# Viral meningitis and encephalitis

Philip Rice

## Abstract

Viral meningitis and encephalitis occur at all stages of life. They can represent disease at its primary site of replication (e.g. rabies) or be part of an infection syndrome (e.g. HIV). A large proportion of cases go unconfirmed by laboratory diagnosis despite use of all available laboratory techniques. They can be sporadic or epidemic, but with changing environmental and societal conditions, infective agents can emerge for the first time (e.g. Nipah, Hendra and Zika viruses) or reappear after a period of good control through vaccination (e.g. mumps virus, poliovirus). Specific antiviral treatment is currently limited. Prevention is by public health measures and vaccination.

**Keywords** Enteroviruses; Hendra; herpes simplex encephalitis; HSV; Japanese encephalitis; MRCP; Nipah; rabies; viral encephalitis; viral meningitis; West Nile virus; Zika

## Key points

- The diagnosis of encephalitis should involve testing blood and other bodily samples in addition to cerebrospinal fluid (CSF)
- Herpes simplex encephalitis is a life-changing diagnosis, and immediate antivirals are mandatory until the diagnosis can be excluded
- Viral meningitis is usually benign and, apart from primary herpes simplex virus (HSV) meningitis, requires no specific antiviral treatment
- The laboratory CSF findings found in varicella-zoster virus and HSV meningitis can mimic those of tuberculous meningitis
- Patients with recurrent HSV meningitis derive no benefit from either acute or suppressive aciclovir treatment

## Viral meningitis

***Definition and epidemiology*** – the term 'aseptic meningitis' was introduced because it seemed to represent a specific aetiological entity, namely patients with symptoms and signs of meningitis in whom bacterial cultures were negative. It is now known that almost all cases are caused by one of a wide range of viruses (Table 1), most commonly enteroviruses (70–90%), herpes simplex virus (HSV-1, HSV-2), varicella-zoster virus (VZV) and mumps virus.

The exact incidence of viral meningitis is unknown, but it is grossly under-reported. In the UK in 2005–2006, 2898 patients were admitted to hospital with the diagnosis, >10 times the number formally notified to the Health Protection Agency.[1] Although any age group can be affected, childhood disease is most common: a Finnish study found an annual incidence of 219 per 100,000 in infants aged <1 year compared with 28 per 100,000 in 1–14-years-olds.

Transmission occurs by droplet infection, close personal and kissing contact, or faeco-orally. Zoonotic infection is seen with lymphocytic choriomeningitis virus, an arenavirus related to Lassa fever virus that is excreted in the urine of small rodents; transmission occurs by inhalation when changing bedding contaminated with urine.

***Clinical features*** – the typical viral meningitis syndrome comprises a triad of symptoms and signs of acute onset: fever, headache and accompanying signs of meningeal irritation (photophobia, neck stiffness, Kernig's sign). Non-specific symptoms include arthralgia, myalgia, sore throat, rash and lethargy. Other symptoms and signs are specific to the causative agent. Clues to the possible organism can be obtained from other information revealed in the history, such as sexual exposure, travel, vaccination status and animal exposure.

### Enteroviruses

There are >70 serotypes of enterovirus, including poliovirus, coxsackievirus A and B, and echovirus; replication is in the gastrointestinal tract. Most infections are asymptomatic and occur seasonally in late summer and autumn. Outbreaks can occur in nurseries and day-care centres. Rarely, outbreaks in neonatal units have been described, with occasionally high mortality. A rash may be seen, often subtle; this can be erythematous, maculopapular or vesicular. When on the palms or soles and inside the mouth, it is termed hand, foot and mouth disease. An enanthem in the oral cavity is seen in herpangina. Enterovirus serotype 70/71 can cause acute flaccid paralysis identical to that caused by poliovirus; this became apparent during an extensive outbreak in South-East Asia in 1997 several years ago.

Aside from this neurological complication, full recovery is the rule. In patients with agammaglobulinaemia, chronic, relapsing meningitis can result, requiring administration of intravenous immunoglobulin. No antiviral agents are licensed for this indication. The antiviral agent pleconaril failed to demonstrate clinical benefit and was rejected because of side effects.

### Herpes simplex and varicella-zoster viruses

Primary HSV infection can occur with either HSV-1 or HSV-2. The risk of clinically apparent meningitis is greatest in a primary infection of the genital tract, with approximately 30% of women and 13% of men developing it. However, clinical meningitis is unusual with a non-primary genital infection (infection with one virus type in an individual with pre-existing antibody to the other type). As the prevalence of childhood oral HSV-1 infection appears to be decreasing, more cases of HSV-induced meningitis are likely.

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**More commonly recognized causes of viral meningitis and encephalitis**

| | Meningitis | Encephalitis | Geographical distribution |
|---|---|---|---|
| **Virus** | | | |
| HSV | +++ HSV-2[a] | +++ HSV-1[a] | Worldwide |
| VZV | +++ | + | Worldwide |
| Enterovirus | +++ | +/− | Worldwide |
| EV 70/71 | +/− | +++ | South-East Asia |
| Poliovirus | ++ | +/− | Nigeria, Somalia, Afghanistan, Pakistan |
| Mumps | +++ | +/− | Underdeveloped countries and age-restricted outbreaks in USA/UK |
| HIV | ++ (Primary infection) | + (Dementia) | Worldwide |
| Rabies | +/− | +++ | Africa, Indian sub-continent, South-East Asia, South and Central America, USA |
| W/E/VEE | − | +++ | The Americas |
| Nipah/Hendra | + | +++ | Malaysia/Singapore |
| WNV | + | +++ | Worldwide (USA — emerging pathogen) |
| TBE | − | +++ | Russia, Balkans, Scandinavia |

EV, enterovirus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; TBE, tick-borne encephalitis; VZV, varicella-zoster virus; W/E/VEE, Western/Eastern/Venezuelan equine encephalitis; WNV, West Nile virus.
[a] Predominant virus type.

**Table 1**

The syndrome of benign recurrent aseptic meningitis is caused by reactivation of genitally acquired HSV infection, most commonly HSV-2. Episodes occur predominantly in women (female:male ratio 6:1), separated by intervals of months or years. The average number of episodes that patients record is four. In one study, the recurrence rate in those presenting with a first episode of HSV meningitis was 19%. Headache can be associated with genital recurrences, but the host and viral factors underlying this association are not understood. Aciclovir has not been shown to affect the course of illness and, when used to suppress attacks, can cause an increased frequency of episodes once therapy has ceased.

Reactivation of VZV usually presents as cutaneous shingles but can also present as meningitis without a skin component. Such patients can suffer excruciating headaches of very sudden onset, mimicking subarachnoid haemorrhage.

### Mumps virus

Mumps meningitis occurs in 1—10% of cases of mumps, typically about 5 days after onset of parotitis; however, cerebrospinal fluid (CSF) abnormalities are seen in approximately 50% of infections. Meningitis can precede parotitis by a week or even follow it after 2 weeks. Symptoms last 7—10 days, but the condition is essentially benign with no long-term complications.

The epidemiology of viral meningitis has changed dramatically since 1988, following the introduction of the MMR (measles, mumps, rubella) vaccine in the UK. Before this, mumps virus was the most common cause of meningitis (annual incidence 5—11/100,000 population, 1200 hospital admissions each year); the current incidence is about 0.3 per 100,000 population. Outbreaks still occur despite good vaccine uptake rates in the UK and USA. This is thought to be because of a mixture of primary and secondary vaccine failure, the relatively high transmissibility of mumps virus and the low immunogenicity of the Jeryl Lynn strain of mumps virus in the vaccine.

### HIV

Headache occurs in about 50% of patients during primary HIV infection, with symptoms of meningitis in 17%. Higher HIV RNA concentrations in the CSF also correlate with neurological symptoms. Early diagnosis of primary infection in cases with a high clinical index of suspicion, by either fourth-generation antigen/antibody assays or viral load testing, may enable post-exposure prophylaxis to be given to sexual contacts. Furthermore, initiation of anti-HIV drugs during the primary infection can prevent wider virus dissemination within the central nervous system (CNS) and preserve immune control of HIV.

## Viral encephalitis

***Definition and epidemiology*** — encephalitis is an uncommon outcome of many common viral infections (Figure 1, Table 1). Infection of the brain parenchyma can have devastating consequences; mortality is high, and there is long-term morbidity in many survivors. Many different viruses are responsible, and the condition can arise from either primary infection or reactivation of latent infection.

Acute encephalitis is a notifiable disease in the UK, with an estimated 700 cases annually. In the USA, the estimated incidence is 20,000 per year, probably because of infection by arthropod-borne (ARBO) viruses, such as West Nile virus (WNV) and St Louis virus. The largest UK prospective survey of encephalitis detected infectious agents in 42% of cases and an immune-mediated cause in 21%, leaving 37% still with no proven aetiology.

***Pathogenesis of infection*** — viruses can reach the CNS by the haematogenous or neuronal route:

- The haematogenous route is used by arthropod-borne viruses (arboviruses), after injection into capillary blood by a tick or mosquito bite. Local replication in surrounding



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