV encephalitis develop some identifiable neurologic sequelae in some series. But among Taiwanese children affected by enterovirus 71, 80% had no detectable deficits when evaluated >2 years after the encephalitis. (8)

The potential for more subtle long-term sequelae, even in cases where there are no obvious short-term deficits, remains a controversial topic. For example, of 86 Taiwanese children evaluated 3 to 7 years after enterovirus 71 meningitis or encephalitis, 20% manifested attention-deficit/hyperactivity disorder–related symptoms, compared with only 3% of matched control subjects. (9) The incidence of similar neurologic complications in other causes of encephalitis remains largely undocumented at this time.

Summary

- The topic of encephalitis encompasses an enormous range of causative agents, clinical syndromes, and outcomes.
- The treatment options remain largely supportive, except in a select number of cases in which a possible or probable causative agent exists and for which there is a specific therapy.
- The specific cause of encephalitis in both the pediatric and adult population remains unknown in a majority of cases, despite extensive diagnostic testing. (1)
- Specific causes of encephalitis often have classically reported features, but the extent of overlap in clinical symptomatology mandates broad consideration of possible causes. (1)
- Parainfectious and inflammatory causes of encephalitis (acute disseminated encephalomyelitis) are as prevalent and clinically significant as direct CNS infection. (9)(10)(11)
- Clinical outcome is determined largely by the nature of the causative agent, but with substantial contribution from factors such as other organ system involvement, seizure control, and cerebral perfusion. (7)

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1. Mosquito control will most likely reduce the frequency of encephalitis caused by
   - A. Adenoviruses.
   - B. Flaviviruses.
   - C. Herpesviruses.
   - D. Myxoviruses.
   - E. Picornaviruses.

2. A 10-year-old child presents with the signs of acute encephalitis. While no pattern of brain involvement is exclusively produced by a single microbiologic agent, the possibility of herpes simplex being the causative agent is enhanced substantially by an MRI finding of lesions concentrated in the
   - A. Basal ganglia.
   - B. Frontal lobes.
   - C. Midbrain.
   - D. Temporal lobes.
   - E. Thalamus.

3. A 17-year-old boy has acute encephalitis associated with weakness in the right arm. He is clinically stable. He had experienced a febrile illness 3 weeks before presenting with signs of encephalitis, but had apparently recovered fully. An MRI demonstrated scattered multifocal abnormalities in both gray and white matter within the brain. Evaluation of serum and CSF has been unrevealing. His most likely diagnosis is
   - A. Acute disseminated encephalomyelitis.
   - B. Enteroviral encephalitis.
   - C. Herpes simplex encephalitis.
   - D. Mycoplasma encephalitis.
   - E. Multiple sclerosis.

4. The form of encephalitis shown to benefit most from the use of high-dose glucocorticosteroids is
   - A. Acute disseminated encephalomyelitis.
   - B. Enteroviral encephalitis.
   - C. Herpes simplex encephalitis.
   - D. Saint Louis encephalitis.
   - E. West Nile virus encephalitis.

5. The likelihood of full recovery from encephalitis most depends upon
   - A. Availability of specific treatment.
   - B. Causative agent.
   - C. Duration of fever.
   - D. Initial CSF findings.
   - E. Timeliness of specific diagnosis.

Encephalitis in the Pediatric Population

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