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UPDATE

Encephalitis- Practice Essential, Pathophysiology, Diagnosis , Management &Prognosis

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Background

Encephalitis, an inflammation of the brain parenchyma, presents as diffuse and/or focal neuropsychological dysfunction. Although it primarily involves the brain, the meninges are frequently involved (meningoencephalitis).

From an epidemiologic and pathophysiologic perspective, encephalitis is distinct from meningitis, though on clinical evaluation both can be present, with signs and symptoms of meningeal inflammation, such as photophobia, headache, or stiff neck. It is also distinct from cerebritis. Cerebritis describes the stage preceding abscess formation and implies a highly destructive bacterial infection of brain tissue, whereas acute encephalitis is most commonly a viral infection with parenchymal damage varying from mild to profound.

Although bacterial, fungal, and autoimmune disorders can produce encephalitis, most cases are viral in origin. The incidence of encephalitis is 1 case per 200,000 population in the United States, with herpes simplex virus (HSV) being the most common cause. Considering the subacute and chronic encephalopathies, the emergency department (ED) physician is most likely to encounter toxoplasmosis in an immune-compromised host.

The relatively common acute arboviral encephalitides vary widely in epidemiology, mortality, morbidity, and clinical presentation, and no satisfactory treatment exists for these infections. However, attempts to distinguish these acute arboviral encephalitides from the treatable acute viral encephalitides due to herpes simplex or varicella are important.

Herpes simplex encephalitis (HSE), which occurs sporadically in healthy and immune-compromised adults is also encountered in neonates infected at birth during vaginal delivery and is potentially lethal if not treated. Varicella-zoster virus encephalitis (VZVE) is life threatening in immune-compromised patients. Swift identification and immediate treatment of HSE or VZVE can be lifesaving. From a risk-benefit standpoint, most authorities recommend initiating ED treatment with acyclovir in any patient whose central nervous system (CNS) presentation is suggestive of viral encephalitis, especially in the presence of fever,

encephalopathy, or focal findings, and in all neonates who appear ill for whom a CNS infection is being considered.

Practice Essentials

Encephalitis presents as diffuse or focal neuropsychological dysfunction. Although it primarily involves the brain, it often involves the meninges as well (meningoencephalitis). From an epidemiologic and pathophysiologic perspective, encephalitis is distinct from meningitis, though on clinical evaluation both can be present, with signs and symptoms of meningeal inflammation. It is also distinct from cerebritis.

Signs and symptoms

The viral prodrome typically consists of fever, headache, nausea and vomiting, lethargy, and myalgias. Manifestations associated with specific types of encephalitis include the following:

- Encephalitis caused by varicella-zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), measles virus, or mumps virus: Rash, lymphadenopathy, hepatosplenomegaly, and parotid enlargement
- St Louis encephalitis: Dysuria and pyuria
- West Nile encephalitis (WNE): Extreme lethargy

The classic presentation is encephalopathy with diffuse or focal neurologic symptoms, including the following:

- Behavioral and personality changes, with decreased level of consciousness
- Neck pain, stiffness
- Photophobia
- Lethargy
- Generalized or focal seizures (60% of children with California virus encephalitis [CE])
- Acute confusion or amnestic states
- Flaccid paralysis (10% of patients with WNE)

The signs of encephalitis may be diffuse or focal. Typical findings include the following:

- Altered mental status
- Personality changes (very common)
- Focal findings (e.g., hemiparesis, focal seizures, and autonomic dysfunction)
- Movement disorders (e.g., St Louis encephalitis, eastern equine encephalitis, and western equine encephalitis)
- Ataxia
- Cranial nerve defects
- Dysphagia, particularly in rabies
- Meningismus (less common and less pronounced than in meningitis)
- Unilateral sensorimotor dysfunction (postinfectious encephalomyelitis)

Findings of herpes simplex virus (HSV) infection in neonates may include the following:

- Herpetic skin lesions over the presenting surface from birth or with breaks in the skin, such as those resulting from fetal scalp monitors
- Keratoconjunctivitis
- Oropharyngeal involvement, particularly buccal mucosa and tongue
- Encephalitis symptoms (e.g., seizures, irritability, change in attentiveness, and bulging fontanelles)
- Additional signs of disseminated, severe HSV include jaundice, hepatomegaly, and shock

Encephalitis may be associated with a number of complications, including the following:

- Seizures
- Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
- Increased intracranial pressure (ICP)
- Coma

Pathophysiology

Portals of entry are virus specific. Many viruses are transmitted by humans, though most cases of HSE are thought to be reactivation of HSV lying dormant in the trigeminal ganglia. Mosquitoes or ticks inoculate arbovirus, and rabies virus is transferred via an infected animal bite or exposure to animal secretions. With some viruses, such as varicella-zoster virus (VZV) and cytomegalovirus (CMV), an immune-compromised state is usually necessary to develop clinically apparent encephalitis.

In general, the virus replicates outside the CNS and gains entry to the CNS either by hematogenous spread or by travel along neural pathways (eg, rabies virus, HSV, VZV). The etiology of slow virus infections, such as those implicated in the measles-related subacute sclerosing panencephalitis (SSPE) and progressive multifocal leukoencephalopathy (PML), is poorly understood.

Once across the blood-brain barrier, the virus enters neural cells, with resultant disruption in cell functioning, perivascular congestion, hemorrhage, and a diffuse inflammatory response that disproportionately affects gray matter over white matter. Regional tropism associated with certain viruses is due to neuron cell membrane receptors found only in specific portions of the brain, with more intense focal pathology in these areas. A classic example is the HSV predilection for the inferior and medial temporal lobes.

In contrast to viruses that invade gray matter directly, acute disseminated encephalitis and postinfectious encephalomyelitis (PIE), most commonly due to measles infection and associated with Epstein-Barr virus (EBV) and CMV infections, are immune-mediated processes that result in multifocal demyelination of perivenous white matter.

Diagnosis

Although bacterial, fungal, and autoimmune disorders can produce encephalitis, most cases are viral in origin. Accordingly, in addition to standard blood and urine tests, studies may be performed to identify the infectious agent causing the encephalitis.[5] It is important, when possible, to distinguish acute arboviral encephalitides from potentially treatable acute viral encephalitides, especially herpes simplex encephalitis (HSE) and varicella-zoster encephalitis, as a high suspicion for these disorders and prompt treatment can reduce the severity of neurological sequelae and can be lifesaving.

Blood and Urine Tests

A complete blood count (CBC) with differential should be performed, although findings are often within the normal range.

Serum electrolyte levels are usually normal unless dehydration is present; the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) occurs in 25% of patients with St Louis encephalitis.

The serum glucose level should be determined to rule out confusion due to treatable hypoglycemia and to compare with the cerebrospinal fluid (CSF) glucose value. Low serum results are found in nutritionally deprived patients, while diabetic patients may present with elevated glucose levels compatible with complicating hyperosmolar state or diabetic ketoacidosis.

Blood urea nitrogen (BUN) and creatinine levels are helpful to assess hydration status, and liver function tests should be performed to assess for end-organ dysfunction or the need to adjust antimicrobial therapy dosing regimens.

A lumbar puncture (LP) should be performed on all patients suspected of having a viral encephalitis. A platelet count and coagulation profile are indicated in patients who are chronic alcohol users, have liver disease, and those in whom disseminated intravascular coagulation (DIC) is suspected. The patient may require platelets or fresh frozen plasma (FFP) before LP.

A urinary electrolyte test should be performed if SIADH is suspected. Urine or serum toxicology screening may be indicated in selected patients presenting with a toxic delirium or confusional state.

Studies to Identify Infectious Agent

Herpes simplex virus (HSV) cultures of suspicious lesions and a Tzanck smear should be obtained. Viral cultures of CSF, including HSV, should be performed, although the incidence of the latter being positive is rare. Blood cultures for bacterial pathogens should be obtained.

Complement fixation antibodies are useful in identifying arbovirus. Cross-reactivity exists among a subgroup of arboviruses, the flaviviruses (e.g., viruses that cause St Louis encephalitis, Japanese virus encephalitis [JE], and West Nile encephalitis [WNE]), and the antibodies found in persons inoculated with yellow fever vaccine.

Heterophile antibody and cold agglutinin testing for Epstein-Barr virus (EBV) may be helpful.

Serologic tests for toxoplasmosis can be helpful in light of an abnormal computed tomography (CT) scan, particularly in the case of single lesions. However, the overlap in titer levels between exposed but currently uninfected and reactivated groups may complicate interpretation.

Computed Tomography, Magnetic Resonance Imaging, and Electroencephalography

Performance of a head CT scan with and without contrast agent should be performed in virtually all patients with encephalitis. This should be done prior to LP if there are focal complaints or findings, signs to search for evidence of elevated intracranial pressure (ICP), obstructive hydrocephalus, or mass effect due to focal brain infection. Head CT scanning also helps exclude brain hemorrhage or infarction as a cause of an encephalopathic state. Magnetic resonance imaging (MRI) is more sensitive than CT scanning in demonstrating brain abnormalities earlier in the disease course.

In HSE, MRI may show several foci of increased T2 signal intensity in medial temporal lobes and inferior frontal gray matter. Head CT commonly shows areas of edema or petechial hemorrhage in the same areas. EEE and tick-borne encephalitis may show similar increased MRI signal intensity in the basal ganglia and thalamus.

In toxoplasmosis, contrast-enhanced head CT typically reveals several nodular or ring-enhancing lesions. Because lesions may be missed without contrast, MRI should be performed in patients for whom use of contrast material is contraindicated.

In HSE, electroencephalography (EEG) often documents characteristic paroxysmal lateral epileptiform discharges (PLEDs), even before neuroradiography changes. Eventually, PLEDs are positive in 80% of cases; however, the presence of PLEDs is not pathognomonic for HSE.

Analysis of Cerebrospinal Fluid

CSF analysis is essential. Typical patterns of findings in the CSF pressure and CSF analysis follow in the Table 1 regarding bacterial versus viral versus fungal (including cryptococcal) meningitis or encephalitis.

CSF Finding (Normal)	Bacterial Meningitis	Viral Meningitis	Fungal Meningitis
Pressure (5-15 cm water)	Increased	Normal or mildly increased	• Normal or mildly increased in most fungal and tuberculous CNS infections • Patients with AIDS and cryptococcal meningitis are at increased risk of blindness and death unless pressure maintained at < 30 cm
Cell counts, mononuclear cells/µL Preterm (0-25) Term (0-22) 6 mo+ (0-5)	• Normal cell count excludes bacterial meningitis • Typically thousands of polymorphonuclear cells, but counts may not change dramatically or even be normal (classically in very early meningococcal meningitis or in extremely ill neonates) • Lymphocytosis with normal CSF chemistry results observed in 15-25% of patients, especially if counts < 1000 or if patient is partially treated • About 90% of patients with ventriculoperitoneal shunts and CSF WBC count >100 cells/µL are infected, though CSF glucose level often normal, and bacteria often less pathogenic • Cell count and chemistry levels normalize slowly (days) with antibiotics	• Usually < 500, nearly 100% mononuclear • < 48 hours, clinically significant polymorphonuclear pleocytosis may be indistinguishable from early bacterial meningitis, particularly with EEE • Nontraumatic RBCs in 80% of patients with HSV meningoencephalitis, though 10% have normal CSF results	• 100s of mononuclear cells
Microorganisms (none)	• Gram stain 80% effective • Inadequate decolorization may cause *Haemophilus influenzae* to be mistaken for gram-positive cocci • Pretreatment with antibiotics may affect stain uptake, causing gram-positive species to appear to be gram-negative and	• No organism	• India ink 80-90% effective for detecting fungi • AFB stain 40% effective for TB; increase yield by staining supernatant

	decrease culture yield by an average of 20		from at least 5 mL of CSF
Glucose[†] Euglycemia (>50% serum) Hyperglycemia (>30% serum	• Decreased	• Normal	• Sometimes decreased • In addition to fulminant bacterial meningitis, TB, primary amebic meningoencephalitis, and neurocysticercosis cause low glucose levels
Protein Preterm (65-150 mg/dL) Term (20-170 mg/dL 6 mo+ (15-45 mg/dL)	• Usually >150 mg/dL • May be >1000 mg/dL	• Mildly increased	• Increased >1000 mg/dL, with relatively benign clinical presentation suggestive of fungal disease

Some bacteria (eg, *Mycoplasma, Listeria, Leptospira, Borrelia burgdorferi* [Lyme disease]) cause alterations in spinal fluid that resemble the viral profile. An aseptic profile is also typical of partially treated bacterial infections (>33%, especially those in children, are treated with antimicrobials) and of the 2 most common causes of encephalitis—the arboviruses and the potentially curable HSV.
Wait 4 hours after glucose load.
(AFB—acid-fast bacillus; CSF—cerebrospinal fluid; EEE-eastern equine encephalitis; HSV—herpes simplex virus; RBC—red blood cell; TB—tuberculosis; WBC—white blood cell).

Management

Management in the prehospital setting includes the following:

- Evaluation and treatment for shock or hypotension
- Airway protection (in patients with altered mental status)
- Seizure precautions
- Oxygen and IV access secured en route to the hospital (all patients)

In the emergency department (ED), beyond supportive care, viral encephalitides are not treatable, with the exceptions of HSV and VZV encephalitis. Important initial measures include the following:

- Administration of the first dose or doses of acyclovir, with or without antibiotics or steroids, as quickly as possible; the standard for acute bacterial meningitis is initiation of treatment within 30 minutes of arrival
- Consideration of an ED triage protocol to identify patients at risk for HSV encephalitis
- Collection of laboratory samples and blood cultures before the start of IV therapy
- Neuroimaging (eg, MRI or, if that is unavailable, contrast-enhanced head CT) before LP

Additional treatment considerations include the following:

- Management of hydrocephalus and increased ICP

- Treatment of systemic complications (eg, hypotension or shock, hypoxemia, hyponatremia, and exacerbation of chronic diseases)
- Empiric treatment of HSV meningoencephalitis and VZV encephalitis

Clinical practice guidelines for treatment of encephalitis have been published by the Infectious Diseases Society of America (IDSA).[1]

Prognosis

The prognosis is dependent on the virulence of the virus and the patient's health status. Extremes of age (< 1 y or >55 y), immune-compromised status, and preexisting neurologic conditions are associated with poorer outcomes.

Untreated HSE has a mortality of 50-75%, and virtually all untreated or late-treatment survivors have long-term motor and mental disabilities. The mortality in treated HSE averages 20%, and the neurologic outcome correlates with the neurological disability present at the time of the first dose of acyclovir or comparable antiviral agents. Approximately 40% of survivors have minor-to-major learning disabilities, memory impairment, neuropsychiatric abnormalities, epilepsy, fine-motor-control deficits, and dysarthria.

Outcomes in arboviral JE and EEE are catastrophic, similar to untreated HSE, with high mortality and severe morbidity, including mental retardation, hemiplegia, and seizures. Other arboviruses cause substantially less morbidity and mortality. For example, St Louis encephalitis and WNE have a mortality rate of 2-20%, the higher rates found in patients older than 60 years. Long-term sequelae with St Louis encephalitis include behavioral disorders, memory loss, and seizures.

WEE is associated with few deaths and much less morbidity, although developmental delay, seizure disorder, and paralysis occasionally occur in children, and postencephalitic parkinsonism may occur in adults. CE is typically associated with mild illness, and most patients make a full recovery; however, the minority of patients with severe disease have a 25% chance of focal neurologic dysfunction. Death rates from WEE and LAC are less than 5%.

PIE secondary to measles is associated with a mortality rate approaching 40% of cases, with a high rate of neurologic sequelae in survivors. SSPE is uniformly fatal, although the disease course may last anywhere from several weeks to 10 years.

suppressed patients. The mortality for EBV encephalitis is 8%, with substantial morbidity found in approximately 12% of survivors.

Rabies encephalitis and acute disseminated encephalitis are virtually 100% fatal, although there are rare survivors reported in the medical literature.

References

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		PANELS AND PROFILE OFFERED BY METROPOLIS FOR NEUROINFECTIOUS DISEASES			
		MENINGITIS PANEL			
Sr No	**Test Name**	**Sample**	**Test Schedule**	**Test reported on**	**Price (Rs)**
1	Bacterial Meningitis Panel	3ml ofCSF	Daily 9am,3pm	After 6hrs	4200
2	Bacterial Meningitis Panel Reflex	3ml of CSF	Daily 9am,3pm	3rd Day	4800
3	Meningitis Panel by PCR	1-2ml CSFin EDTA Vacutainer	Daily 9am	4th Day	17000
4	Meningo Encephalitis panel by PCR	1-2ml CSFin EDTA Vacutainer	Daily 9am	4th Day	12000
5	Leptospiralmeningitis panel(Smear Examination)	1ml CSF	Daily 9am	Same day at 5pm	550
6	Leptospiralmeningitis panel By PCR	5 ml EDTA Whole Blood	Mon, Thu: 9am	5th day	2000
7	Neisseria Meningitidis	2 ml of CSF	Daily: 9am, 3pm	After 6 hrs	2200
8	TB meningitis panel	CSF In Sterile Container. (Min 2 ml)	Daily: 9am to 9pm	Upto 6 weeks	900
9	TB meningitis panel (AFB-Xpert panel by GenexpertReflex AFB Rapid culture	CSF	Daily: 9am to 9pm	Upto 6 weeks	2600
		HERPES SIMPLEX VIRUS (HSV) INFECTION			
1	HSV-1,HSV 1&2,HSV-2	3ml CSRF &3 ml Serum	Tue.Fri 9am	Next 4pm	2500
2	HSV-1&2 by PCR	2 ml of CSF In Sterile Container	Mon, Thu: 9am	Next day 5pm	3200
		ZOSTER INFECTION			
1	VZV-Varicella Zoster Virus by PCR	1 ml CSF In Sterile Container	Mon , Thu: 9am	Next day 5pm	2900
2	VZV-Varicella Zoster Virus(IgG antibody),	3 ml CSF And 3 ml Serum	Tue, Fri: 9am,7am	Next day 5pm	2500
		MEASLES AND MUMP INFECTIONS			
1	MeaslesRubella Virus, Mumps Virus,Rubella German measles	3 ml CSF And 3 ml Serum	Tue, Fri:7am,German Measles (at 9am)	Next day 5pm ,German Measles (at 1pm)	2500
2	Rubella (German measles) virus by PCR	2 ml of CSF In Sterile Container	Daily: 9am	5th day	2700
		CYTOMEGALOVIRUS (CMV)			
1	CMV	2 ml of CSF In Sterile Container	Mon, Thu: 9am	Next day 5pm	4000
2	CMV	3 ml CSF, 3 ml Serum collected same time	Tue, Fri: 9am	Next day 11am	2500
		OTHER VIRAL INFECTIONS			
1	EBV	1 ml CSF In Sterile Container	Daily: 9am	7th day	3500

2	Enteroviruses RNA	2 ml of CSF	Daily: 7am	5th day	4000
3	Parvovirus B19	2 ml of CSF In Sterile Container	Daily: 9am	7th day	2700
4	JEV-Japanese Encephalitis Virus	2 ml of CSF In Sterile Container	Fri: 9am	Next day 5pm	3950
5	JC/Bk Virus	2 ml of CSF In Sterile Containe	Daily: 7am	7th day	4800
		PARASITE INFECTIONS			
1	Cysticercus (Taenia Solium)	2 ml of CSF	Tue, Fri: 7:30am	Same day 5pm	1600
2	Toxoplasma	2 ml of CSF In Sterile Container	Mon, Thu: 9am	Next day 5pm	2800
3	Toxoplasma-IgG	3 ml CSF And 3 ml Serum	Tue, Fri: 9am	Next day 1pm	2500
4	Malaria Parasite	3 ml EDTA Whole Blood; Direct smear	Daily: 9am, 1pm, 5pm	After 4 hrs	230
5	Malarial Antigen	3 ml EDTA Whole Blood	Daily: 9am, 1pm, 5pm	After 4 hrs	600
6	Fungal culture CSF	2 ml CSF In Sterile Container Or Bactec Myco F / Lytic Bottle	Daily: 9am to 9pm	20th day	990
7	Cryptococcus	2 ml of CSF	Daily: 9am, 1pm, 6pm	After 6 hrs	2000
8	Cryptococcus by PCR	2 ml CSF In Sterile Container	Daily: 7am	10th day	7400
9	Microfilaria	3 ml of EDTA Whole Blood	Daily: 9am, 3pm	After 6 hrs	1150
10	Panfungal	CSF In Sterile Container	Daily: 7am	10th day	3500
		OTHERS			
1	Culture & Sensitivity, Aerobic bacteria	2 ml CSF Sample In Sterile Container	Daily: 9am to 9pm	Upto 1-5 days	850
2	TORCH-5 IgG	2 ml of CSF and 3 ml of serum	Daily 9am	Same day 5pm	9500
3	TORCH by PCR	5 ml of CSF	Daily: 9am	5th day	7500