# CLINICAL APPROACH TO ACUTE ENCEPHALITIS

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**1. Background**. Encephalitis refers to inflammation of the brain parenchyma and may be diffuse, focal, or multi-focal. Inflammation may also involve other parts of the CNS including the spinal cord (encephalomyelitis) or meninges (meningoencephalitis). Patient demographics and risk factors, pattern of involvement, and timing of onset often suggest the underlying etiology. While infections account for the majority of cases in which an etiology is identified, autoimmune conditions are increasingly recognized as a significant cause of encephalitis. Specific infectious etiologies vary with environmental factors including local disease prevalence, travel to endemic areas, and season. They also occur with varying frequency and severity in patients of different age and immune status. Viruses are the most commonly identified infectious cause of encephalitis. Herpes simplex type 1 (HSV-1) is the most common cause of sporadic encephalitis. In North America, the most common epidemic cause of viral encephalitis is West Nile virus; Japanese encephalitis virus is the leading cause worldwide but is restricted to Asia and northern Australia. In general, bacteria, mycobacteria, spirochetes, fungi, and parasites tend to cause meningitis or rarely more focal brain disease in the form of walled off mass lesions. Important non-infectious causes of encephalitis include acute disseminated encephalomyelitis (ADEM), systemic autoimmune disease with CNS involvement, and autoimmune and paraneoplastic encephalitis. Despite extensive testing, the etiology of encephalitis remains unknown in up to 40-50% of cases.

**2. Pathophysiology**. Infectious agents may cause CNS inflammation through direct invasion (viremia or sepsis with subsequent traversal through the blood-brain barrier), via peripheral infection and intra-axonal transport to the CNS, or through bystander damage from the accompanying immune response. Systemic infection, vaccination, or malignancy may also initiate an attack of CNS through “molecular mimicry,” in which the host response to infectious or neoplastic antigens cross reacts with host self-antigens.

**3. Clinical Presentation**. The classic clinical features of encephalitis include headache, fever, and evidence of encephalopathy (global cerebral dysfunction resulting in altered mental status, with accompanying confusion, disorientation, behavioral changes, or cognitive impairments). Other common symptoms and signs include seizures, language disturbance, and focal neurological signs. While some patients with encephalitis may lack classic features on presentation, it should also be noted that the features above are not unique for encephalitis. Additional supportive evidence for brain inflammation can be provided by brain imaging (typically MRI) or cerebrospinal fluid findings (i.e. white blood cell pleocytosis, elevated protein, or oligoclonal banding), and electroencephalography may suggest specific causes in a minority of cases.

4. **Differential Diagnosis.**

**A. Encephalopathy or encephalitis?** Causes of encephalopathy are manifold, and include toxic/metabolic, vascular, neoplastic, and traumatic causes. In all patients with suspected encephalitis, alternate etiologies should be aggressively investigated **(Table 1).**

**Table 1. Encephalitis mimics**

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| **Vascular** |
| Ischemic stroke |
| Subarachnoid hemorrhage |
| Intracerebral hemorrhage |
| Cerebral venous sinus thrombosis |
| Posterior reversible encephalopathy syndrome (PRES) |
| Reversible vasoconstriction syndrome (RCVS) |
| **Metabolic derangement** |
| Hepatic and/or renal encephalopathy |
| Hypoglycemia, hyponatremia |
| Septic encephalopathy |
| Mitochondrial encephalopathy |
| Wernicke's encephalopathy |
| **Toxic** |
| Alcohol, drugs |
| **Trauma** |
| **Neoplastic** |
| Primary brain tumor |
| Metastases |
| **Epileptic** |
| Nonconvulsive status epilepticus |

**B. Acute bacterial meningitis**: Once inflammatory CNS disease is suspected or confirmed, acute bacterial meningitis (ABM) and HSV encephalitis must be simultaneously evaluated and treated. Patients with ABM often present with fever, headache, and mental status changes. These patients are more likely to have a fulminant course with high fever and hypotension, as well as symptoms and signs of meningeal irritation. Early neuroimaging is often normal. CSF examination is key to distinguishing ABM from viral encephalitis (**table 2**), and for determining the specific pathogen (Gram stain and culture). For suspected cases, empiric broad-spectrum antibiotics should be initiated while awaiting microbial studies.

**Table 2. Cerebrospinal fluid (CSF) profiles of bacterial vs. viral meningoencephalitis**

| CSF parameter | Bacterial | Viral |
|---|---|---|
| Opening pressure | >180 mm $H_2O$ | 100-350 mm $H_2O$ |
| Glucose | <40 mg/dL | Normal to mildly decreased[a] |
| Total protein | Elevated > 45 mg/dL, often 100-500 mg/dL | Mildly elevated 50-100 mg/dL |
| Red blood cells | Absent unless traumatic tap | Absent unless traumatic tap, may be present in minority of herpes simplex encephalitis |
| White blood cell count | 1,000-10,000 WBC/$mm^2$ | 10-1000 WBC/$mm^2$ |
| White blood cell differential | Predominantly polymorphonuclear cells | Predominantly lymphocytes[b] |
| Gram stain | Positive in 70-90% when tested prior to antibiotics | Negative |

[a]Mumps, lymphocytic choriomeningitis virus may cause moderate decrease, and herpes simplex virus (HSV), eastern equine encephalitis virus may cause mild decrease in glucose.
[b]May be predominantly polymorphonuclear (PMN) cells early (especially in enterovirus and HSV), but then shifts to lymphocytes; exceptions are West Nile virus and cytomegalovirus, which may have persistent PMN predominance.

**C. HSV encephalitis**: HSV encephalitis (HSE) is a neurological emergency as outcomes are improved with early initiation of acyclovir. Compared to ABM, HSE is typically more subacute and focal with a frontotemporal predilection on examination, EEG, and imaging (relatively unique among infectious encephalitis). Diagnosis is made by CSF PCR (highly sensitive and specific). Treatment with acyclovir should be initiated as soon as HSVE is suspected. Notably, false negatives can occur with CSF PCR testing, particularly if the lumbar puncture is performed early in the disease course; therefore, if there is strong clinical suspicion for HSE despite a negative HSV CSF PCR, acyclovir should be continued until a second lumbar puncture, performed several days later, is also negative.

**D. Acute disseminated encephalomyelitis**: ADEM is often associated with fever and other symptoms of infection, but unlike viral encephalitis it occurs at the *end* of the infectious process (or after vaccination). It is much more common in children and is frequently associated with other demyelinating syndromes such as optic neuritis and transverse myelitis. CSF patterns are similar in ADEM and viral encephalitis. The MRI pattern in ADEM is more distinctive with multifocal areas of acute demyelination, often with incomplete rim enhancement and sometimes with a peripheral rim of restricted diffusion. First-line is treatment is intravenous corticosteroids.

**E. Systemic autoimmune disease**: Encephalitis may rarely represent the first manifestation of systemic autoimmune disease. ***Sarcoidosis*** is a multisystem granulomatous disease of unknown etiology, most commonly affecting the lungs. When the brain is involved, headache and seizures are common. The CSF pattern may be similar to viral encephalitis but neurosarcoidosis most often presents over a longer time course and preferentially affects the base of the brain including cranial neuropathies. CSF ACE level, which may be elevated in neurosarcoidosis, does not appear to have sufficient sensitivity or specificity to be particularly useful. ***Behcet's disease*** is a multisystem vasculitic disease most common in patients of Mediterranean and Asian ethnicity. Oral and genital aphthous ulcers are hallmark features. Patients with neuro-Behcet's frequently present with headache, corticospinal tract signs, and cranial neuropathies, with corresponding MRI changes in the brainstem. CSF may be neutrophilic or lymphocytic. The presence or history of genital ulcers and the predilection for the cerebral peduncles and basis pontis are important distinguishing features.

**F. Hashimoto's encephalopathy**: Hashimoto's encephalopathy (HE) is an acute-subacute encephalopathy characterized by fluctuating behavioral and cognitive disturbances. By definition patients have negative microbiological studies and positive evidence of thyroid antibodies – thyroid peroxidase (TPO) and/or thyroglobulin antibody (TGA) which are thought to be non-specific markers of autoimmunity – and a favorable response to systemic corticosteroids. Thus, an alternate name for the condition is steroid responsive encephalopathy associated with autoimmune thyroiditis (SREAT). Patients rarely have fever or other infectious prodrome, typically have little to no CSF inflammation, and usually have a normal MRI.

**G. Antibody-mediated autoimmune encephalitis**: Several encephalitis syndromes have been associated with antibodies against neuronal proteins. Two of these have particular importance due to their frequency and specific treatment. Antibodies against neuronal ***N-methyl D-aspartate receptor (NMDAR)*** may cause a cortical-subcortical encephalopathy with distinctive clinical phases. An infectious prodrome is common, including fever and either upper respiratory or gastroenteritis symptoms. This is followed by prominent psychiatric disturbances in addition to global cognitive dysfunction. Next abnormal movements, autonomic dysfunction, and hypoventilation ensue. Patients may progress to decreased arousal including catatonia and coma. Most patients have normal or nonspecific MRI and EEG, though a small subset will have a "delta brush" pattern on EEG. Abnormal CSF may be found early in the disease course, although normal CSF white blood cells/protein and absence of oligoclonal bands does not obviate the diagnosis. Antibodies (IgG to NR1 subunit) should be tested in both serum and CSF, as the latter is more sensitive. In female patients of child-bearing age, the presence of an occult teratoma should be sought as removal is curative. Anti-NMDAR encephalitis has emerged as one of the most commonly identified causes of encephalitis in young individuals (i.e. under 30 years of age). ***Leucine-rich glioma inactivated 1 (LGI1)***, is the most commonly identified neuronal surface autoantigen in autoimmune limbic encephalitis. It is associated with the voltage gated potassium channel (VGKC) complex and initial reports identified the VGKC protein as the autoantigen; however it has subsequently been recognized that the autoimmune targets are other proteins, such as LGI1 and Caspr2, associated with the VGKC protein. Patients with LGI1 encephalitis present with psychiatric disturbances, anterograde amnesia, and (often refractory) temporal lobe seizures, along with medial temporal lobe signal changes on MRI – a pattern that can mimic HSV encephalitis. CSF is generally normal or only

mildly abnormal. Serum LGI1 antibodies confirm the diagnosis, but empiric treatment with acyclovir may be necessary until the diagnosis is established. Treatment for both LGI1 limbic encephalitis and anti-NMDAR encephalitis includes first line agents such as corticosteroids, IVIG, and/or plasma exchange, and second-line agents such as rituximab or cyclophosphamide.

**5. Evaluation.**

In all individuals with suspected encephalitis, common and/or treatable etiologies should be considered (HSV, VZV, enterovirus, Cryptococcus neoformans, Treponema pallidum, gram positive or negative bacteria). Additional considerations are described below.

**A. Host Factors, Demographics, and Epidemiology:** In children, additional etiologies to consider include EBV and Mycoplasma pneumonia; in those under the age of 3, parechoviruses should also be considered. Opportunistic infections are additional considerations in those who are immunocompromised (see below). Specific exposures should also prompt additional considerations (i.e. cats, Bartonella; bats and/or animal bite, rabies; fresh water or nasal irrigation, *Naegleria fowleri*). Geographic and/or seasonal factors can also suggest specific etiologies (i.e. United States, Lyme disease; Africa, malaria; Asia, Japanese encephalitis).

**B. Extra-CNS clinical clues**: Certain systemic symptoms may give clues to the etiology. A diffuse rash may indicate enterovirus or a childhood exanthem. A vesicular rash in a dermatomal pattern suggests zoster. Influenza and adenovirus are often associated with pharyngitis or upper respiratory symptoms. Mumps and lymphocytic choriomeningitis may be associated with parotitis, oophoritis, orchitis, and/or pancreatitis. Both adenovirus and St. Louis encephalitis virus may cause conjunctivitis, while CMV and West Nile virus may cause retinitis. Non-healing skin lesions may suggest Balamuthia mandrillaris as a cause.

**C. Tropism within CNS**: Some etiologies have a tropism for specific CNS regions (**table 3**). Importantly, it has become increasingly recognized that the acute onset of psychotic features or movement disorders suggests anti-NMDAR encephalitis as a cause.

**Table 3. Causes of specific encephalitis syndromes**

| Limbic encephalitis | Cerebellitis | Basal ganglia | Rhombencephalitis | Encephalomyelitis |
|---|---|---|---|---|
| HSV-1 | VZV | JEV | Listeria | WNV[a] |
| LGI-1 | EBV | WNV | WNV | EV71[a] |
| HHV-6 | Paraneoplastic | St. Louis | JEV | JEV[a] |
| NMDAR | St. Louis | Nipah | EV71 | Tick-borne encephalitis[a] |
| T pallidum | Whipples | Influenza | TB | Poliomyelitis[a] |
| | Brucella | | Brucella | Rabies |
| | Mumps | | Paraneoplastic | VZV |
| | | | NMO | HSV |
| | | | Behcet's | CMV |
| | | | | EBV |
| | | | | ADEM |
| | | | | NMO |

[a]Particularly acute flaccid paralysis

**D. Laboratory diagnosis**: Chemistry profile, complete blood count with differential, coagulation studies, blood cultures, HIV antibody screening, and serum samples to be stored for acute and convalescent testing should be obtained in all patients (**Table 4)**. Common additional testing, based upon specific signs and symptoms, environmental and host factors, and clinical and imaging localization, might include serologies for EBV, Lyme, mycoplasma, Rickettsia, Ehrlichia, Anaplasma, and coccidioides; PCR and acute and

convalescent serologies for arboviruses targeted geographically; blood smear for parasites and atypical lymphocytes; serum cryptococcal antigen, and urine histoplasma antigen. A tuberculin skin test or interferon-gamma release assay for latent TB may be valuable both diagnostically and as information which may affect potential treatment with corticosteroids.

CSF is essential for the diagnosis of encephalitis. CSF in all potential infectious settings should be examined urgently for opening pressure, glucose, total protein, red blood cell count, and white blood cell count with differential. Gram stain, bacterial culture, PCR for HSV, VZV and enterovirus, cryptococcal antigen testing, and VDRL should be performed on all samples (as well PCR for enterovirus and WNV IgM in the appropriate season). Oligoclonal bands and IgG index should be evaluated to determine whether there is intrathecal antibody synthesis suggestive of an immune or infectious process. Extra CSF should always be obtained and stored for additional tests as more information is obtained. In appropriate settings, other testing might include mycobacterial smear, culture, and PCR; fungal culture; PCR for EBV, Bartonella, and mycoplasma; IgM or paired serum/CSF IgG for arboviruses; and testing for anti-neural autoantibodies (i.e. NMDAR, LGI1, etc.). In immunocompromised patients, additional CSF tests might include PCR for CMV, HHV-6, and EBV. Further CSF testing applies in limited specific settings. As the pace of new technologies expands the clinically available diagnostic testing options, clinicians should consult with local laboratory and microbiology experts or governmental agency regarding appropriate testing in specific cases.

**Table 4. Routine studies for evaluation of encephalitis in adults**

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| **Serum** |
| Blood counts, chemistries, coagulation, blood cultures X 2 |
| HIV serology |
| Treponemal testing |
| **CSF** |
| Opening pressure, protein, glucose, WBC count with differential, RBC count |
| Gram stain and bacterial culture |
| PCR for HSV-1/2, VZV, enterovirus |
| Cryptococcal antigen or India Ink staining |
| VDRL |
| Oligoclonal bands and IgG index |
| **Imaging** |
| Neuroimaging (MRI preferred to CT) |
| Chest X-ray and/or CT |
| **Neurophysiology** |
| EEG |

**6. Treatment**.

In patients with fever and focal neurological symptoms and signs, consideration should be given early to empiric treatment for ABM and HSVE. If atypical bacteria (Bartonella, Mycoplasma), rickettsiosis, or ehrlichiosis are suspected, doxycycline should be added to the regimen. Specific antiviral treatments are limited (**table 5**).

**Table 5. Treatment for select CNS viral infections.**

| CNS infection | Treatment | Comments |
|---|---|---|
| HSV encephalitis | Acyclovir 10mg/kg IV q8h for 10-21d | Adequate hydration to avoid renal toxicity from tubular precipitation |
| VZV encephalitis | Acyclovir 10-15 mg/kg IV q8h for 10-21d (duration poorly define); valacyclovir 1000mg PO tid suppression may be indicated in immunosuppressed | In cases of vasculopathy or myelitis, short course corticosteroids may be of added benefit |
| CMV encephalitis | Ganciclovir 5 mg/kg IV q12h + foscarnet 90 mg/kg IV q12h for 21d, followed by maintenance | If HIV+, cART should be initiated concurrently |
| Human herpes virus-6 encephalitis | Ganciclovir 5 mg/kg IV q12h *or* foscarnet 90 mg/kg IV q12h for 21d, followed by maintenance | If toxicity develops to one agent, may change to the other |
| Herpes B virus encephalitis | Ganciclovir 5 mg/kg IV q12h for 14-21d, followed by valacyclovir 1g PO q8 for 1 yr | Prophylaxis with valacyclovir 1g PO q8 for 14d |
| EBV encephalitis | Consider corticosteroids, IVIG, or plasmapheresis | Balance with risks, severity of encephalitis |
| HIV encephalitis | Consider cART initiation with input from experts; regimen may be targeted at CNS penetration in some cases | CNS-IRIS[a] is sometimes treated with corticosteroids |
| Rabies encephalomyelitis | No effective treatment | Postexposure prophylaxis with rabies immune globulin and vaccine |

[a]Immune reconstitution inflammatory syndrome

Despite major advances in antiviral therapies, the majority of viral encephalitides have no specific effective antiviral treatment. However, many complications require treatment. These include antiepileptic medications for seizures, monitoring and treatment of increased intracranial pressure, cerebral edema, and nonconvulsive status epilepticus, and correction of hyponatremia or other metabolic abnormalities. Particularly in patients with brainstem involvement, careful cardiorespiratory monitoring and support are important to avoid sudden cardiac or respiratory arrest.

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