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# Meningitis, Viral

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## Introduction

The concept that agents other than bacteria can invade the central nervous system (CNS) began with the emergence of poliomyelitis as an epidemic infection and, subsequently, with the realization that similar meningeal inflammation and cerebrospinal fluid (CSF) pleocytosis occurred in as many as 60% of patients with mumps parotitis. That meningitis could be caused by other 'filterable agents' (i.e., viruses) was demonstrated by Rivers and Scot, who in 1935 recovered lymphocytic choriomeningitis virus (LCMV) from the CSF of an affected patient. It is now known that a wide and constantly changing variety of viruses may invade the CNS to produce meningitis or encephalitis.

Viral meningitis is important in three respects. First, viral meningitis must be differentiated from the much more dangerous condition, bacterial meningitis: Until this is accomplished, patients presenting with signs and symptoms of meningitis must be considered medical emergencies, and antibiotic treatment for presumptive bacterial meningitis must be instituted. Second, viral meningitis, although rarely fatal, may produce clinical impairment that can persist for weeks to months, especially in the immunosuppressed patient. Finally, 'lymphocytic' or 'aseptic' meningitis may be caused by agents other than viruses, and the possibility of other, more readily treated (and sometimes more dangerous) conditions must be kept in mind when diagnosing a patient with presumed viral meningitis.

## Pathogenesis

Before meningitis can occur, the causative agent must first penetrate the body from the external environment and then gain entry to the CNS across the blood–brain barrier (BBB). Entry of the virus into the host may occur by gastrointestinal inoculation (as is the case with the enteroviruses), cutaneous inoculation (as occurs with the arthropod-borne agents), the respiratory route (as is the case with mumps), or transmucosal penetration or intravenous inoculation (as occurs with human immunodeficiency virus (HIV)). Early workers in the field of viral CNS infections believed that invasion of the nervous system occurred by the spread of viruses along neurons, as is the case with rabies virus. Currently, however, it is known that the majority of viral meningitis results from hematogenous dissemination of virus following symptomatic or clinically inapparent systemic infection. Penetration across the BBB may occur at the choroid plexus or through meningeal capillaries. Exceptions to this include meningitis following genital herpes simplex infection, meningitis associated with herpes zoster, and Mollaret's meningitis, in which reactivated infection of herpes simplex virus type 2 (HSV-2) within the dorsal root

ganglia leads to repeated episodes of meningitis. Viral replication in the meninges, superficial brain or spinal cord parenchyma, and the ventricular system elicits an inflammatory response, which is predominantly lymphocytic. This results in an alteration of the BBB so that protein levels increase within the CSF. Unlike bacteria or fungi, however, viral replication does not lower glucose within the CSF, nor does it usually result in altered transport of glucose across the BBB. Thus, in contrast to bacterial, mycobacterial, or fungal infections, CSF glucose concentrations during viral meningitis are usually normal.

## Epidemiology

Meningitis is the most common phenotype of a neuroviral infection, and it is a far more common condition than bacterial or fungal meningitis. Approximately 75 000 cases of lymphocytic or presumed viral meningitis occur each year in the United States although numbers are difficult to ascertain because it is not a reportable illness. CSF pleocytosis has also been reported in individuals infected with measles, mumps, and HIV without signs and symptoms of meningeal irritation. Similar asymptomatic CNS involvement probably occurs with other viruses as well. Although viral meningitis affects all age groups, it is predominantly a disease of childhood.

The agents causing viral meningitis can be divided into three broad groups: (1) common agents of viral meningitis, including the enteroviruses, arthropod-borne agents, and HSV-2; (2) less common agents, including HIV, mumps, LCMV, human herpesvirus 6 (HHV-6), and parvovirus B19; and (3) agents known to cause lymphocytic meningitis only in rare cases. Outside the United States, new viruses like Toscana virus and Chikungunya virus are emerging causes of viral meningitis. In addition, a number of nonviral, and occasionally noninfectious, conditions may cause a clinical syndrome indistinguishable from viral meningitis.

## Major Agents Causing Viral Meningitis

### Enteroviruses

Enteroviruses account for approximately 90% of cases in which the causative virus is identified (Table 1). Enteroviruses are small, nonenveloped single-stranded positive-sense ribonucleic acid (RNA) viruses within the family Picornaviridae. Although more than 70 serotypes of enteroviruses have been identified, coxsackievirus A9 and echoviruses E7, E9, E11, E19, and E30 account for 70% of all cultured isolates of CSF. Poliovirus, although no longer found in developed countries due to mass vaccination efforts, still causes aseptic meningitis and paralytic disease in countries like Pakistan, Afghanistan, and Nigeria where cultural taboos, lack of development, and

war have stymied vaccination efforts. Enteroviruses are disseminated by fecal–oral spread, and cases in developed countries cluster during summer months when sanitation tends to be most relaxed. Recent studies employing polymerase chain reaction (PCR) methods, however, confirm older observations that enteroviral CNS infections occur throughout the year, and many previously undiagnosed cases of viral meningitis occurring during winter months are also caused by these viruses. Coxsackieviruses, echoviruses, and enteroviruses may cause encephalitis and, rarely, paralytic disease, especially in neonates and the immunosuppressed. This was vividly illustrated in 2012 with the enterovirus 71 outbreak in Cambodia that killed more than 60 children.

### Arthropod-borne agents

Arthropod-borne viruses, or arboviruses, include agents from several different families whose hosts are typically small mammals or birds. They spread to humans through the bite of an arthropod vector (Table 2). Although these agents are most commonly considered to cause encephalitis, all of them, with the exception of eastern equine encephalitis, more frequently cause meningitis. The most common domestic arthropod-borne agents associated with viral meningitis include St. Louis encephalitis virus, the California/LaCrosse group of viruses, Colorado tick fever, and West Nile virus, which caused an explosive outbreak when it first arrived in the United States in 1999 and more recently in 2012. These agents, like enteroviruses,

have a peak incidence in summer and early fall. The exception to this rule is Colorado tick fever, which is more frequently transmitted in the spring and early summer.

### Herpesviruses

Herpesviridae are enveloped, double-stranded DNA viruses. HSV-1 and HSV-2, varicella-zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), and HHV-6 all cause viral meningitis. Of these, however, only HSV-2 has been associated with a significant number of cases. Older data suggest that HSV-2 accounts for 2–3% of viral meningitis cases. Recent work employing PCR suggests that it may be the most common cause of viral meningitis in adult women. HSV-2 most often causes meningitis following primary genital infection. Occasional cases may also follow primary genital infection with HSV-1. Patients with recurrent (Mollaret's) meningitis often have recurrent infection due to HSV-2. CSF pleocytosis occurs during both chicken pox and herpes zoster with or without skin lesions; this pleocytosis is usually asymptomatic but may occasionally be associated with meningitic symptoms. HSV-2 is also the most common cause of nonepidemic viral encephalitis, commonly producing an asymmetric lesion in the anterior and medial temporal lobes. In the immunosuppressed and elderly, VZV can cause a multitude of other CNS syndromes including stroke due to vasculitis, herpes zoster ophthalmicus, myelitis, encephalitis, and cranial neuropathies. CMV can cause ventriculitis and radiculitis in patients with HIV. Lastly, HHV-6 is now appreciated to produce a bilateral medial temporal lobe encephalitis in bone marrow transplant patients.

**Table 1** Viruses causing meningitis

Major causes of viral meningitis	
Enteroviruses (coxsackie- and echoviruses)	
Arboviruses	
Herpes simplex virus type 2	
Human immunodeficiency virus	
Less common causes of viral meningitis	
Herpes simplex virus type 1	
Epstein-Barr virus	
Mumps virus (rare in Western countries; common in underdeveloped countries)	
Lymphocytic choriomeningitis virus	
Parvovirus B19	
Rare causes of viral meningitis	
Varicella-zoster virus (usually in the setting of cutaneous zoster)	
Influenza A and B viruses	
Parainfluenza viruses	
Rotaviruses	
JC virus	
Measles virus	
Coronaviruses	
Adenoviruses	

### HIV

HIV has been associated with both acute and persistent lymphocytic meningitis. Onset is most commonly at the time of seroconversion, and for the astute clinician, this represents an opportunity to make an early diagnosis of HIV during a period of time when the patient's viral load is very high, and thus, is at high risk for transmission. The course may be uniphasic, chronic, or, occasionally, recurrent. In recurrent cases that happen despite the patient achieving systemic virologic control with antiretroviral medications, the differential diagnosis should include the possibility of CNS HIV escape either due to a resistant strain of HIV having evolved in the CNS compartment or due to inadequate CNS penetration of antiretroviral medications. HIV RNA can be identified in CSF using reverse transcriptase–polymerase chain reaction (RT-PCR) methods, which also allow an assessment of viral burden and the resistance mutation profile. Although HIV itself typically causes a CSF pleocytosis of less than 20 cells/mm<sup>3</sup> with a

**Table 2** Arboviral agents associated with meningitis in the United States

Family	Genus	Virology	Agents	Vector	Seasonal incidence
Togaviridae	Alphaviruses	Single-stranded positive sense RNA	Western equine encephalitis	Mosquito	Summer, early autumn
	Flaviviruses	Single-stranded positive sense RNA	St. Louis encephalitis	Mosquito	Summer, early autumn
			West Nile virus	Mosquito	
Bunyaviridae	Bunyavirus	Single-stranded negative sense RNA	California/LaCrosse encephalitis virus	Mosquito	Summer, early autumn
Reoviridae	Orbivirus	Double-stranded RNA	Colorado tick fever	Tick	Spring, early summer

mild-to-moderate elevation in total protein. Cell numbers higher than this should raise early suspicion for a concomitant CNS infection like syphilis, *Cryptococcus*, VZV, HSV, or CMV.

### Less Frequent Causes of Viral Meningitis

#### Other herpesviruses

As discussed previously, HSV-1, HHV-6, VZV, CMV, and EBV occasionally cause meningitis.

#### Mumps virus

Mumps virus, like measles virus, is a paramyxovirus, containing a single-stranded negative-sense RNA genome. Before the advent of the mumps vaccine, mumps was the most common cause of viral meningitis, accounting for more than 15% of isolates. Currently, mumps virus meningitis is rare in developed countries. The virus is still a common cause of CNS infection in underdeveloped countries and countries like Japan in which vaccination programs have been suspended due to vaccine-induced cases of lymphocytic meningitis. In these countries, mumps virus is an important cause of sensorineural deafness. In experimental animals infected *in utero*, mumps can cause aqueductal stenosis, and there are approximately 60 human cases of this in the literature.

#### Lymphocytic choriomeningitis virus

LCMV is an arenavirus containing a single-stranded ambisense RNA genome. Wild and laboratory mice are the natural hosts, and there is recent evidence that snakes harbor these viruses as well. LCMV is associated with human cases of meningoencephalitis as a consequence of exposure to laboratory or wild mice, and in rare epidemics it is associated with pet hamsters. Cases are more common in impoverished areas with poor hygiene. Important outbreaks of fatal LCMV meningoencephalitis have also occurred in clusters of solid organ transplant patients infected by organs from asymptomatic donors. LCMV meningitis typically occurs during autumn and early winter, and it has been suggested that this reflects more extensive mouse–human contact as mice move inside to escape winter weather. In studies before 1960, the virus was thought to account for 9–11% of cases of viral meningitis. In recent years, reports of meningitis due to LCMV have been rare. However, congenital LCMV infection is a significant, often unrecognized cause of chorioretinitis, hydrocephalus, microcephaly or macrocephaly, and mental retardation. Acquired LCMV infection likewise may be an underappreciated illness. The meningitis caused by LCMV may be extremely persistent and has been associated with symptoms and CSF abnormalities lasting for months. Acquired LCMV infection may also be associated with encephalitis, transverse myelitis, a Guillain-Barré-type syndrome, and both transient and permanent hydrocephalus.

#### Parvovirus B19

Parvovirus B19 most commonly causes an acute febrile illness, accompanied by erythema infectiosum. The virus can also produce meningitis and meningoencephalitis in both immunocompetent and immunocompromised patients. The combination of rash and signs of meningeal irritation may mimic acute meningococcal infection. Other items to always

consider in the differential of rash and meningitis include West Nile virus, syphilis, rickettsial infection (i.e., Rocky Mountain spotted fever), enteroviruses, Lyme disease, human granulocytic anaplasmosis, and human monocytic ehrlichiosis, many of which are treatable. CSF findings are typical of viral infection. Occasionally, CSF may be normal.

### Rare Causes of Viral Meningitis

Rare causes of viral meningitis include influenza A and B viruses, parainfluenza viruses, rotaviruses, coronaviruses, measles virus, and adenoviruses. Lastly, although JC virus is typically associated with progressive multifocal leukoencephalopathy, it can also cause viral meningitis, especially in the immunosuppressed.

### Clinical Symptoms and Signs

Onset of viral meningitis may occur following a symptomatic, systemic illness, or as an isolated event following inapparent systemic infection. Patients can present with fever (85%), headache (50%), photophobia, neck stiffness (70%) and/or back pain. Significant alteration of consciousness is far less common than in bacterial meningitis. Immunocompromised patients may have even more subtle exam findings and histories, and there should be a low threshold for further investigation with lumbar puncture in these cases. Seizures or focal neurological signs are unusual although cranial neuropathies are seen with certain viruses like VZV, HSV, West Nile virus, and HIV. Focal signs should raise concerns about a concomitant viral encephalitis or a focus of infection, such as a brain abscess. Patients are usually uncomfortable but do not appear severely ill. Physical examination may reveal evidence of systemic illness, including rash, lymphadenopathy, pharyngitis, or splenomegaly, depending on the infectious agent. Neurological examination commonly reveals nuchal rigidity with the patient unable to touch chin to chest. Resistance to passive neck flexion and Kernig's and/or Brudzinski's signs may be present but are inconsistent. Both signs may be absent in milder cases. A useful test of nuchal rigidity is to ask the patient to touch forehead to knee; this will often be positive when all other tests of meningeal irritation are questionable or absent. Papilledema is rare. Routine blood studies may reveal a lymphocytic leukocytosis. Liver function tests may be elevated if there is hepatic involvement.

### Laboratory Diagnosis of Viral Meningitis

The most important diagnostic test in viral meningitis is the lumbar puncture. This should be preceded by head magnetic resonance imaging (MRI) or, less optimally, computed tomography if focal signs are present, there is significant altered mental status, or if there is any suspicion of increased intracranial pressure. Spinal fluid will usually show mildly elevated opening pressure, lymphocytic pleocytosis, elevated protein, and normal glucose (Table 3). The cell count is usually less than 300 cells/mm<sup>3</sup>. Protein is usually in the range of

**Table 3** CSF findings in bacterial, viral, tuberculous, and fungal meningitis

	<i>Bacterial meningitis</i>	<i>Viral meningitis</i>	<i>Tuberculous meningitis</i>	<i>Fungal meningitis</i>
Protein	Elevated	Mildly elevated	Elevated	Elevated
Glucose	< 50% blood glucose	Normal <sup>a</sup>	< 50% blood glucose	< 50% blood glucose
Cells	Polys	Lymphs or lymphs + polys <sup>b</sup>	Lymphs + polys	Lymphs
Other	Gram stain, culture <sup>c</sup>	PCR (viral culture)	AFB stain culture (20 ml CSF) PCR	India ink prep cryptococcal Ag culture (20 ml CSF) PCR

<sup>a</sup>CSF glucose may occasionally be depressed in meningitis due to mumps, lymphocytic choriomeningitis virus, or herpes zoster.

<sup>b</sup>CSF during the first 24 h of viral meningitis may contain a mixture of lymphocytes and polymorphonuclear leukocytes. In these cases, in contrast to bacterial meningitis, CSF glucose is usually normal and follow-up lumbar puncture 24 h later will often but not always show lymphocytes only.

<sup>c</sup>Positive Gram stain requires approximately 10<sup>5</sup> colony-forming units (CFU)/ml of CSF. Approximately 25% of Gram stains will be positive if CSF contains 10<sup>3</sup> CFU/ml. Prior antibiotic treatment will reduce this amount by 20%.

Abbreviations: AFB, acid-fast bacillus; CSF, cerebrospinal fluid; PCR, polymerase chain reaction.

50–100 mg/dl. Exceptions exist to this CSF formula, however. Cell count may be as high as 1000 cells/mm<sup>3</sup>. During the first 24–48 h of infection, CSF may contain a mixture of polymorphonuclear leukocytes and lymphocytes with even a polymorphonuclear predominance early in infections with West Nile virus, HSV, and VZV. Glucose concentrations, although usually > 50% of blood values, may be significantly depressed. This has been reported with meningitis due to herpes zoster, mumps, and LCMV. Return of CSF parameters to normal may be extremely prolonged following viral meningitis, and isolated reports have described persistent CSF pleocytosis and elevated protein over periods of weeks to months.

Before the advent of PCR, diagnosis of viral meningitis was difficult and often an exercise in futility: viruses may take considerable time to grow in culture, and many viral agents cannot be readily grown from CSF. Viral serologies comparing acute and convalescent sera have been used for retrospective diagnosis, and serological diagnosis can be accelerated by comparing serum and CSF antibody titers to identify the synthesis of specific antiviral antibodies within the CNS; however, serological tests only rarely allow rapid enough diagnosis to direct therapy.

The advent of PCR methods has revolutionized the diagnosis of both meningitis and encephalitis. PCR for enteroviruses, HSV-1, HSV-2, VZV, and CMV are readily available in many laboratories, and PCR diagnosis of other agents is often available through larger commercial laboratories or the Centers for Disease Control. Although PCR is highly specific, it has limited sensitivity in certain circumstances. It is relatively insensitive in the first 3 days of infection with HSV as well as after day 10 of infection. The overall sensitivity of PCR for VZV is 60%; if VZV is suspected, immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies should always be sent from the CSF as well. In the case of HIV, RT-PCR methods are available not only for diagnosis but also for determining viral load and resistance mutations. Even with the use of PCR, the causative agents in many cases of viral meningitis remain undiagnosed.

### Other Causes of Lymphocytic Meningitis

Viral meningitis should be considered in the differential diagnosis of any patient presenting with headache, photophobia, and neck stiffness. However, the presence of

these findings also makes it mandatory to exclude bacterial infection. Although patients with viral meningitis are less severely ill, bacterial meningitis may also appear mild in its early stages. Conversely, patients with viral meningitis may deteriorate.

Many other infectious conditions can also cause lymphocytic meningitis. These include secondary syphilis, leptospirosis, brucellosis, infections by *Mycobacterium tuberculosis*, Lyme disease caused by *Borrelia burgdorferi*, infections due to Ehrlichiae or, rarely, other rickettsial agents, *Mycoplasma pneumoniae*, and fungi (particularly *Cryptococcus neoformans*, *Histoplasma*, *Blastomyces Coccidioides*, and *Candida*). Tuberculous and fungal meningitis are often, but not always, accompanied by a significant decrease in CSF glucose. Lyme meningitis may produce CSF findings identical to those seen in viral meningitis. However, erythema migrans, multiple cranial neuropathies and polyradiculopathies are common features of Lyme meningitis. Similarly, patients with Lyme meningitis tend to have fewer white blood cells (mean, 80 vs. 301/mm<sup>3</sup>) and a significantly greater percentage of mononuclear cells than patients with viral meningitis. Both *M. tuberculosis* and *M. pneumoniae* are difficult to culture but are readily detectable by PCR; PCR tests for Ehrlichiae are in limited use.

Noninfectious etiologies can also cause a lymphocytic or aseptic meningitis including side effects of a number of medications like nonsteroidal anti-inflammatory drugs, serum immunoglobulins, carbamazepine, lamotrigine, and trimethoprim sulfamethoxazole. Recurrent meningitis can occur in patients with periodic leakages from dermoid or epidermoid cysts abutting the meninges. In such patients, the diagnosis can be made by a detailed MRI examination of the brain and the spinal cord. Lastly, autoimmune disease can manifest as a lymphocytic meningitis, sometimes representing the initial presentation of systemic lupus erythematosus and sarcoidosis. It can also be seen associated with Sjögren's syndrome and rheumatoid arthritis, particularly in patients who take nonsteroidal anti-inflammatory drugs.

### Treatment

Most cases of viral meningitis are self-limited, and antiviral therapy is usually not indicated. Controlled studies of antiviral

agents in viral meningitis have not been reported in detail. Recent data from controlled studies presented in abstract form, however, suggest that virological and clinical improvements are better in patients with severe enteroviral meningoencephalitis treated with the antiviral agent pleconaril than with placebo. Similarly, depending on the severity of illness, consideration should be given to the therapy for HSV meningitis with acyclovir or similar agents. Use of antiviral agents in the treatment of viral meningitis is still essentially experimental and must be balanced against the severity of disease and complications of the therapy. An exception to this is HIV meningitis, in which diagnosis of HIV infection is in itself an indication for highly active antiretroviral therapy.

## Prognosis

Viral meningitis is almost always a self-limiting disease. Recovery may occur within days. However, symptomatic illness is not infrequently prolonged, and patients may require weeks or months to return to full health. Permanent neurological deficits or intellectual impairment are rare and, if present, should prompt a more thorough workup for nonviral etiologies of meningitis.

*See also:* Encephalitis, Viral. Herpesviruses, Human. Meningitis, Bacterial. Meningitis, Fungal

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