Encephalitis

These diseases are notifiable in the UK, see NOIDs article for more detail. Encephalitis is inflammation of the brain parenchyma, often caused by viral infections but also by other pathogenic organisms and occasionally by other conditions - eg, toxins, autoimmune disorders. Meningoencephalitis is an inflammatory process, most often due to viral infection, involving both the brain and meninges.

Epidemiology

- One review estimated the incidence of acute encephalitis in England to be 5.23 cases/100,000/year but possibly as high as 8.66 cases/100,000/year.[1]
- Infections are most frequent and severe in children and the elderly.
- Herpes simplex can cause a benign lymphocytic meningitis in adults but usually produces a severe encephalitis in neonates. Infection in adults can also be very severe.
- Post-infectious encephalitis is the most common demyelinating condition and is most often seen in children, as it may complicate the common childhood exanthemas.

Aetiology

- HIV infection is of increasing importance; toxoplastic meningoencephalitis was one of the first opportunistic infections to be described in HIV-infected patients.[2]
- Viral:
  - Viral encephalitis may be due either to:
    - Acute viral encephalitis (caused by a direct viral infection of the brain).
    - Post-infectious encephalitis (also called acute disseminated encephalomyelitis) which is an autoimmune process, following a viral infection elsewhere in the body.
  - Most viral infections in childhood are able to cause encephalitis.
  - Herpes simplex encephalitis (HSE) is recognised worldwide as the most frequent infectious encephalitis. [3]
  - In children older than 3 months and in adults: HSE is usually caused by herpes simplex virus type 1 (HSV-1) and is localised to the temporal and frontal lobes.
  - In neonates: HSE is usually caused by herpes simplex virus type 2 (HSV-2) acquired at the time of delivery, and brain involvement is generalised.
  - Other herpes viruses may cause encephalitis but much less frequently than HSV. However, cytomegalovirus (CMV) encephalitis should be considered in those with immunodeficiency.
  - Other viral causes include CMV, adenovirus, influenza virus, poliovirus, rubella, rabies, arbovirus (eg, California virus, Japanese B encephalitis, St Louis encephalitis, West Nile encephalitis, Eastern and Western equine encephalitis), reovirus (Colorado tick fever virus) and parvovirus B19.
- Bacterial causes: tuberculosis (TB), mycoplasma, listeria, Lyme disease, Bartonella henselae (cat scratch fever), leptospira, brucella, legionella, neurosyphilis, all causes of bacterial meningitis.
- Rickettsial: Rocky Mountain spotted fever, endemic typhus, epidemic typhus, Q fever, human monocytic ehrlichiosis.
- Fungal: cryptococcosis, coccidiomycosis, histoplasmosis, North American blastomycosis, candidiasis.
- Parasitic: African trypanosomiasis, toxoplasmosis, echinococcus, schistosomiasis.
- Tick-borne encephalitis is a rapidly growing public health problem in Europe and other parts of the world. [4] It is caused by tick-borne encephalitis virus, a member of the family Flaviviridae. See separate Tick-borne Encephalitis and Tick-borne Encephalitis Vaccination article for more information. [5]
• Primary amoebic meningoencephalitis is caused by infection from an amoeba such as *Naegleria fowleri* or *Balamuthia mandrillaris*.

**Presentation**

The clinical hallmark of acute encephalitis is the triad of fever, headache and altered mental status.\[^6\]

Most patients with viral encephalitis present with the symptoms of meningitis (fever, headache, neck stiffness, vomiting) followed by altered consciousness, convulsions, and sometimes focal neurological signs, signs of raised intracranial pressure, or psychiatric symptoms. There may be an association with a history of infection elsewhere in the body.

- Encephalitis may begin with a flu-like illness or with a headache, followed by a rapid development of altered consciousness, with confusion, drowsiness, seizures and coma.
- Symptoms may also include symptoms of increased intracranial pressure, such as severe headache, vertigo, nausea, convulsions and mental confusion. Other possible symptoms include photophobia, sensory changes and neck stiffness.
- Epilepsy, focal neurological signs and cognitive impairment may develop.
- Subacute sclerosing panencephalitis is a late complication of measles and presents four to ten years after the initial infection. Progression may be slow or rapid with personality change, dementia, seizures, ataxia and death. Progressive rubella panencephalitis is similar.

Neonatal HSE usually presents between 4 and 11 days after birth, with lethargy, irritability, poor feeding, tremors, seizures and a bulging fontanelle. Disseminated infection causes constitutional signs, such as shock, jaundice, gastrointestinal bleeding and purpura. 50-60% of those with disseminated infection develop a characteristic vesicular rash. Disseminated infection has a poor prognosis and high mortality.

**Differential diagnosis**

- Meningitis.
- Behçet's disease.
- Systemic lupus erythematosus.
- Post-vaccine encephalomyelitis.
- Autoimmune encephalitis.\[^7\]
- Stroke.
- Multiple sclerosis.
- Syphilis.
- Intracerebral tumour.
- Leukaemia.
- Lymphoma.

Clues to the origin of the encephalitis may be ascertained from the presentation. For example:

- A history of recent foreign travel, contact with animals, insect bites, immune status and occupation may all give a clue to the infecting organism.
- Chickenpox encephalitis often has cerebellar involvement.
- HSE is often associated with temporal lobe epilepsy.

**Investigations**

The investigations and management of viral encephalitis should be as detailed in:

- Current guidelines for adults.\[^8\]
- Current guidelines for children.\[^9\]

Laboratory diagnosis of viral encephalitis is ideally based on examination of CSF for cells, protein and glucose, lactate and virology PCR. All patients with suspected encephalitis should have a CSF PCR test for HSV (1 and 2), varicella-zoster virus (VZV) and enteroviruses, as this will identify 90% of cases due to known viral pathogens.
**CSF:**
- Viral encephalomyelitis leads to a lymphocytosis with normal CSF/plasma glucose ratio. Opening pressure is usually normal or high and the CSF is clear.
- CSF protein levels are usually normal or high.
- Elevated CSF specific antibody levels relative to serum indicate CNS infection with the respective organism.
- All patients with suspected encephalitis should have a CSF PCR test for HSV (1 and 2), VZV and enteroviruses, as this will identify 90% of cases due to known viral pathogens.
- PCR analysis of the CSF can be useful to diagnose several viral infections, including herpes simplex, Epstein-Barr, varicella-zoster, CMV, HIV, rabies and TB.

- FBC and film: leukocytosis. May indicate atypical lymphocytes in Epstein-Barr viral infections, morulae of Ehrlichia, trypanosomes in trypanosomiasis, borreliae in relapsing fever, or the gametes of *Plasmodium falciparum* in malaria.
- Other blood tests should include blood cultures, renal function and electrolytes, LFTs, glucose, ESR and CRP.
- Other cultures - eg, throat swabs and stool cultures - may be indicated.
- CT scan:
  - Can help to rule out space-occupying lesions, strokes and basilar fractures of the skull and to detect CSF leaks to localise fracture sites.
  - CT scan is also used to identify raised intracranial pressure, which will then need to delay a lumbar puncture.
- MRI scan:
  - Provides a sensitive detection of demyelination and can provide evidence of oedematous changes that occur in the early stage of encephalitis.
- Electroencephalogram (EEG):
  - Frequently abnormal (diffuse slowing with periodic discharges) in chronic and acute HSE and can sometimes help to determine the localisation in the early stages.
  - Is more useful than a CT scan in the first week.

**Management**

- Urgent hospital admission.
- Immediate parenteral antibiotics for possible diagnosis of meningitis. Intravenous or intramuscular benzylpenicillin should be given as long as the patient is not allergic to penicillins.
- In any case of possible encephalitis, prompt treatment with aciclovir by intravenous infusion, to cover herpes simplex. Aciclovir can be life-saving but must be started immediately the diagnosis is suspected. Aciclovir has been shown to greatly improve the prognosis if given before coma develops but any delay in starting treatment leads to a much worse prognosis.
- There is no specific treatment for other viral causes and the emphasis of treatment is supportive.
- The role of steroids in the treatment of HSE is not established.
- Intravenous fluids need to be given very carefully in order not to aggravate cerebral oedema.
- Other treatments may include anticonvulsants and sedatives (to reduce agitation).
- Intensive care, including ventilation, may also be necessary in severe cases, to reduce brain swelling.
- Intravenous broad-spectrum antibiotics may be given to treat secondary bacterial infections.
- Amphotericin is usually given for primary amoebic meningoencephalitis.

**Complications**

- Inappropriate antidiuretic hormone secretion.
- **Disseminated intravascular coagulation.**
- Cardiac and respiratory arrest.
- **Epilepsy.**
- There is a broad range of potential neuropsychiatric impairments. Significant changes may occur in personality and in the ability to function, even if there is a complete physical recovery. Residual impairment may be cognitive, behavioural or emotional and vary greatly in severity. Severe amnesic syndrome caused by profound damage to the temporal lobes may occur.
- Physical problems include mild balance, co-ordination and dexterity problems or major neurological problems, with speech and swallowing problems and total dependency.
Prognosis

- Encephalitis causes high rates of illness and death.\(^1\)
- The prognosis depends on the age of the patient and the underlying aetiology.
- The poorest prognosis for viral encephalitis occurs in patients with untreated HSE and subacute sclerosing panencephalitis.
- Untreated HSE is progressive and often fatal within 7-14 days. There is a 70% mortality rate in untreated patients and more than half of the untreated survivors have severe neurological deficits. Among treated patients, the mortality rate is 19%.\(^10\)
- Factors indicating a worse prognosis for acute encephalitis include increasing age, immunocompromised state, coma, mechanical ventilation and acute thrombocytopenia.\(^11\)

Prevention

- Some encephalitides can be reliably prevented by vaccination - eg, Japanese encephalitis, tick-borne encephalitis and rabies.\(^12\)
- Vector control is the main method of prevention for some pathogens - eg, arboviruses.
- Neonatal HSE:
  - There is currently insufficient evidence to determine if antiviral prophylaxis reduces the incidence of neonatal herpes.\(^13\)
  - In genital herpes in pregnancy, caesarean section may prevent HSV-2 encephalitis in neonates.
  - If maternal infection is discovered during or after delivery, apply topical aciclovir to the eyes of the neonate and consider prophylactic intravenous aciclovir therapy.

Further reading & references

- The Encephalitis Society
  12. Immunisation against infectious disease - the Green Book (latest edition); Public Health England

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