## REVIEW

# Diagnosis and treatment of viral encephalitis

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Acute encephalitis constitutes a medical emergency. In most cases, the presence of focal neurological signs and focal seizures will distinguish encephalitis from encephalopathy. Acute disseminated encephalomyelitis is a non-infective inflammatory encephalitis that may require to be treated with steroids. Acute infective encephalitis is usually viral. Herpes simplex encephalitis (HSE) is the commonest sporadic acute viral encephalitis in the Western world. Magnetic resonance imaging of brain is the investigation of choice in HSE and the diagnosis may be confirmed by the polymerase chain reaction test for the virus in the cerebrospinal fluid. In this article, we review the diagnosis, investigations, and management of acute encephalitis. With few exceptions (for example, aciclovir for HSE), no specific therapy is available for most forms of viral encephalitis. Mortality and morbidity may be high and long term sequelae are known among survivors. The emergence of unusual forms of zoonotic encephalitis has posed an important public health problem. Vaccination and vector control measures are useful preventive strategies in certain arboviral and zoonotic encephalitis. However, we need better antiviral therapy to meet the challenge of acute viral encephalitis more effectively.

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The diagnosis of acute encephalitis is suspected in a febrile patient who presents with altered consciousness and signs of diffuse cerebral dysfunction. Worldwide, infection of the central nervous system is the commonest cause of acute encephalitis. Herpes simplex virus (HSV), varicella zoster virus (VZV), Epstein-Barr virus (EBV), mumps, measles, and enteroviruses are responsible for most cases of acute viral encephalitis among immunocompetent individuals in the United Kingdom. In a large Finnish study reported recently, VZV was found to be the commonest virus associated with encephalitis as well as meningitis and myelitis, comprising 29% of all confirmed or probable aetiological agents while HSV and enteroviruses accounted for 11% each and influenza A virus 7% of the cases.[1] Tuberculosis, rickettsial diseases, and human African trypanosomiasis are important non-viral causes of meningoencephalitis but will not be covered in this article. Acute disseminated encephalomyelitis (ADEM) and its more severe form, acute haemorrhagic leucoencephalitis (AHLE) represent non-infective central nervous system inflammatory diseases. Non-

inflammatory diffuse brain dysfunction is termed encephalopathy; metabolic dysfunction and intoxications are its best examples.

In encephalitis, a degree of leptomeningeal inflammation is invariably present and the clinical symptoms reflect both diffuse and focal cerebral pathology as well as meningitis (fever, headache, and signs of meningism). The degree of altered consciousness is a measure of the severity of acute encephalitis and may range from drowsiness to coma. Seizures, both focal and generalised, are common. In contrast to aseptic viral meningitis, neuropsychiatric symptoms often predominate in encephalitis, for example, anomia, hallucinations, psychosis, personality changes, and agitation. Acute encephalitis constitutes a neurological emergency and it is imperative that appropriate treatment is started as soon as possible based on the likely clinical diagnosis (see box 1).

## ESTABLISHING THE DIAGNOSIS
### Encephalopathy

The presence of fever in itself is not sufficient to make a diagnosis of infective encephalitis since encephalopathy may be precipitated by systemic infections or sepsis without cerebral inflammation (septic encephalopathy). Cerebral malaria is considered to be an example of infective encephalopathy rather than true encephalitis since the neurological symptoms of cerebral malaria result from brain hypoxemia and metabolic complications (hypoglycaemia and acidosis) due to the heavy parasitaemia of the red blood cells by *Plasmodium falciparum* leading to capillary occlusion.[2] Patients with neuroleptic malignant syndrome have fever, altered consciousness, and nuchal rigidity and may present even after the offending neuroleptic has been withdrawn.[3] Traumatic brain injury and ongoing epileptic seizures must be excluded before making a diagnosis of acute encephalitis. Seizures are generalised in encephalopathy, although focal seizures and focal neurological deficit may rarely occur (for example, hypoglycaemic encephalopathy and hemiplegia). Clues must be sought to distinguish encephalitis

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**Abbreviations:** ADEM, acute disseminated encephalomyelitis; AHLE, acute haemorrhagic leucoencephalitis; EBV, Epstein-Barr virus; EEG, electroencephalography; HmPAO, $^{99m}$Tc-hexamethylpropyleneamineoxime; HSE, herpes simplex encephalitis; HSV, herpes simplex virus; NINAID-CASG, National Institutes of Allergy and Infectious Diseases Collaborative Antiviral Study Group; SPECT, single photon emission computed tomography; VZV, varicella zoster virus

## Box 1: Clinical diagnosis

**Acute or subacute onset global cerebral dysfunction: three diagnostic categories**
- Infective encephalitis (typically viral; see box 2).
- Encephalopathy (typically metabolic or toxic; see box 3).
- Acute disseminated encephalomyelitis (ADEM).

**The physician addresses three important questions:**
- How likely is the diagnosis of encephalitis?
- What could be the cause of encephalitis?
- Which is the best treatment plan for the patient with encephalitis?

## Box 2: Causes of infectious meningoencephalitis

**Viral**
*DNA viruses*: herpes simplex virus (HSV1, HSV2), other herpes viruses (HHV6, EBV, VZV, cytomegalovirus), and adenovirus (for example, serotypes 1, 6, 7, 12, 32).
*RNA viruses*: influenza virus (serotype A), enterovirus (for example, serotypes 9, 71), poliovirus, measles, rubella, mumps, rabies, arboviruses (for example, Japanese B encephalitis, La Crosse strain of California virus, St Louis encephalitis virus, West Nile encephalitis virus, lymphocytic choriomeningitis virus, Eastern, Western, and Venezuelan equine encephalitis viruses), reovirus (Colorado tick fever virus), and retrovirus (HIV).

**Bacterial**
*Mycobacterium tuberculosis, Mycoplasma pneumoniae, Listeria monocytogenes, Borrelia burgdorferi* (Lyme disease), *Tropheryma whippeli* (Whipple's disease), *Bartonella henselae* (cat scratch fever), leptospira, brucella (particularly *Brucella melitensis*), legionella, *Salmonella typhi* (typhoid fever), nocardia, actinomyces, *Treponema pallidum* (meningovascular syphilis), and all causes of bacterial (pyogenic) meningitis.

**Rickettsial**
*Rickettsia rickettsii* (Rocky Mountain spotted fever), *Rickettsia typhi* (endemic typhus), *Rickettsia prowazekii* (epidemic typhus), *Coxiella burnetii* (Q fever), *Erlichia chaffeensis* (human monocytic erlichiosis).

**Fungal**
Cryptococcosis, coccidioidomycosis, histoplasmosis, North American blastomycosis, candidiasis.

**Parasitic**
Human African trypanosomiasis, *Toxoplasma gondii*, *Nagleria fowleri*, *Echinococcus granulosus*, schistosomiasis.

## Box 3: Common causes of encephalopathy

- Anoxic/ischaemic.
- Metabolic.
- Nutritional deficiency.
- Toxic.
- Systemic infections
- Critical illness.
- Malignant hypertension.
- Mitochondrial cytopathy (Reye's and MELAS syndromes).
- Hashimoto's encephalopathy.
- Paraneoplastic.
- Neuroleptic malignant syndrome.
- Traumatic brain injury.
- Epileptic (non-convulsive status).

## Box 4: Helpful diagnostic pointers for encephalopathy

- Absence of fever, headache, and meningism.
- Steady deterioration of mental status.
- Absence of focal neurological signs or focal seizures (except hypoglycaemia).
- Characteristic biochemical abnormalities in blood and urine.
- No peripheral leucocytosis.
- Normal cerebrospinal fluid.
- Diffuse slowing in electroencephalography.
- Normal magnetic resonance imaging.

nerve roots. A syndrome of isolated acute ataxia due to postinfectious meningocerebellitis in children (acute ataxia of childhood) is commonly associated with VZV infection (chickenpox). Acute childhood cerebellar syndrome has also been reported after enterovirus, EBV, mycoplasma and rarely, after HSV infection. This syndrome is relatively abrupt in onset and may be associated with confusion and corticospinal signs in addition to the cerebellar symptoms (gait ataxia, limb ataxia, dysarthria, and nystagmus).[6] In the latter cases, neuroimaging is usually normal and the cerebrospinal fluid typically shows a mild pleocytosis with raised protein. Despite some ambiguity as to whether the acute cerebellar syndrome is infectious or postinfectious, it is currently held to be a benign variant of ADEM. Early treatment of ADEM with large doses of steroids (intravenous injections of methylprednisolone at a dose of 500 mg daily for 5–7 days in adults) may possibly improve the outcome of severe ADEM, although few controlled trials of steroid therapy in ADEM have been undertaken.[7]

### Infective encephalitis
The diagnosis of infective encephalitis should be based on positive evidence and not by exclusion. Infective encephalitis may be the obvious diagnosis in a patient presenting with an abrupt history of fever and headache progressing to declining mental status with development of focal neurological symptoms and focal seizures. However, establishing the diagnosis of central nervous system infection can be difficult. Because herpes simplex encephalitis (HSE) is the most common cause of sporadic acute viral encephalitis, it is now a common practice to start treatment with aciclovir once a diagnosis of infective encephalitis is clinically suspected even if the aetiology of the infective agent is unknown. However, there is no therapeutic benefit from the use of aciclovir in nonherpetic encephalitis.

### ESTABLISHING THE CAUSE OF INFECTIVE ENCEPHALITIS
This requires a careful and systematic assessment of the patient (see box 5).

from encephalopathy and box 4 summarises a number of features that may help to make this distinction.[4 5] However, this distinction may not always be possible on clinical grounds.

### Acute disseminated encephalomyelitis (ADEM)
ADEM is characterised by focal neurological signs and a rapidly progressive course in a usually apyrexial patient, usually with a history of febrile illness or immunisation preceding the neurological syndrome by days or weeks (postinfectious or postvaccinal encephalomyelitis). ADEM may be distinguished from infective encephalitis by the younger age of the patient, prodromal history of vaccination or infection, absence of fever at the onset of symptoms, and the presence of multifocal neurological signs affecting optic nerves, brain, spinal cord, and peripheral

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**Box 5: Evaluation of a patient with infective encephalitis**

**History**
- Geographic and seasonal factors.
- Foreign travel or migration history.
- Contact with animals (for example, farm house) or insect bites.
- Immune status.
- Occupation.

**Clinical signs**
- General: skin and mucous membrane, lymph nodes.
- Neurological: focal cortical, brain stem, autonomic signs.

**Investigations**
- Blood (biochemical and haematological), chest radiography.
- Electroencephalography.
- Computed tomography, magnetic resonance imaging of head (with contrast).
- Single photon emission computed tomography (SPECT, optional, depending on availability).
- Cerebrospinal fluid: cells, biochemistry, and molecular diagnostic tests (polymerase chain reaction).
- Brain biopsy (in a very few selected cases).

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## History

A detailed history needs to be taken from the relatives since a patient with encephalitis is likely to be confused, disorientated, delirious, or comatose. Both the geographical distribution and seasonal occurrence may offer important clues.[4] Japanese encephalitis is endemic in the Asian countries and often exhibits a seasonal pattern with cases peaking at the rainy season. Occasionally farm animal diseases might indicate a possible risk of viral encephalitis in the community because animals act as reservoirs for certain types of viruses causing encephalitis in humans. The 1999 outbreak of West Nile virus encephalitis in New York[8] was preceded by the death of city birds due to avian encephalitis. Four weeks after the outbreak of human encephalitis, specimens obtained from a Chilean flamingo in a nearby zoo identified the flavivirus as the cause of the West Nile virus encephalitis affecting both birds and humans.[9] Emerging infections due to the Nipah virus and the avian influenza viruses had also posed potentially serious risk of encephalitis in specific geographical areas.[10]

It is essential that a history should always be sought for recent foreign travel, insect or animal bites, and possible contact with individuals suffering from infectious diseases. The underlying medical condition is also relevant since immunosuppressed individuals are more susceptible to certain specific infective encephalitis, for example, listeriosis, cryptococcus, and cytomegalovirus. Cytomegalovirus encephalitis is common in HIV infected patients, particularly in neonates.[11] The mode of onset and progression of the viral illness may provide valuable clues to the aetiology, for example, biphasic course of the enterovirus infection.[12] Neurological complications of viral haemorrhagic fevers are often caused by aseptic meningitis and intracerebral bleed. Rabies is an example of a zoonotic encephalitis that presents with very distinctive clinical symptoms (hydrophobia and aerophobia), or rarely, as an ascending paralysis simulating Guillain-Barré syndrome.[13] Early neurological symptoms of human African trypanosomiasis (irritability, sleep disorder, changes in personality) are indistinguishable from viral encephalitis and may be associated with deep hyperaesthesia of the soft tissues, especially in Europeans.[14] Important clues may also be provided by the occupational history, for example, Lyme disease or Kyanasur Forest disease in a forestry worker inhabiting appropriate geographical area.

## Clinical signs
### (A) General examination

Skin rashes are common in rickettsial fever, varicella zoster and Colorado tick fever. Parotitis often occurs with mumps and erythema nodosum may be associated with granulomatous infections (tuberculosis and histoplasmosis). Mucous membrane lesions are common in herpes virus infections. Concurrent or prodromal upper respiratory tract infecion is characteristic of influenza virus and mycoplasma.

### (B) Neurological examination

Neurological signs in acute encephalitis do not reliably identify the underlying aetiology despite the propensity of certain neurotropic viruses to affect specific focal areas of the central nervous system. The most commonly reported focal abnormalities are hemiparesis, aphasia, ataxia, pyramidal signs (brisk tendon reflexes and extensor plantar responses), cranial nerve deficits (oculomotor and facial), involuntary movements (myoclonus and tremors), and partial seizures. The evolution of the clinical signs will depend on the virus, the age, and the immune status of the patient. In general, the very young and the very old have the most serious clinical manifestations of encephalitis. A constellation of frontotemporal signs with aphasia, personality change, and focal seizures is characteristic of HSE. The presence of multifocal lower motor neurone signs in a febrile patient might indicate poliomyelitis. Symptoms of autonomic or hypothalamic dysfunction may also be seen in acute encephalitis. These include loss of temperature and vasomotor control (dysautonomia), diabetes insipidus, and the syndrome of inappropriate secretion of antidiuretic hormone.

## Investigations
### (A) General

Relative lymphocytosis in the peripheral blood is common in viral encephalitis. Leukopenia and thrombocytopenia are characteristic of rickettsial infections and viral haemorrhagic fevers. The most sensitive and specific test for cerebral malaria is the peripheral blood film and both thick and thin peripheral smears are necessary. Peripheral blood monocytes may reveal the characteristic cytoplasmic inclusions in patients with human monocytic ehrlichiosis, 10% of whom are known to develop a meningoencephalitic syndrome.[15] Chest radiography is also advisable in all patients with acute encephalitis. Characteristic changes on chest radiography may point to the possibility of mycoplasma, legionella, or tuberculous infections.

### (B) Electroencephalography (EEG)

EEG is strongly recommended in any suspected case of acute encephalitis since it may help in distinguishing focal encephalitis from generalised encephalopathy. In the latter, EEG shows diffuse, bihemispheric slow wave forms, for example, triphasic slow waves in hepatic encephalopathy. EEG is invariably abnormal in HSE, though earlier the changes may be non-specific (slowing) with more characteristic changes (2–3 Hz periodic lateralised epileptiform discharges originating from the temporal lobes) limited to about half the cases in the later stages.

### (C) Neuroimaging

Brain imaging is now an established practice in patients with suspected acute encephalitis and usually precedes any other specific investigations. Magnetic resonance imaging is the cranial imaging of choice in acute encephalitis, although it may be simpler to obtain a computed tomogram quickly and easily in restless patients. Characteristic neuroimaging changes may offer clues as to the specific infective aetiologies—for example, frontotemporal changes in HSE and thalamic haemorrhage in Japanese encephalitis. Small haemorrhagic changes and pathognomonic lesions in the limbic

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**Box 6: Neuroimaging and EEG in acute encephalitis**

**Neuroimaging**

- Magnetic resonance imaging is the imaging of choice and should be considered as an emergency.
- Magnetic resonance imaging appearances may be diagnostic (HSE, Eastwern equine encephalitis, Japanese encephalitis).
- Computed tomography is the logical choice if on-site magnetic resonance imaging facility is not available or patient is restless.
- Cerebral SPECT scanning (HmPAO) is an optional test for suspected HSE and may have prognostic value.

**EEG**

- May help in the differential diagnosis of encephalitis v encephalopathy.
- Some EEG changes may be relatively specific (for example, periodic lateralised epileptiform discharges (PLEDS) in HSE or triphasic slow waves in hepatic encephalopathy).

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**Box 7: Lumbar puncture in acute encephalitis**

Essential to confirm the pathology of meningoencephalitis (cerebrospinal fluid lymphocytosis).
Must await neuroimaging (computed tomography/ magnetic resonance imaging).

**During the procedure**

- Measurement of cerebrospinal fluid opening pressure is important.
- Samples must be dispatched immediately for cell counts and morphology.
- Gram stain as well as acid and alcohol fast bacilli (AAFB) stain should be requested routinely.
- Simultaneous blood glucose sample must be collected.

**Microbiological tests in cerebrospinal fluid**

- Polymerase chain reaction for HSV, VZV, and *M tuberculosis*.
- Enteroviruses (appropriate cases).
- Polymerase chain reaction for cytomegalovirus and cryptococcal antigen test (especially if immunosuppressed).
- Specific viral antigen and antibody (see text).

**Lumbar puncture should be delayed**

- If computed tomography/magnetic resonance imaging is indicative of raised intracranial pressure.
- If patient has convulsive status epilepticus.
- Soon after a generalised seizure.
- If coagulopathy or severe thrombocytopenia (for example, haemorrhagic fever) is present.

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system in HSE are visualised better on magnetic resonance imaging than on computed tomography.[16] Meningeal and gyral enhancement after Gd-DTPA administration has been reported in HSE.[17] Changes in magnetic resonance imaging in Eastern equine encephalitis are characterised by disseminated lesions in the brainstem and basal ganglia.

### (D) Functional neuroimaging

Bitemporal hyperperfusion in the cerebral blood flow study using technetium labelled hexamethylpropyleneamineoxime ($^{99m}$Tc-HmPAO) and single photon emission computed tomography (SPECT) may offer supportive evidence favouring the diagnosis of HSE.[18] Temporal lobe hyperperfusion in the $^{99m}$Tc-HmPAO cerebral SPECT scan is a sensitive marker of HSE and the changes often persist beyond clinical recovery.[19] This test may be considered where facilities exist and is of particular value in cases where the symptom onset is relatively subacute because brain magnetic resonance imaging in paraneoplastic limbic encephalitis may mimic changes seen in HSE. An early study of localised $^{1}$H$^{1}$-proton magnetic resonance spectroscopy was promising in assessing the neuronal loss due to HSE.[17]

### (E) Cerebrospinal fluid analysis by lumbar puncture

This is an essential part of the investigation of encephalitis and should be the next logical step after neuroimaging provided it is considered safe. While cerebrospinal fluid abnormalities support the diagnosis of a meningoencephalitic syndrome, the changes in the cerebrospinal fluid constituents are often non-specific and may not be helpful in securing a specific aetiological diagnosis in many cases. Cerebrospinal fluid in viral encephalitis typically shows a lymphocytic pleocytosis with normal glucose and normal or mildly raised protein. The cerebrospinal fluid profile in acute viral encephalitis is indistinguishable from aseptic meningitis. Cerebrospinal fluid pleocytosis (>5 lymphocytes/mm³) is present in >95% cases of acute viral encephalitis.[5 19]

Absence of cerebrospinal fluid lymphocytosis should alert to an alternative aetiology (encephalopathy). A caveat to this is the possibility that the cells in the cerebrospinal fluid might lyse during the storage and transport of the sample if the analysis was delayed. Initial cerebrospinal fluid pleocytosis may be absent in atypical HSE. Patients who are immunocompromised (for example, by cancer chemotherapy or irradiation) often fail to mount an inflammatory response. The cell count in cerebrospinal fluid exceeds 500/mm³ in 10% cases of acute viral encephalitis.[20]

A high cerebrospinal fluid lymphocytosis might indicate tuberculous meningitis, mumps encephalitis, or uncommon viruses—for example, Eastern equine encephalitis, California

encephalitis, lymphocytic choriomeningitis virus; atypical lymphocytes in cerebrospinal fluid are occasionally seen in EBV, cytomegalovirus, and rarely in HSV encephalitis.[20] The presence of a higher number of polymorphonuclear leucocytes in the cerebrospinal fluid after first 48 hours indicates bacterial meningitis as the likely aetiology. Other than bacterial meningitis, cerebrospinal fluid polymorphonuclear leucocytosis may be present in ADEM and AHLE, primary amoebic meningoencephaltis due to *Naegleria fowlerii*, and occasionally in enteroviral, echovirus 9, and Eastern equine virus encephalitis. Approximately 20% of patients with acute encephalitis will have an excess of red blood cells (>500/mm³) in the cerebrospinal fluid in the absence of a traumatic tap.[20] This is typically associated with necrotising and haemorrhagic encephalitis (HSE and AHLE), listerial and primary amoebic meningoencephalitis. Cerebrospinal fluid xanthochromia is more typical of tuberculous meningitis and is rarely seen in HSE. However, presence or absence of red cells or xanthochromia is of virtually no use in discriminating HSE from other causes of acute encephalitis.[21] Any significant reduction in cerebrospinal fluid glucose (as a ratio of the corresponding plasma glucose) is unusual in viral encephalitis. Cerebrospinal fluid lymphocytic pleocytosis and reduced glucose is highly characteristic of tuberculous meningoencephalitis. A low cerebrospinal fluid glucose is also seen in other bacterial, fungal, parasitic, or neoplastic meningoencephalitis, occasionally in mumps and lymphocytic choriomeningitis virus encephalitis, and very rarely in the late stages of HSE.[22] Differentiating viral encephalitis from tuberculous meningoencephalitis may be difficult in the endemic areas, especially in children because cerebrospinal fluid lymphocytosis is common in both the conditions and the yield for smear positivity of *M tuberculosis* in the cerebrospinal fluid is low. In this situation, serial samples of cerebrospinal fluid and contrast enhanced neuroimaging (computed tomography/magnetic resonance imaging) may offer the only opportunity to distinguish tuberculous meningoencephalitis from viral encephalitis.

## (F) Cerebrospinal fluid virological studies

Measuring anti-HSV antibodies in the cerebrospinal fluid may be diagnostically useful, but detectable cerebrospinal fluid antibody levels usually develop after the first week of the illness. These assays are of little use, therefore, within the first few days of the illness when early diagnosis and treatment are essential.[22] There are several problems with the interpretations of serum and cerebrospinal fluid viral antibodies.[23] These tests take time to perform and a clinician would be best advised not to wait for these results before initiating treatment. Rises in antiviral antibody titres may be non-specific and indicate polyclonal activation due to the infection. Also, raised antiviral antibodies in a single serum sample may reflect persistent viral antibody levels from previous infection, or reactivation rather than a primary infection. Further, precise timing of the paired samples may be difficult, false negative results may occur and do not exclude the diagnosis of infective encephalitis.

More recently, diagnostic polymerase chain reaction for viral DNA amplification technique has significantly facilitated the diagnosis of infective encephalitis. Cerebrospinal fluid polymerase chain reaction is diagnostic for encephalitis due to HSV, VZV, cytomegalovirus, and EBV. There are several advantages of the polymerase chain reaction technique. This technique is exquisitely sensitive for the presence of viral genome in spinal fluid, can be rapidly accomplished (within 6–8 hours), requires only a very small volume of cerebrospinal fluid, and is highly specific for certain viruses—for example, HSV since the primers, if appropriately chosen, will not amplify DNA sequences from other viruses.[22]

## (G) Brain biopsy

Isolation of HSV from brain tissue obtained at biopsy was previously considered the gold standard for the diagnosis of HSE. Brain biopsy was a part of all the major treatment trials of HSE conducted by the National Institutes of Allergy and Infectious Diseases Collaborative Antiviral Study Group (NINAID-CASG) in the 1980s.[24 25] In these trials, 1 cm³ of the brain tissue was obtained from the anterior portion of the involved inferior temporal gyrus by subtemporal craniectomy under general anaesthesia. The sensitivity of the brain biopsy in HSE exceeds 95% with specificity greater than 99%. Brain biopsy in acute encephalitis was routinely advocated during the days when vidarabine was the only therapeutic agent in HSE. The introduction of aciclovir early in the treatment of HSE has largely rendered this policy unnecessary. Presently, brain biopsy in the setting of acute encephalitis may still have to be considered only if the diagnosis of HSE itself is doubtful. Brain biopsy in acute encephalitis may also be considered when surgical decompression is the treatment of choice for raised intracranial pressure refractory to medical management.

## SELECTED SYNDROMES OF VIRAL ENCEPHALITIS

HSE is the commonest acute meningoencephalitis in the Western world[26 27] and will be discussed below because of its clinical importance. Two other types of viral encephalitis will also be briefly covered; the first as a representative example of encephalitis in an immunocompromised host (cytomegalovirus encephalitis) and the other as an emerging zoonotic encephalitis (Nipah virus encephalitis).
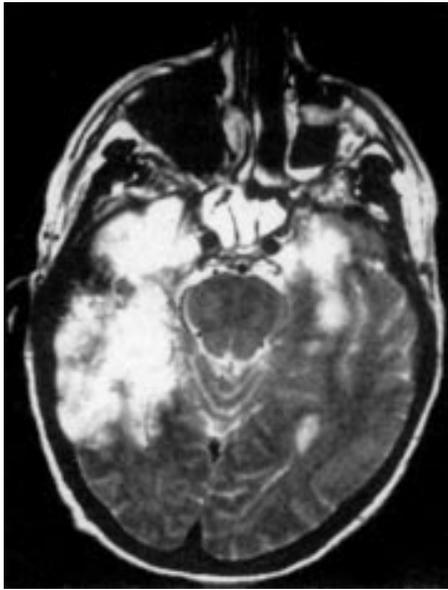
### Herpes simplex encephalitis

The annual incidence of HSE approximates 2000 cases in the USA alone.[27] HSV-1 accounts for more than 90% of childhood and adult cases of HSE. In contrast, HSV-2 is responsible for most neonatal and occasional adult cases of HSE. Unlike HSV-1, HSV-2 is a common cause of aseptic meningitis (usually in patients with primary genital herpes) and both HSV-1 and HSV-2 have been implicated in patients with recurrent meningitis (Mollaret meningitis).[28] Neonatal HSE results from the disseminated HSV-2 infection in the newborn acquired during the genital passage at the time of delivery. HSE can occur at any time during the year and affects both sexes, children and adults. Pathologically, HSE is an acute necrotising encephalitis with preferential involvement of the frontotemporal, cingulate, and insular cortex.[29] There is no clinical symptom or sign that is specific or sensitive for HSE. A preceding history of labial fever blisters is not necessarily of diagnostic value in HSE.[27] The onset of HSE is usually abrupt, with the clinical course rapidly progressing over several days. Acute anomia and recent memory loss occurs in one fifth of cases.[5] Personality changes may be subtle and easily missed. Seizures are common, usually complex partial, and often with secondary generalisation. Focal neurological deficits such as hemiparesis and aphasia develop when HSE is untreated, and may progress to coma. In a retrospective clinicopathological analysis of 46 cases of HSE, symptoms on admission included a prodromal influenza-like illness (48%), sudden onset of headache, confusion and alteration of conscious level (52%), meningism (65%), aphasia or mutism (46%), deep coma (35%), raised intracranial pressure (33%), focal neurological signs (89%), and seizures occurring in 61% of cases during the course of the illness.[29] One third cases develop in patients less than 20 years and half of all the cases are seen in patients over 50 years of age.[30]

It is the combination of the clinical features and laboratory findings that establishes the diagnosis of HSE. Peripheral white cell counts may be raised with a shift to the left. About 50% of patients with HSE have focal abnormalities on a non-contrast computed tomogram (reduced attenuation over one or both temporal and/frontal regions) and midline shift in half of those with abnormalities on computed tomography.[29] Computed tomography of the head within the first 4–5 days of symptom onset in HSE may even be normal.[31] Cranial magnetic resonance imaging remains the most sensitive anatomic neuroimaging not only for the early diagnosis but also for defining the distribution of cerebral injury in HSE. The magnetic resonance imaging scan in HSE typically shows early changes of focal oedema in the medial aspects of the temporal lobes, orbital surfaces of the frontal lobes, insular cortex, and cingulate gyrus (fig 1). Magnetic resonance imaging remains the imaging of choice in suspected HSE and should ideally be the first diagnostic step after initial clinical examination. Electroencephalography is abnormal in practically all cases.[29] Cerebrospinal fluid may show a normal or raised pressure, typically show lymphocytic pleocytosis (10–200 cells/mm³), normal glucose, and raised protein (0.6 to 6 g/l). In some, cerebrospinal fluid will have red blood cells (10–500 cells/mm³) and in even fewer cases, borderline hypoglycorrhachia (2–2.5 mmol/l). Cerebrospinal fluid polymerase chain reaction for HSV in experienced laboratories is virtually 100% specific and the sensitivity of this test exceeds 90%.[22] The likelihood of a false negative result for HSV in the cerebrospinal fluid polymerase chain reaction in a case of HSE is extremely low and is usually encountered if the cerebrospinal fluid was collected too early (first 24–48 hours), too late (after 10–14 days), after aciclovir therapy, or if there was a long delay in processing the sample that was stored inappropriately after collection. False negative tests can also occur when haemoglobin or heparin are present in the cerebrospinal fluid assay.[5]

Recently, cases of atypical HSE have been described.[32] These cases are often mild, presenting with a syndrome of febrile encephalopathy in the absence of focal neurological features, initial cerebrospinal fluid pleocytosis or abnormal computed tomography. Mild or atypical HSE is due to infection with either HSV-1 or HSV-2. These cases may be associated with an immunocompromised state or asymmetric HSV infection affecting predominantly the non-dominant temporal lobe. It is estimated that atypical forms may contribute to 20% of all cases of HSE. These cases also emphasise the importance of

**Figure 1** T2-weighted magnetic resonance image showing extensive area of increased signal in the right, and to a lesser extent, left temporal lobe in a case of HSE (reproduced with permission from Baringer, 2000). [22]

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**Box 8: Herpes simplex encephalitis**

- Commonest cause of non-endemic, acute fatal encephalitis in the Western world.
- High level of clinical suspicion is necessary.
- First central nervous system viral infection to be successfully treated with antiviral therapy.
- One of the first to have routine cerebrospinal fluid polymerase chain reaction diagnosis with high specificity and sensitivity.
- Seen in neonates and adults.
- Abrupt onset with frontotemporal features.
- Treatment initiation on clinical suspicion is required.
- A combination of magnetic resonance imaging, EEG, and cerebrospinal fluid tests is usually diagnostic.
- High motality and morbidity in untreated patients.
- Milder symptoms in atypical HSE.

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performing HSV cerebrospinal fluid polymerase chain reaction study on all patients presenting with febrile encephalopathy even in the absence of cerebrospinal fluid pleocytosis or focal neurological findings.

### Cytomegalovirus encephalitis

Cytomegalovirus encephalitis is rare in normal subjects but is a common encephalitis among the immunosuppressed and neonates. In an autopsy study, 12% of all HIV infected patients and 2% of transplant recipients had cytomegalovirus encephalitis.[33] In an immunocompetent host, cytomegalovirus encephalitis is usually self limiting, presenting with a febrile episode and non-specific clinical manifestations of meningoencephalitis (headache, confusion, rarely seizures, dysphasia, and coma). The cerebrospinal fluid shows pleocytosis, mildly raised protein, and normal glucose.[34] Cases of coexisting HSV and cytomegalovirus encephalitis have been reported both in the immunocompetent[35] and immunocompromised[36] hosts. Cytomegalovirus encephalitis is relatively common in HIV infected patients, usually in the course of systemic cytomegalovirus infection, cytomegalovirus radiculmyeltis, or retinitis. The characteristic neuropathopathology is of ventriculoencephalitis and nearly half

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**Box 9: New emergence of zoonotic encephalitic viruses**

- West Nile virus.
- Nipah and Hendra viruses.
- B virus (cercopthecine herpesvirus).

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of these patients will have coexisting processes due to HIV encephalopathy, toxoplasmic encephalitis, or primary central nervous system lymphoma.

The clinical picture of cytomegalovirus encephalitis in an immunosuppressed host is typically dominated by confusion and fatigue with a relatively rapid progression to coma and death. Polymorphonuclear cerebrospinal fluid pleocytosis is only seen in patients with coexisting radioculomyelitis whereas the pleocytosis is predominantly mononuclear and sparse in isolated ventriculoencephalitis. Protein level is relatively high (over 1 g/l) and viral cultures of cerebrospinal fluid are negative in patients with AIDS and cytomegalovirus encephalitis. Sensitivity of cerebrospinal fluid polymerase chain reaction for the detection of cytomegalovirus encephalitis is around 79% with a specificity of 95%.[33] A potential pitfall of polymerase chain reaction as a diagnostic tool for cytomegalovirus encephalitis is that it might be too sensitive, detecting cytomegalovirus in the absence of encephalitis among HIV infected patients.

### Nipah virus encephalitis

Nipah virus encephalitis was first recognised among pig farmers in Malaysia between 1998 and 1999 and subsequently documented among the abattoir workers in Singpore. Cerebrospinal fluid samples from several affected patients yielded a new paramyxovirus (named Nipah virus).[9] This virus was closely related, but not identical, to another animal virus (Hendra virus) that had previously caused disease among horses and three patients in Australia.[37] Nipah virus encephalitis is the first wide scale epizoonotic encephalitis with direct animal-to-human transmission, unlike most other epizoonotic encephalitis (for example, Japanese encephalitis, West Nile virus encephalitis, Eastern equine virus encephalitis), where vectorial transmission is the rule. Over 200 people were affected in Malaysia alone and the cluster outbreak severely disrupted the pig farming industry. The affected pigs died unusually and suddenly. The human illness was characterised by a history of direct contact with pigs in the livestock farm, short incubation period (two weeks), rapidly declining level of consciousness, prominent brain stem dysfunction, and high fatality rates. Distinctive clinical signs included segmental myoclonus, areflexia, hypotonia, and dysautonomia (hypertension and tachycardia). Initial findings in the cerebrospinal fluidwere abnormal in 75% cases, EEG showed diffuse slow waves with focal abnormalities over temporal regions (75%), computed tomograms were normal and magnetic resonance imaging of the brain during the acute phase of illness showed widespread focal lesions in the subcortical and deep white matter.[10]

### TREATMENT OF ACUTE VIRAL ENCEPHALITIS

Where possible, specific treatment must be targeted to the suspected or identified aetiological agent. Antiviral therapy with aciclovir is indicated in HSV encephalitis. Aciclovir is an analogue of 2'-deoxyguanosine and is selectively inhibits viral replication. It exerts its antiviral effect after being metabolised to aciclovir triphosphate. Monophosphorylation of aciclovir is the first step in this process and is catalysed by a viral thymidine kinase induced in cells selectively infected by HSV, VZV, or by a phosphotransferase produced by cytomegalovirus.[38] Host enzymes subsequently phosphorylate the monophosphate to

diphosphate and triphosphate. Aciclovir triphosphate inhibits the synthesis of viral DNA by competing with a 2′-deoxyguanosine triphosphate as a substrate for viral DNA polymerase. Viral DNA synthesis is arrested once aciclovir (rather than 2′-deoxyguanosine) is inserted into the replicating DNA. The incorporation of aciclovir into viral DNA is an irreversible process and it also inactivates viral DNA polymerase. The potency of aciclovir triphosphate to inhibit HSV-1 DNA polymerase is 30 to 50 times more than its ability to inhibit human cellular alpha-DNA polymerase.[39] Aciclovir has a relatively short half life in plasma and more than 80% of aciclovir in circulation is excreted unchanged in urine,[40] thus renal impairment can rapidly precipitate aciclovir toxicity. Studies have consistently confirmed that aciclovir is most effective when given early in the clinical course of HSE before the patient becomes comatose and reduces both mortality and morbidity in treated patients.[26 30 41] The standard dose of aciclovir for HSE is 10 mg/kg three times daily (30 mg/kg/day) for 14 days. The dose for neonatal HSE is 60 mg/kg/day. The duration of treatment is 21 days for immunosuppressed patients. Aciclovir is effective against encephalitis due to HSV-1, HSV-2, and VZV.[38] Doses of aciclovir in VZV encephalitis are similar to HSE.

It has become a common medical practice to initiate aciclovir treatment in every patient with suspected acute infective encephalitis. While this practice is justified and carries the advantage of initiating early treatment of HSE, there are certain potential problems with "blunderbuss" aciclovir therapy. Despite its remarkable safety, the decision to treat every case that could even remotely be HSE with aciclovir has two potential drawbacks. First and most importantly, giving aciclovir may delay or obscure the actual diagnosis (if not HSE) due to a false sense of security. Thus, diagnosis of other infective encephalitis, ADEM, or non-infective encephalopathies like Reye's syndrome, MELAS, or Hashimoto's encephalopathy may be delayed or even missed. Secondly, aciclovir is not completely innocuous and can precipitate a toxic encephalopathy[38] that can confound the diagnosis of acute encephalitis if this has not been made before the treatment was initiated.

Since early aciclovir treatment for HSE is essential, more patients than those actually having HSE will be initiated on this treatment based on clinical suspicion. In an immunocompetent host, evidence of lesions on magnetic resonance imaging affecting any of the temporal or frontobasal lobes supports the diagnosis of HSE and such a patient must be treated with aciclovir for a minimum of 14 days. If aciclovir is started on admission and magnetic resonance imaging of brain is found to be normal, then the treatment should continue until the cerebrospinal fluid polymerase chain reaction results for HSE become available and the treatment withdrawn in cases where this test is negative and an alternative diagnosis has been established. If an alternative diagnosis has not been reached and the cerebrospinal fluid polymerase chain reaction is negative for HSV, then it is our policy to continue aciclovir therapy for 10 days. There has been only a single case of HSE with normal cerebral magnetic resonance imaging in the current literature. In this patient, the diagnosis of HSE was made by polymerase chain reaction from a sample of cerebrospinal fluid obtained on the day of admission but a repeat cerebrospinal fluid polymerase chain reaction after eight days of ongoing aciclovir therapy was negative.[42] Recurrence of HSE has been reported weeks to three months later when the treatment was given for 10 days or less.[5] Reports have indicated that relapse after therapy may be as high as 5% but relapse has not been documented when higher doses were administered for 21 days.[43] Although aciclovir resistance has been reported in mucocutaneous herpes simplex among AIDS patients,[44] the development of aciclovir resistance in HSE has not yet been reported and it is only a theoretical possibility at present.

| Box 10: Aciclovir treatment in HSE |
|---|
| • Specific and highly effective. |
| • Safe, but requires dose adjustment for renal function. |
| • Treatment increase survival likelihood to 65%–100% if disease is present for four days or less.[30] |
| • Dose is 10 mg/kg every eight hours for at least 14 days in an immunocompetent host. |

The clinical response of cytomegalovirus encephalitis to antiviral drugs is not known and anecdotal experience suggests it is not dramatic. Aciclovir is ineffective in cytomegalovirus encephalitis. Combination therapy with ganciclovir (5 mg/kg intravenously twice daily) with or without foscarnet (60 mg/kg every eight hours or 90 mg/kg every 12 hours) is currently recommended[45]; cidofovir is a possible alternative. Antiretroviral therapy must be added or continued in HIV infected patients. Appropriate antibacterial chemotherapy will be required where tuberculous, listerial, rickettsial infections are suspected or diagnosed as the cause of meningoencephalitis. The role of large doses of corticosteroids (dexamethasone or methylprednisolone) in the setting of acute infective encephalitis is debatable. While steroids might be specifically indicated in certain situations such as tuberculous meningoencephalitis or granulomatous angiitis after varicella zoster infection, its efficacy in the setting of acute viral encephalitis is unproven and cannot be generally recommended. A study that had evaluated high dose dexamethasone in Japanese encephalitis found no benefit of steroid therapy.[46]

Supportive therapy for acute encephalitis is an important cornerstone of any treatment strategy. Seizures are controlled with intravenous fosphenytoin. Principles for the medical management of raised intracranial pressure should be followed where clinically indicated. Careful attention must be paid to the maintenance of respiration, cardiac rhythm, fluid balance, prevention of deep vein thrombosis, aspiration pneumonia, and secondary bacterial infections. Since some of the treatments may have specific toxicity (for example, aciclovir is nephrotoxic, raises serum liver enzymes, and can cause thrombocytopenia), appropriate blood counts and biochemical parameters must be closely monitored. Each dose of aciclovir should be given intravenously slowly as an infusion over at least one hour and the dose may require adjustment based on renal function. All cases of acute encephalitis must be hospitalised and should have access to intensive care unit equipped with mechanical ventilators. Isolation for patients with community acquired acute infective encephalitis is not required; rabies encephalitis, however, is an exception. Consideration of isolation should also be given for severely immunosuppressed patients, patients with an exanthematous encephalitis, and those with a potentially contagious viral haemorrhagic fever.

## COMPLICATIONS AND OUTCOME OF ACUTE VIRAL ENCEPHALITIS

Mortality rates in non-herpes viral encephalitis may range from very low (for example, EBV encephalitis) to very high (for example, Eastern equine encephalitis). Established rabies encephalitis is invariably fatal. Mortality rates in untreated HSE is around 70% and fewer than 3% would return to normal function.[26 27] In a retrospective analysis of patients with a diagnosis HSE, only 16% of untreated patients had survived.[29] Early diagnosis with aciclovir reduces the mortality of HSE to 20%–30%.[25–27] Among the aciclovir treated patients in the NINAID-CASG trials, 26 of the 32 (81%) treated patients survived and serious neurological disability was seen in nearly half of the survivors.[26] Older patients with poor level of consciousness (Glasgow coma scale of 6 or less) had the worst

outcome. Young patients (aged 30 years or under) with good neurological function at the time of initiating aciclovir therapy did substantially better (100% survival, over 60% had little or no sequel).[30] Persistent unilateral hyperperfusion in the cerebral SPECT scan is also a poor prognostic marker for recovery.[19]

A number of secondary complications may also arise in the course of an acute viral encephalitis.[12] These are raised intracranial pressure, cerebral infarction, cerebral venous thrombosis, syndrome of inappropriate secretion of antidiuretic hormone, aspiration pneumonia, upper gastrointestinal bleeding, urinary tract infections, and disseminated intravascular coagulopathy. The late sequelae of viral encephalitis largely depend on the age of the patient, aetiology of the encephalitis, and the severity of the clinical episode. Epilepsy, persistent anomia, aphasia, motor deficit, and a chronic amnestic state similar to Korsakoff's psychosis have been known among the survivors of severe HSE. Very rarely, a neuropsychiatric syndrome marked by oral exploratory behaviour (incomplete Kluver-Bucy syndrome) has been anecdotally observed during the early phase of recovery in HSE. Extrapyramidal syndrome (parkinsonism) as a late sequel of viral encephalitis was first recognised after the epidemic of influenza virus encephalitis that was characterised by a somnolent-ophthalmoplegic syndrome and fatigue (encephalitis lethargica or von Economo's disease).[47] Occasional cases of postencephalitic parkinsonism have since been reported after sporadic viral encephalitis, especially after Japanese encephalitis.[48] Nearly a third of all children with Japanese encephalitis will die and up to 75% of the surviving children may be left with major neurological sequelae, including mental retardation, epilepsy, behavioural abnormalities (obsessive-compulsive personality), speech and extrapyramidal (parkinsonian) movement disorders.[49] The syndrome of prolonged and persistent fatigue, myalgia, nervousness, concentration impairment, and postexertional malaise is well recognised after viral encephalitis (postviral chronic fatigue syndrome).[50]

## CONCLUSIONS

In all cases of acute encephalitis, appropriate investigations and supportive care form the integral part of the management strategy. The availability of aciclovir, an excellent anti-HSV therapy, has led to early initiation of the treatment with substantial improvement in the clinical outcome of HSE. The outlook of the non-herpes viral encephalitis, for example, Japanese encephalitis, is often less satisfactory. It is yet unknown if the availability of newer antiviral therapy (ribavarin and pleoconaril) will substantially change the natural course of non-herpes viral encephalitis. Some viral encephalitis may be prevented by immunisation (for example, mumps, measles, rubella, Japanese encephalitis, and rabies). Adequate vector control and environmental sanitation are essential to prevent large outbreaks of arboviral encephalitis such as Japanese encephalitis. Cluster outbreaks of West Nile virus encephalitis in New York City[8] and the emergence of zoonotic encephalitis due to Nipah virus in Malyasia[9] continue to signal an important public health principle that any new outbreaks of unusual and fatal diseases in animals may herald related events, maybe new infections, in humans.[51]

## ACKNOWLEDGEMENT

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