Viral meningitis and encephalitis

Philip Rice

Abstract

Viral meningitis and encephalitis occur at all stages of life. They may 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 may be sporadic or epidemic, but with changing environmental and societal conditions, infective agents may emerge for the first time (e.g. Nipah and Hendra viruses) or reappear after a period of good control through vaccination (e.g. mumps virus and poliovirus). Specific antiviral treatment is limited at present. Prevention is by public health measures and vaccination.

Keywords enteroviruses; Hendra; herpes simplex encephalitis; HSV; Japanese encephalitis; Nipah; rabies; viral encephalitis; viral meningitis; West Nile virus

What's new?

- Enterovirus 70/71 vaccine has been shown in a Chinese trial to be 90% effective
- Suppressive aciclovir for 6 months after neonatal herpes simplex virus infection improves neurodevelopment
- New biologicals vastly increase the risk of developing untreatable progressive multifocal leuco-encephalopathy
- In over one-third of cases of encephalitis, no aetiological agent can be identified

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 such 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) or 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 such a diagnosis, more than 10 times the number formally notified to the Health Protection Agency.[1] Whilst any age group can be affected, childhood disease is most common; a study from Finland found an annual incidence of 219 per 100,000 in infants aged under 1 year compared with 28 per 100,000 in those 1—14 years old.

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 that is excreted in the urine of small rodents; transmission of this organism occurs by inhalation when changing bedding contaminated with urine.

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

Enteroviruses

The enteroviruses comprise over 70 serotypes, including poliovirus, Coxsackievirus A and B, and echovirus. Most infections are asymptomatic and occur seasonally in late summer and autumn. Outbreaks may also occur in nurseries and day-care centres. Rarely, outbreaks in neonatal units have been described; these can occasionally have a high mortality. A rash may be seen; often subtle, this may be erythematous, maculopapular or vesicular. When on the palms, soles of feet 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 SE Asia several years ago. Aside from this complication full recovery is the rule. In patients with agammaglobulinaemia, chronic, relapsing meningitis may result requiring administration of intravenous immunoglobulin. There are no licensed anti-viral agents. The anti-viral agent pleconaril failed to demonstrate clinical benefit.

HSV and VZV

Primary genital HSV infection can occur with either HSV-1 or HSV-2. The risk of clinically apparent meningitis is greatest in a primary genital infection, with approximately 30% of women and 13% of men developing this complication. However, if a non-primary genital infection occurs (infection with one virus type in an individual who possesses pre-existing antibody to the other type), clinical meningitis is unusual. As the prevalence of childhood oral HSV-1 infection appears to be decreasing, at least in the UK, more cases of HSV-induced meningitis are likely. 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 recorded by patients is four. In one study, the recurrence rate in those presenting with a first episode of HSV meningitis was found to be 19%. Headache may be associated

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More commonly recognized causes of viral meningitis and encephalitis

	Meningitis	Encephalitis	Geographic distribution
Virus			
HSV	+++ HSV-2[a]	+++ HSV-1[a]	Worldwide
VZV	+++	+	Worldwide
Enterovirus	+++	+/−	Worldwide
EV 70/71	+/−	+++	SE Asia
Poliovirus	++	+/−	Nigeria, Somalia, Afghanistan, Pakistan
Mumps	+++	+/−	Underdeveloped countries and age-restricted outbreaks in USA/UK
HIV	++ (Primary infect)	+(Dementia)	Worldwide
Rabies	+/−	+++	Africa, ISC, SE Asia, S and C 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; W/E/VEE, Western/Eastern/Venezuelan equine encephalitis; VZV, varicella-zoster virus; WNV, West Nile virus.
[a] Predominant virus type.

Table 1

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 may cause the frequency of episodes to increase once the therapy has been stopped.

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

Mumps virus

Mumps meningitis occurs in 1—10% of cases of mumps, typically about 5 days after onset of parotitis, though abnormalities in the cerebrospinal fluid (CSF) are seen in approximately 50% of cases of infection. Meningitis may precede parotitis by a week or even follow it after 2 weeks. Symptoms last for 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 and 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 0.3/100,000 population. Outbreaks still continue to occur despite the good uptake rates of vaccine seen primarily in the UK and USA.[2] This is thought to be due to a mixture of primary and secondary vaccine failure, the relatively high transmissibility of mumps virus and the low reactogenicity of the Jeryl—Lynn strain of mumps virus in the vaccine.

HIV

Headache occurs in about 50% of patients during primary HIV infection, and symptoms of meningitis are seen in 17% during HIV sero-conversion. Higher HIV RNA concentrations in the CSF also correlate with neurological symptoms. Early diagnosis of primary infection in clinically highly suspected cases, by either fourth-generation Ab/Ag 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 may 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 and 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/year, probably because of infection by arthropod-borne (ARBO) viruses, such as West Nile and St Louis viruses. The largest UK prospective survey of encephalitis detected infectious agents in only 42% of cases, an immune-mediated cause in 21%, leaving 37% still with no aetiology.

Pathogenesis of infection — viruses may reach the CNS by the haematogenous or neuronal route.

- The haematogenous route is used by ARBO viruses, after injection into capillary blood by a tick or mosquito bite. Local replication in the surrounding skin is followed by primary viraemia, which seeds the major organs. A second bout of multiplication produces secondary viraemia; if of sufficient magnitude, this can lead to the virus crossing the blood—brain barrier via infected leucocytes or locally in vascular endothelia.
- The neuronal route of entry is exemplified by rabies and HSV, which are transported directly into the brain by retrograde axoplasmic flow. This is a viral immune evasion mechanism — once inside the axon, the virus is invulnerable to immune control.