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Viral meningitis

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Viruses probably account for most cases of acute meningitis. Viral meningitis is often assumed to be a largely benign disease. For the commonest pathogens causing meningitis, enteroviruses, this is usually the case; however, for many of the other pathogens causing viral meningitis, and for common pathogens in the immunocompromised or infants, viral meningitis is frequently associated with substantial neurological complications and a significant mortality. Diagnostic methods for rapid and accurate identification of pathogens have improved over recent years, permitting more precise and earlier diagnoses. There have been fewer developments in therapies for viral meningitis, and there remain no effective therapies for most pathogens, emphasising the importance of prevention and early diagnosis. This review focuses on the presentation, diagnosis and management of viral meningitis and also covers the prevention of meningitis for pathogens where effective vaccines are available.

Keywords: meningitis, virus, viral, meningoencephalitis, herpesvirus, enterovirus, diagnosis.

Introduction

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Viral meningitis is an important cause of admission to hospital, with an estimated incidence of around 5–15 cases per 100 000 per year in the UK [1]. The reported incidence almost certainly underestimates the true level, particularly for enteroviral meningitis, the commonest pathogen identified. Of the remaining causes of viral meningitis and central nervous system (CNS) infections, herpes simplex virus (HSV) and flaviviral meningoencephalitis are the most important in terms of morbidity and mortality, although mumps infection has recently reemerged as an important pathogen in young adults in the UK. Other significant causes of viral meningitis are illustrated in Table 1. Most viruses causing meningitis exhibit a marked seasonality, with a number also having specific geographical distributions, underlining the importance of obtaining an accurate travel history in patients presenting with aseptic meningitis.

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Distinguishing viral from bacterial meningitis on presentation or admission to hospital, on the basis of clinical features and initial cerebrospinal fluid (CSF) parameters, presents a considerable challenge. There are considerable benefits in making this distinction swiftly, in terms of both reducing antibiotic usage and hospital bed occupancy and reassuring contacts of cases and health care staff of a non-bacterial cause [2]. For the purposes of this review, the term viral meningitis will be used to describe both acute and chronic meningitis as well as meningoencephalitis. Although some viruses cause a pure encephalitis, myelitis or post-infectious encephalitis, discussion of these disorders is beyond the scope of this review.

Pathophysiology

Viruses enter the CNS through several mechanisms [3]. Many, such as enteroviruses, replicate outside the CNS and then invade by haematogenous spread. Viral particles pass directly across the blood–brain barrier, or are carried across in infected leukocytes (e.g. mumps, measles or herpesviruses), and then infect vascular endothelial cells. Other viruses invade through peripheral and cranial nerves, as for polio and HSV, respectively. Once within the CNS, viruses may spread through the subarachnoid space in CSF, with consequent inflammatory response leading to meningitis. Viruses may also spread directly or via inflammatory leukocytes through neural tissue to neurones and glial cells.

Once CNS infection has taken hold, inflammatory cells, including lymphocytes specifically targeting the infecting virus, accumulate in the CNS. This is accompanied by the release of inflammatory cytokines such as interleukin (IL)-1β, IL-6 and tumour necrosis factor (TNF)-α as well as local immunoglobulin production by plasma cells. Inflammatory responses leading to increased permeability of the blood–brain barrier also permit entry of circulating immunoglobulins. Viruses may evade effective immune response either through immune tolerance or through escape of immune surveillance. T lymphocyte responses are an essential part of the immune response to some viruses, as illustrated by the increased frequency and morbidity associated with chronic cytomegalovirus (CMV) or varicella-zoster virus (VZV) meningitis in patients with impaired cell-mediated immunity. Viruses such as VZV may cause disease through a cerebral vasculitis, with immunocompetent patients usually developing a large-vessel vasculitis and immunocompromised patients developing a small-vessel, more diffuse vasculitis.

Epidemiology and clinical features

Enteroviruses

Human enteroviruses cause a wide variety of diseases including polio, hand, foot and mouth disease, myocarditis, and aseptic meningitis, most commonly affecting and transmitted through children [4–7]. They are now classified into five species: human enteroviruses A–D (including echoviruses and coxsackieviruses) and polio. Enteroviruses are thought to cause over 75 000 cases of meningitis in the USA each year and cause substantial morbidity in adults as well as children [7]. Enteroviral meningitis is the commonest cause of aseptic meningitis, with both epidemic and endemic patterns of disease, and the predominant serotypes identified are echoviruses 6, 9, 11, 13, 19 and 30. The reported incidence is almost certainly a great underestimate because most cases are mild and do not result in hospital admission and diagnostic lumbar puncture. Earlier this decade, there were large summer epidemics of enteroviral meningitis in the UK, due mostly to the type B enteroviruses: echovirus types 13 and 30 [1]. In temperate climates, enteroviral infections are commonest during the summer and autumn months, and spread is predominantly through the faecal–oral route, with infections often commonly acquired in child-care facilities. Meningitis is most commonly seen in school-aged children, although is frequently the cause of admission in pre-school children and adults. Endemic polio is now confined to many Central African and west Asian countries, although sporadic cases still occur in other areas of the world. The incubation period of non-polio enteroviral infections is usually around 3–7 days and that of polio is usually between 1 and 3 weeks.

The typical presentation of enteroviral meningitis in children is with vomiting, anorexia, rash or respiratory symptoms as well as meningism, often preceded by flu-like symptoms and a sore throat [6]. Focal neurological signs or seizures are rare, except in neonates who are most at risk of developing meningoencephalitis and severe systemic complications such as myocarditis or necrotizing enterocolitis, which are associated with substantial mortality. Specific clinical features may identify particular enteroviruses: for example, herpangina is typically found with coxsackievirus A infection, whereas a scattered maculopapular rash is frequently seen with echovirus 9 infection. The presentation in adults is often similar to that of bacterial meningitis, with photophobia perhaps more prominent in enteroviral meningitis [2, 7]. A subtle rash, which is sometimes noted, may lead to a suspicion of meningococcal septicaemia. Although often thought to be a benign cause of meningitis, enteroviral meningitis is associated with significant morbidity in adults in terms of hospitalization and time taken to return to work [7]. Nonetheless, severe

complications of enteroviral meningitis are extremely rare and mostly seen in the immunocompromised.

Whilst acute and chronic complications of enteroviral meningitis appear to be unusual in the immunocompetent, during epidemics of hand, foot and mouth disease, enterovirus 71 meningitis has led to significant morbidity and mortality in children [4]. There is some uncertainty regarding the long-term outcome in children with enteroviral meningitis, particularly those who had meningitis as infants. There is some evidence that in children with meningitis under 1 year of age, subtle neurodevelopmental problems such as language may later be detected [8]. A UK study of children with meningitis in the first year of life found that 42% of children with echovirus meningitis had mild or moderate neurological disability by the age of 5 years [9].

One well-recognized group of patients developing a more severe and chronic form of infection, particularly associated with echovirus 11, are those with primary immune deficiencies, mostly X-linked agammaglobulinaemia [10]. This complication has acquired the synonym CEMA (chronic encephalitis and meningitis with agammaglobulinaemia), although a significant proportion of cases also develop dermatomyositis, hepatitis, arthritis or myocarditis. Patients developing CEMA often seem to have had inadequate immunoglobulin replacement, and mortality is around 50% 5 years after diagnosis [11]. The immunocompromised are also at a higher risk of developing paralytic poliomyelitis, which in developed countries has been acquired through receipt of (or contact with those who have received) oral polio virus (OPV).

Herpesviruses

The most important cause of CNS infections amongst herpesviruses are the HSVs (HSV-1 and HSV-2), which are the commonest cause of acute sporadic encephalitis in adults and children over 6 months of age [12]. The spectrum of CNS infection of these viruses includes meningitis, encephalitis, myelitis and, occasionally, radiculitis (usually sacral); however, the most serious of these is encephalitis, with a mortality of around 70% if untreated [13]. There is a bimodal distribution in the age range of those affected, most being over 50 years of age and the younger subgroup being under 20 years of age, possibly reflecting reactivation of HSV infection and primary infection, respectively. HSV encephalitis is predominantly caused by HSV-1, whereas meningitis is more often caused by HSV-2, although is not always associated with episodes of genital herpes. HSV-2 has more often been established as a cause of recurrent aseptic meningitis, sometimes labelled Mollaret's meningitis, than HSV-1 [12].

HSV meningitis presents similarly to other types of meningitis, with most patients reporting headaches, a stiff neck and fever. Encephalitis usually manifests as a focal, rather than diffuse, encephalitis [14], although it is important to consider HSV in patients presenting with reduced levels of consciousness. The typical anatomical site affected by HSV is the temporal lobe; hence, encephalitis may present with personality change, mutism or hallucinations as well as more common focal neurological signs. HSV-2 meningitis causes neurological complications more often than most other viral meningitis: around one-third of all patients in one study developed complications; however, virtually all of these had resolved after 6 months [15]. HSV-2 meningitis has also been identified as a significant cause of morbidity and mortality in immunocompromised patients [16]. Between 10 and 30% of HSV meningoencephalitis cases appear to relapse, normally between 1 week and 3 months following completion of therapy. As with other types of meningitis, adverse prognostic indicators of HSV meningitis or encephalitis include a low Glasgow coma scale at presentation, extremes of age and a delay in starting antimicrobial therapy.

Other herpesviruses associated with meningoencephalitis include Epstein–Barr virus (EBV), CMV, VZV and human herpesvirus 6 (HHV-6). CNS infections with these viruses are mostly seen in the immunocompromised, and CMV in particular has been associated with a chronic meningoencephalitis in advanced human immunodeficiency virus (HIV) infection. CMV and VZV may also cause a myelitis or, occasionally, a ventriculitis, and VZV has been associated with a large-vessel cerebral vasculitis causing strokes, particularly in the elderly. Systemic clinical features may point to the possibility of a herpesviral cause: a mononucleosis-like syndrome would suggest the possibility of EBV or CMV, a widespread vesicular rash VZV and infantum roseola HHV-6 infection.

Flaviviruses

These mosquito- or tick-borne viruses have specific geographical areas of endemicity, and their incidence is also related to seasons [17]. The Japanese encephalitis complex is the most important antigenic group causing meningitis. Japanese B encephalitis is endemic in Southeast Asia, whereas West Nile virus is found in west Asia, the Middle East, Africa, Central and Southern Europe and North America. Tick-borne encephalitis is endemic in some areas of forests and meadows in Central and Eastern Europe, and Asia. St. Louis encephalitis virus is found only in the Americas, whereas Murray Valley encephalitis virus is confined to

Australia and New Zealand. The main host for these viruses are birds; however, pigs are also an important host for Japanese B encephalitis. West Nile virus has received much attention in recent years because it emerged as a new pathogen on the West Coast of the USA in 1999, then spread east, culminating in nearly 3000 cases of meningitis and 276 deaths in 2002 [17]. There were also reports in that year, for the first time, of transmission through transfusions and organ transplants [18]. In the USA, West Nile virus has predominantly affected adults, whereas elsewhere in the world it is mainly children and non-immune adults who are affected, as happens for Japanese B encephalitis and Murray Valley encephalitis. St. Louis encephalitis, on the other hand, tends to occur in epidemics across all age groups, mostly in the southern and eastern states of the USA.

Most flaviviral infections are either asymptomatic or cause mild febrile illness without overt meningitis, with an incubation period of 5–15 days. The characteristic presentation of West Nile fever is arthralgia, rash and fever [19], whilst Japanese B encephalitis may present with abdominal pain or nausea and vomiting. CNS manifestations vary between each virus, with between 1 in 25 and 1 in 1000 cases developing some form of involvement. Japanese B encephalitis is predominantly an encephalitis, whereas up to 40% of West Nile virus and St. Louis encephalitis infections (and 50% of Murray Valley encephalitis) present with meningitis. Tick-borne encephalitis, on the other hand, is a biphasic illness, with meningitis or encephalitis developing in a small proportion of patients a few days after the initial febrile illness subsides. Apart from the typical presentation of meningitis, many infections (especially in children) present with seizures or an altered level of consciousness; other complications of encephalitis such as hemiparesis or cranial nerve palsies may also occur. Two other neurological manifestations include a poliomyelitis-like syndrome, with features of flaccid paralysis, and a parkinsonian syndrome, reflecting the involvement of the anterior spinal cord and basal ganglia, respectively, in these infections. Severe neurological and systemic complications including death are more common in elderly adults, the immunocompromised and (for West Nile virus) diabetics. Around 50% of those with meningoencephalitis are left with long-term neurological disability or psychiatric sequelae.

Other flaviviruses including dengue and yellow fever groups can potentially cause CNS infections, although they are very rare manifestations. The tick-borne complex viruses, on the other hand, are a well-recognized cause of meningoencephalitis in Central Europe and Asia, with the greatest incidence during the summer months. Several other insect-borne viruses (arboviruses) causing meningitis, particularly in the Americas, are described in the footnotes to Table 1.

Table 1 Aetiology, epidemiology and potential complications of the more significant causes of viral meningitis

Virus	Epidemiology	Systemic manifestations and complications
Enteroviruses[a]	Common in children; highest incidence in summer/autumn in temperate climates	Usually benign; however, significant morbidity and mortality in neonates, immunocompromised (especially agammaglobulinaemia) and in association with epidemic enterovirus 71 infections. Meningoencephalitis and myo/pericarditis are the commonest serious complications
Mumps	Frequently seen in non-immunized populations; males more often affected than females	Usually self-limiting; salivary gland swelling in around 50%
West Nile virus[b,c]	Mosquito-borne infection, peaking in late summer in temperate climates. Endemic in Asia, Europe, Africa and, more recently, North America. As yet, has not been acquired in the UK	Case fatality 4–13%, and higher amongst elderly, immunosuppressed and diabetics. Fifty per cent with encephalitis left with permanent neurological or psychiatric impairment
Japanese B[b,c] encephalitis	Mosquito-borne infection, predominantly Southeast Asia. Major natural host is pigs; commoner during wet seasons and in rural areas. Most frequently in children and non-immune adults	Mortality around 20–30%, with up to 30% having long-term neurological disability
Tick-borne encephalitis	Tick-borne infection contracted mainly in Europe and Asia; commonest in spring and early summer	Case fatality 1–20%; highest in the Far Eastern form. Usually a more prolonged illness than other viral encephalitides
Human immunodeficiency virus (HIV)	Develops in 5–10% of patients around or shortly after a seroconversion illness and occasionally during chronic infection	Complications are rare in early HIV infection. Chronic infection associated with HIV–dementia complex; seroconversion illness may also include maculopapular rash, fever, myalgia and lymphadenopathy
Herpes simplex virus (HSV-1 and HSV-2)[c,d]	Both the viruses cause sporadic infections. HSV-1 is more associated with encephalitis, and HSV-2 with meningitis	Mortality of 70% in encephalitis if untreated. Typically a focal encephalitis (affecting temporal lobes). Many HSV-2 cases not associated with genital herpes. May cause recurrent meningitis (Mollaret's meningitis)
Cytomegalovirus (CMV)[c,d]	Mostly occurs in immunocompromised patients	Usually a focal encephalitis. May present with a mononucleosis-like illness. CMV retinitis may accompany this infection
Varicella-zoster virus (VZV)[c,d]	A rare complication of chickenpox or shingles (more commonly in the immunocompromised)	Occasionally meningitis seen without vesicles (zoster sine herpete). May present with stroke following zoster in elderly or with more diffuse chronic encephalitis in the immunocompromised

[a]Includes polio, echoviruses and coxsackieviruses.

[b]Other arboviruses causing meningitis include dengue, St. Louis, Murray Valley, eastern, western and Venezuelan equine encephalomyelitis and California encephalitis.

[c]More frequently cause meningoencephalitis.

[d]Other herpesviruses that cause meningitis are Epstein–Barr virus and human herpesvirus 6 (HHV-6).

Mumps

Mumps meningitis is one of the commonest causes of viral meningitis in populations not immunized against this virus, estimated to occur in between 10 and 30% of those infected. Males are 2–5 times more likely than females to develop this infection, and children are most commonly affected, although a recent resurgence in cases in the UK has largely affected late teenagers and young adults who did not receive a full

course of measles–mumps–rubella (MMR) or mumps vaccine. Meningitis is a more common manifestation than mumps encephalitis, typically associated with fever and vomiting; however, parotid or other salivary gland enlargement is only evident in around half of all cases. Very few of those affected develop complications such as encephalitis, neuropathies, myelitis or Guillain–Barré syndrome, and mortality is rare. Aseptic meningitis is also a rare consequence of mumps or MMR vaccination.

HIV

HIV meningitis is principally a seroconversion phenomenon, occurring in up to 10% of all symptomatic seroconversion illnesses. It is characteristically associated with a mononucleosis-like syndrome, with fever, lymphadenopathy, sore throat or a rash. A small proportion of cases progress to a chronic meningitis, sometimes complicated by cranial neuropathies or other focal signs. HIV counselling and testing should be performed on anyone presenting with aseptic meningitis, where risk factors of HIV infection are evident or an alternative pathogen is not identified. Patients with opportunistic viruses causing meningitis, such as CMV, should also be routinely tested unless another cause of immunosuppression is evident. HIV encephalopathy [or acquired immune deficiency syndrome (AIDS)–dementia complex] results from chronic HIV infection of the CNS and is more common in advanced disease, although now rarer since the advent of highly active antiretroviral therapy (HAART).

Other viruses

A wide variety of other viruses are capable of causing meningitis; however, they are less commonly identified. Measles may occasionally cause meningitis; however, a post-vaccination (to single vaccine or MMR) aseptic meningitis is more common in countries with high levels of vaccine coverage. Lymphocytic choriomeningitis virus (LCMV) is normally acquired from house mice, although occasionally has been linked to pet hamsters, possibly via an airborne route. Its peak incidence is in the autumn months. Meningitis normally follows a non-specific prodromal illness, and in addition, patients may also report symptoms of pharyngitis and myalgia. Later complications include arthritis, pericarditis or alopecia. Congenital LCMV is an underdiagnosed cause of foetal abnormalities. An aseptic meningitis may complicate adenovirus, influenza and parainfluenza viral infections, and influenza vaccination has been associated with an acute aseptic meningitis. Although many other viruses are known to cause an acute meningoencephalitis, including

rhabdoviruses (rabies), parvovirus B19, Nipah and Hendra viruses (*Morbillivirus*), bunyaviruses and togaviruses, meningitis due to these infections is very rare, especially in Europe.

Diagnosis

The most useful investigations to establish the cause of viral meningitis require CSF [20]; however, many other tests are sometimes useful (Table 2). Microscopy of CSF not only establishes the diagnosis of meningitis, but also allows a differential white cell count, and a Gram stain (and other stains for pathogens) will often establish a bacterial or fungal cause. CSF cytology will also exclude a neoplastic meningitis. The possibility of a viral aetiology of meningitis usually arises once bacterial stains (and later cultures) of CSF are negative; however, it is important to consider other causes of aseptic meningitis. These include fungal or mycobacterial [particularly in the immunocompromised and in those from communities with a high incidence of tuberculosis (TB)] and non-infectious aetiologies. A lymphocyte pleocytosis is often cited as a hallmark of viral meningitis, although a preponderance of polymorphs is sometimes seen early in the infection, particularly in enteroviral meningitis [2, 21]. CSF white cell counts in viral meningitis are typically in the 20–500 cells ml^{-1} range; however, they may occasionally reach the 1000 cells ml^{-1} level.

Isolation of viruses (on tissue culture) from CSF, blood or urine is the gold standard for diagnosing many viral pathogens causing meningitis; however, the procedure is slow, expensive and not always sensitive. The most valuable development in recent years has been the establishment of CSF polymerase chain reaction (PCR) as a rapid, sensitive and specific method of diagnosis [22]. Many reference laboratories now offer a CSF PCR service covering enteroviruses and HSV, with the option of also testing for CMV, VZV or EBV. Reverse transcriptase PCR (RT–PCR) assays for enteroviruses have been shown to be more sensitive (and rapid) than cultures of CSF [23] and PCR assays for herpesviruses have proved equally effective at improving the accuracy and speed of diagnosis [24]. Many developments in PCR technology have improved specificity and the time taken to perform assays, including multiplex nested PCRs, real-time PCR and time-resolved fluorometric PCR [25–27]. Rapid diagnosis by CSF RT–PCR assays has allowed reductions in both hospital stays and antibiotic usage in patients admitted with enteroviral meningitis [2, 21, 28] and limited the use of acyclovir in patients with suspected HSV encephalitis. There is therefore a strong case for regional reference laboratories providing a rapid CSF PCR service (within 48 h of receipt) to reduce drug costs and inpatient stays. Although PCR assays for a variety of

other viruses in CSF samples have been developed, they have yet to become established as their main diagnostic modality.

When obtaining CSF is difficult, culture of throat and stool samples is helpful in diagnosing enteroviral infections; however, the correlation between positive cultures and proven enteroviral meningitis is not well established. Nevertheless, one study indicated that RT–PCR of stool samples may be useful (in addition to CSF samples) in enteroviral meningitis when patients present later [29]. Immunoassays on serum (±CSF samples) are currently the main method for diagnosing several virus causing meningitis. Serological assays are the most widely used method for diagnosing meningitis due to mumps, flaviviruses (and other arboviruses), HIV and LCMV. These tests may be negative during the early stages of infection, so they require a second convalescent sample to be sent 2 weeks later. Although measuring CSF as well as serum antibody titre is often undertaken, the practical value in diagnosing viral meningitis is limited. In practice, where viral PCR results are negative in aseptic meningitis, serological tests for a variety of other pathogens are requested, depending on clinical features and exposure history. When acute HIV infection is suspected, a negative serological test should prompt alternative investigations (such as p24 assay, HIV PCR or viral load) in those with strong risk factors for HIV infection or with other features of an HIV seroconversion illness; alternatively, a repeat HIV test should be arranged several weeks later.

There has been considerable interest in the utility of blood inflammatory markers in distinguishing viral from bacterial meningitis. Many studies have suggested that a C-reactive protein (CRP) on presentation of less than 50 mg l^{-1} is predictive of viral meningitis [2, 30]; however, a meta-analysis showed that CRP was not so useful apart from very low levels indicating a high negative predictive value [31]. Serum procalcitonin levels appear more promising in this respect [32, 33]. Neuroimaging, either by computerized tomography (CT) or by magnetic resonance imaging (MRI) scans with contrast enhancement, may be useful in determining the aetiology of encephalitis, particularly for herpesviruses and flaviviruses. MRI scans are more sensitive at detecting demyelination and more subtle parenchymal changes associated with encephalitis [34]. Flaviviral encephalitis is typically manifest by increased enhancement in the basal ganglia and brainstem, whereas in HSV encephalitis, changes are usually seen in the temporal lobes. An electroencephalogram (EEG) may also help in distinguishing viral encephalitides from one another [35] or other encephalopathies. Some distinctive abnormalities on EEGs are illustrated in Table 2.

It is important to consider the differential diagnosis of aseptic meningitis, in terms of both non-viral infections and non-infectious causes of meningitis, when considering investigations. The most significant non-viral pathogens causing aseptic meningitis are mycobacteria, spirochetes (syphilis, *Borrelia* spp. and *Leptospira* spp.), rickettsiae, protozoa and helminths.

Table 2 Useful investigations in suspected viral meningitis

Investigation	Typical abnormality/utility	Comments
CSF microscopy	Raised white cell count: 10–1000 (typically <200 and mostly lymphocytes). Absence of organisms on Gram and other stains	Neutrophils may predominate early in infection
CSF protein and glucose	Protein raised (typically 0.5–1 g l^{-1}); CSF : plasma glucose ratio normally >0.5	CMV meningoencephalitis has occasionally been associated with low CSF glucose
CSF (or blood) viral culture	Cytopathic effect observed on cell culture. Definitive method of diagnosis for most types of viral meningitis, including most enteroviruses and mumps	Limited availability and takes 4–10 days
CSF (or blood) PCR	Detection of viral RNA or DNA	Has become the standard diagnostic tool for enteroviral and herpesvirus (HSV, CMV, VZV and EBV) meningoencephalitis; meningococcal PCR may establish this diagnosis where CSF not obtainable or in partially treated meningitis
Serum (or CSF) immunoassays	Mainstay of diagnosis for flaviviruses (WNV and JBE) and HIV. Also useful for mumps and lymphocytic choriomeningitis virus	Necessary to exclude alternative aetiologies of aseptic meningitis (e.g. syphilis, Lyme's, leptospirosis) or partially treated bacterial meningitis (meningococcal)
CT or MRI head scan with contrast enhancement	Meningeal or other focal areas of enhancement may be seen, typically the limbic system for HSV and brainstem and basal ganglia for flaviviruses	Only necessary if there are clinical features of encephalitis or if indicated before lumbar puncture. MRI is more sensitive at detecting demyelination or oedema associated with encephalitis
EEG	Useful for evaluating meningoencephalitis, especially where non-infectious aetiologies are suspected	A variety of EEG abnormalities are seen in encephalitis, some specific for HSV (e.g. high-voltage sharp and slow complexes) or WNV (periodic lateralized epileptiform discharges)

CMV, cytomegalovirus; CSF, cerebrospinal fluid; CT, computerized tomography; EBV, Epstein–Barr virus; EEG, electroencephalogram; HSV, herpes simplex virus; JBE, Japanese B encephalitis; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; VZV, varicella-zoster virus; WNV, West Nile virus.

Furthermore, partially treated bacterial meningitis or, occasionally, a brain abscess may present as apparent aseptic meningitis, and some bacteria such as *Listeria monocytogenes* and *Nocardia* spp. are often not easily identified on CSF stains and cultures. Post-vaccination aseptic meningitis or encephalitis is a recognized, if rare complication of immunization with mumps, measles, pertussis, rabies, vaccinia and influenza vaccines. Significant non-infectious causes of aseptic meningitis are intracranial neoplasms, connective-tissue diseases and vasculitis [including systemic lupus erythematosus (SLE)], drugs [including non-steroidal anti-inflammatory drug (NSAID) and some antimicrobial agents], sarcoidosis and Behçet's disease.

Therapies for viral meningitis

Acyclovir, given intravenously (10 mg kg^{-1} 8 hourly), is the most important antiviral therapy available for the treatment of HSV (or VZV)

meningoencephalitis, reducing the mortality of HSV encephalitis to 20% [36, 37]. It should be used empirically in any patient with clinical signs of encephalitis or with other features of HSV infection such as cold sores or genital lesions, whilst awaiting CSF PCR results or until an alternative pathogen is identified. In established cases of HSV or VZV encephalitis, it should be continued for 2–3 weeks. Intravenous ganciclovir is the preferred antiviral therapy for CMV meningoencephalitis (5 mg kg^{-1} 12 hourly for 2 weeks), although the oral prodrug valganciclovir, which achieves similar blood levels to intravenous ganciclovir, is a useful alternative. Other, second-line anti-herpesvirus drugs are foscarnet and cidofovir. These as well as ganciclovir are associated with significant renal toxicity, and close monitoring is mandatory.

There are currently no licensed therapies for enteroviral infection; however, pleconaril, a drug with anti-picornavirus activity, was recently evaluated both in patients with primary immunodeficiency (through a compassionate release programme) and in several clinical trials in enteroviral infections in adults and children, including meningitis in infants [38]. Although this drug appeared to be effective in many patients with primary immunodeficiency [39], the results of the trials did not support an unequivocal benefit and there have been some concerns regarding drug interactions. Licensing by the Food and Drug Administration (FDA) was therefore refused, and the drug is no longer available. In patients with enterovirus-associated CEMA, many would advocate a high-dose immunoglobulin therapy, particularly for complications outside the CNS. In patients with meningitis, in the context of an established HIV seroconversion illness or a chronic HIV meningoencephalitis, the use of HAART is reasonable for symptomatic control, although there is little experience of its use in aseptic meningitis specifically.

There are no licensed therapies for flaviviral infections, although recent interest in therapies for West Nile virus has included specific antiserum and interferon-α-2b [40], following case reports of possible improvement; trials of the latter are currently underway. Amantadine has been used for influenza meningoencephalitis, although there are few reports on its efficacy. The neuraminidase inhibitors may also be effective in this infection, although there are no published reports of its use in encephalitis. There are very few other antiviral agents in development; however, synthetic nucleic acid inhibitors appear promising in many animal models of viral infection.

Prevention

Active immunizations to prevent viral meningitis are available for mumps and measles (MMR), Japanese B encephalitis, tick-borne encephalitis,

rabies, influenza, varicella and polio; the only polio vaccine available in the UK now is the inactivated polio vaccine, combined with diphtheria and tetanus. Given the rate of severe adverse reactions to Japanese B encephalitis vaccine (severe allergic reactions in 4-8 per 100 000 and encephalitis in 1 in 2.5 million, vaccination is usually limited to long-stay residents in endemic regions and to those travellers at a high risk of infection. Those travelling to areas of the world with a high incidence of flaviviral infections should be advised to take stringent precautions to prevent mosquito and tick bites, particularly using impregnated bed nets and insect repellents.

Immunoglobulin therapy prevents enteroviral meningitis in patients with primary immunodeficiency; however, intramuscular delivery is not as effective as intravenous therapy in preventing infections. Human immunoglobulin preparations are also available for post-exposure prophylaxis for rabies and tick-borne encephalitis. To prevent congenital LCMV infection, pregnant women should avoid potential contact with rodents.

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