Acute Viral Meningitis

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Abstract

Acute infections of the nervous system are among the most important problems in medicine because early recognition, efficient decision-making, and rapid institution of therapy can be lifesaving.

Although acute viral meningitis has usually a benign course, it requires hospitalization in some patients. The development of the polymerase chain reaction (PCR) has allowed the detection of viral genomes, facilitated a rapid diagnosis, and enabled the use of antiviral treatment in selected cases. Common etiologies include enteroviruses, followed by arboviruses and herpesviruses. Clinical presentation is not specific and includes fever, headache, and variable evidence of meningeal irritation. Prognosis overall is favorable.

Keywords

Meningitis • Encephalitis • Aseptic meningitis • Cerebrospinal fluid • Central nervous system disease • Antiviral therapy

Meningitis is an inflammation of the meninges, the thin membranes (especially the leptomeninges, i.e., pia mater and arachnoid) that surround the brain and spinal cord, most often caused by a bacterial or viral infection. The subarachnoid space lying between both meningeal layers contains the cerebrospinal fluid (CSF) and is

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also affected by inflammation. Since the subarachnoid space surrounds the brain and spinal cord, meningitis is by definition cerebrospinal.

Acute meningitis is defined as a syndrome characterized by the onset of meningeal symptoms over a period of hours to several days. Among them, headache is a prominent early symptom, often followed by a state of abnormal consciousness or coma, usually accompanied by signs of meningeal irritation.

Encephalitis is distinguished from meningitis, on a clinical basis, by the presence of an early abnormal level of consciousness with minimal meningeal signs [1]. On a pathological basis, in encephalitis the inflammatory process predominantly affects the brain parenchyma. However, secondary meningeal affection is usually present, and hence the term meningoencephalitis is applied.

Definition

Viral meningitis is an infection of the meninges and subarachnoid space (the covering of the brain and spinal cord) caused by a virus. The term is used interchangeably with aseptic meningitis, which refers to meningitis with negative cultures and clear CSF. Aseptic meningitis, however, may also be caused by drugs and systemic disorders, among others.

Epidemiology

The exact incidence of viral meningitis is difficult to determine since most cases go unreported to public health authorities. The etiological panorama varies in different parts of the world as well as over time and must be adapted to the individual history of each patient, including recent travels [2]. In temperate climates, there is a substantial increase in cases during the summer and early autumn, reflecting the seasonal predominance of enteroviruses and arthropod-borne encephalitis virus (arboviruses) infections. In contrast, herpes simplex virus (HSV) and human immunodeficiency virus (HIV) have no seasonal predilection.

Clinical Manifestations

Viral meningitis presents with fever, headache, and signs of meningeal irritation and may be accompanied by malaise, myalgia, anorexia, nausea and vomiting, abdominal pain, and/or diarrhea. Mild lethargy and drowsiness are not uncommon. Headache associated with viral meningitis is usually frontal or retro-orbital and often associated with photophobia and pain on moving the eyes.

The presence of more profound alterations in consciousness, such as stupor, coma, or marked confusion, should prompt the consideration of alternative diagnoses. Similarly, seizures or other focal neurological signs or symptoms suggesting involvement of the brain parenchyma do not usually occur in uncomplicated viral meningitis.

Table 4.1 Viruses causing acute meningitis.

Common	Less common	Rare
Enteroviruses	HSV-1	Adenoviruses
Arboviruses	LCMV	CMV
HIV	VZV	EBV
HSV-2		Influenza A and B, parainfluenza, mumps, rubella

CMV cytomegalovirus, *EBV* Epstein-Barr virus, *HIV* human immunodeficiency virus, *HSV* herpes simplex virus, *LCMV* lymphocytic choriomeningitis virus, *VZV* varicella-zoster virus

Nuchal rigidity (or neck stiffness) is present in most cases but may be mild and present only near the limit of the neck anteflexion. Other meningeal signs such as Kernig's and Brudzinski's signs are generally absent [3].

Etiology

The development of modern molecular techniques has greatly improved the diagnostic yield and is now widely applied to CSF samples [2, 4].

Using a variety of diagnostic techniques including CSF real-time polymerase chain reaction (PCR) tests, culture, and serology, a specific viral etiology can be found in 75–90% of cases of viral meningitis [3]. Enteroviruses account for 85–90% of aseptic meningitis cases in most series (see Table 4.1) [4].

Diagnosis

Cerebrospinal Fluid Examination

The most important laboratory test in the diagnosis of viral meningitis is examination of the CSF. The typical CSF profile shows a lymphocytic pleocytosis (25–500 cells/mm^3), although neutrophils may predominate in the first 48 h of illness (they shift to lymphocytes in 24–48 h); mildly increased CSF proteins and normal or mildly decreased CSF glucose concentrations can also be found. Viral organisms are not seen on Gram's or acid-fast stain smears or India ink preparations (see Table 4.2).

Amplification of viral-specific DNA or RNA using real-time PCR has become the single most important method for diagnosing central nervous system viral infections. It allows a rapid and accurate diagnosis for enterovirus, herpes simplex virus (HSV), varicella-zoster virus (VZV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV) infections and assists in clinical decision-making, particularly regarding the potential use of antiviral therapy [5].

The overall results of viral CSF cultures for the diagnosis of viral infection are disappointing, presumably because of the generally low concentration of infectious virus present and the need to customize isolation procedures for individual viruses

Table 4.2 Cerebrospinal fluid (CSF) cyto-biochemical parameters associated with acute meningitis

	Normal CSF	Viral meningitis	Bacterial meningitis
White cells	<10/μl	100–500/μl	>1000/μl
Neutrophils	–	<50%	>50%
Protein (mg/dl)	<30–40	<100	>100
Glucose (mg/dl)	>50	>50	<40
Gram's stain	Negative	Negative	Positive (60%)

[3]. A delay in transporting or processing the sample further decreases the minimum number of viable viruses necessary to replicate in cell lines. However, the combination of both methods (PCR amplification and culture) remains useful [6].

Other Sources for Viral Isolation

Viruses may also be isolated from sites and body fluids other than the CSF, including the throat, stool, blood, and urine. Enteroviruses and adenoviruses may be found in feces; arboviruses, some enteroviruses, and lymphocytic choriomeningitis viruses (LCMVs) in blood; mumps and CMV in urine; and enteroviruses, mumps, and adenoviruses in throat washings. Nevertheless, the presence of enteroviruses in stool is not diagnostic and may result from residual shedding from a previous enteroviral infection [3].

Serologic Studies

Serology is the method of reference for meningitis caused by West Nile virus and LCMV, which are quite uncommon. Serum serologic studies are less useful for other viruses such as HSV, VZV, CMV, and EBV, for which the prevalence of antibody seropositivity among the general population is high. The demonstration of specific serum IgM to VZV, IgG seroconversion between serum of acute disease and the convalescent phase, or intrathecal production of specific antibodies can be useful for VZV meningitis (see Table 4.3) [6, 7].

Brain CT

Upon presentation, patients who are immunocompromised and have a prior history of central nervous system disease, papilledema, or focal neurological deficits should have a brain CT performed prior to lumbar puncture. However, the need for a brain CT should not mean delaying specific antimicrobial therapy if deemed necessary. This is especially important when bacterial etiologies are considered. The same is applicable in presumed cases of HSV encephalitis.

Table 4.3 Performance of the main methods for microbiological diagnosis of viral meningitis [6]

	CSF			Other sources		
Microorganisms	PCR	Culture	Serology	PCR	Culture	Serology
Enteroviruses	+++	++	–	+++ (throat, feces)	+++ (throat, feces)	+
Herpesviridae						
HSV	+++	–	+	–	–	–
VZV	+++	+/–	++	++ (vesicle)	++ (vesicle)	++
Mumps	+++	++	++	++ (urine, saliva)	++ (urine, saliva)	++
Arbovirus						
TOSV	+++	++	+	–	–	+++
WNV	++	+	++	++ (serum)	–	+++
LCMV	++	++	++	–	–	+++

CSF, cerebrospinal fluid; *PCR*, polymerase chain reaction; *HSV*, herpes simplex virus; *VZV*, varicella-zoster virus; *TOSV*, Toscana virus; *WNV*, West Nile virus; *LCMV*, lymphocytic choriomeningitis virus.
+++, high performance; ++, moderate; +, low; –, not recommended.

Differential Diagnosis

The most important issue in the differential diagnosis is the exclusion of nonviral causes that may mimic viral meningitis. The major categories of disease that should always be considered are [2, 5]:

- Bacterial meningitis and other infectious meningitides (*Listeria monocytogenes*, *Mycobacterium tuberculosis*, *Treponema pallidum*, *Brucella*, *Cryptococcus*, *Coxiella*, and *Rickettsia*). However, in these cases, presentation is not acute, there are predisposing factors, or meningitis represents a complication of a preexisting infection.
- Parameningeal infections or partially treated bacterial meningitis.
- Carcinomatous meningitis.
- Meningitis secondary to noninfectious, inflammatory diseases such as sarcoidosis, Behçet's disease, and the uveomeningitic syndrome.
- Vascular and metabolic diseases.
- Some medications or drug toxicity (i.e., NSAIDs).

Specific Viral Etiologies

Enteroviruses

They are the most common cause of viral meningitis (accounting for more than 85% of all cases). They belong to one of the three types of the viral family *Picornaviridae* that cause disease in humans. Nearly 70 serotypes exist, and they are divided into three subgroups: echoviruses, coxsackieviruses A and B, and polioviruses [8].

They are highly contagious and most often spread from person to person through fecal contamination but may also be spread through respiratory secretions (saliva, sputum, or nasal mucus) of an infected person. Waterborne infection has also been documented [2]. Cases appear most often during the summer and autumn in temperate climates. However, sporadic cases are seen all year-round.

Patients typically present with an acute onset of fever, chills, headache, photophobia, and pain on eye movement. Nausea and vomiting are also common. Other clues to the presence of enteroviral disease include the presence of exanthemas, myopericarditis, conjunctivitis, pleurodynia, herpangina, and hand-foot-and-mouth disease [1, 3, 9].

Molecular diagnostics using PCR for detection of enteroviruses RNA is the method of choice for central nervous system (CNS) infections.

Herpes Simplex Virus (HSV)

Two distinct epidemiologic and antigenic types of HSV exist: HSV type 1 and HSV type. 2. HSV has worldwide distribution, and direct contact with infected secretions is the principal mode of spread.

In some series, HSV-2 has been the most important cause of aseptic meningitis in adults, especially women, and overall, it is probably second only to enteroviruses as a cause of viral meningitis.

HSV-1 usually establishes latency in the trigeminal ganglion, and CNS infection typically results in an encephalitic illness, whereas HSV-2 establishes latency in the sacral sensory ganglia and typically causes meningitis [5]. Neurological disease after primary HSV-2 is seen most often in neonates.

Meningitis (usually by HSV-2) is usually characterized by a stiff neck and an acute onset of headache, fever, and photophobia; about 50% of patients have transient neurological manifestations including seizures, hallucinations, diplopia, cranial nerve palsies, or altered consciousness. Sometimes it is associated with urinary retention, constipation, dysesthesia radiating pain, or weakness in the lumbosacral area and lower limbs, indicating sacral myeloradiculitis [2].

Meningitis appears in 36% of women and 13% of men at the time of an initial (primary) episode of genital herpes [1]. Herpetic mucocutaneous lesions may precede the meningitis by about 2–14 days, but sometimes it can appear after the onset of meningitis, and the two manifestations may occur independently. However, more than 50% of patients with HSV do not report any herpetic blisters [2].

Of these patients, 20% will develop a few or up to ten episodes of meningitis lasting 2–5 days followed by spontaneous recovery [10]. Almost all cases of recurrent HSV meningitis are due to HSV-2. Genital lesions may not be present, and most patients report no history of genital herpes.

Although HSV can be cultured from CSF during a first episode of meningitis, cultures are invariably negative during recurrences [11]. The diagnosis is verified in the acute stage by detection of HSV-1 or HSV-2 DNA in the CSF by

PCR. False-negative results appear very early, 1–3 days from the onset of neurological symptoms [2].

Varicella-Zoster Virus (VZV)

Primary VZV infection, chicken pox (varicella), usually occurs during childhood as a mild-to-moderate disease. Latent VZV infection may occur in the cranial nerve ganglia, any dorsal root ganglia, and autonomic ganglia along the entire neuraxis. Years later, usually in association with a decline in cell-mediated immunity in elderly and immunocompromised individuals, VZV reactivates and causes a wide range of neurological disease; in fact, in recent years, VZV has been implicated with increasing frequency as a meningitis-producing agent and especially meningoencephalitis with or without rash [12].

The sensitivity and specificity of PCR in the CFS have not been studied systematically, but a high viral load is usually seen in meningitis [2]. Serological analyses have been hampered by cross-reactivity between HSV and VZV.

Epstein-Barr Virus (*EBV*), *Cytomegalovirus* (*CMV*), *and Human Herpesvirus 6* (HHV-6)

EBV, CMV, and HHV-6 are all members of the HHV family and therefore share some characteristics. Primary infection often occurs early in life and is usually asymptomatic, but all of these viruses can cause aseptic meningitis, particularly in immunocompromised hosts but also in immunocompetent adults [2]. EBV and CMV are almost never cultured from CSF, but DNA can be amplified in some patients [13]. Finding DNA from CMV in CSF is strongly indicative of CMV-related disease. However, EBV- and HHV-6-positive DNA findings must be interpreted with caution [2].

Human Immunodeficiency Virus (HIV)

It has been estimated that HIV infection is the cause of 5% of cases of aseptic meningitis. Aseptic meningitis may occur as part of the primary exposure to HIV (in up to 24% of cases during or after the mononucleosis-like syndrome) or may be detected in an already infected patient (more commonly in patients with 200–500 CD4/mm^3 than in earlier stages) and can assume the form of chronic meningitis [14–16].

HIV meningoencephalitis may be the presenting form of HIV primary infection in around 8% of patients. Cranial nerve palsies, most commonly involving cranial nerves V, VII, or VIII, are more common in HIV meningitis than in other viral infections.

This syndrome usually resolves spontaneously within 2–4 weeks. The diagnosis of HIV meningoencephalitis is an accepted indication for starting antiretroviral therapy during primary HIV infection.

Mumps

Parotiditis (mumps) is asymptomatic in nearly 30% of children. Mumps meningitis has been reported in 1–10% of persons with mumps and usually follows the onset of parotiditis, when present, by about 5 days. The most frequent clinical presentation is the triad of fever, vomiting, and severe headache, but only half of patients will have the salivary glands enlarged [2]. Most patients have signs of meningitis but no evidence of cortical dysfunction. Mumps meningitis is usually self-limited, although cranial nerve palsies have occasionally led to permanent sequelae, particularly deafness [1, 17]. Hydrocephalus is frequent, particularly in children, and CSF analysis shows lymphocytic pleocytosis and increased proteins; in one-fourth of patients, glucose levels are decreased [18].

Recently, concern has been raised about vaccine failure and infection resurgence, with important outbreaks in the UK in 2005 and in the USA in 2006 [1, 3]. Prior to widespread vaccination, mumps was the main cause of aseptic meningitis. The vaccine with live attenuated virus is protective but imperfect, and outbreaks still occur even among vaccinated individuals [19].

Mumps meningitis should be considered during late winter or early spring, especially in males. Mumps infection confers lifelong immunity, so a documented history of previous infection excludes this diagnosis.

Diagnosis is typically made by isolation of virus from the CSF and/or demonstration of seroconversion between acute phase and convalescent sera [2, 3].

Lymphocytic Choriomeningitis Virus (LCMV)

LCMV was one of the earliest and seemingly most significant viruses to be associated with human aseptic meningitis.

It is transmitted to humans by contact with rodents (rats, mice, hamsters, etc.) or their excreta; the greatest risk of infection is in laboratory workers, pet owners, and persons living in impoverished and unhygienic situations. Presumed routes of transmission are ingestion of food contaminated with animal urine and exposure of open wounds to dirt [1]. Person-to-person transmission has occurred only through maternal-fetal transmission (associated with congenital hydrocephalus, chorioretinitis, and mental retardation) and solid organ or hematopoietic transplantation [21–23].

Human cases are most common in autumn due to the result of seasonal population densities of rodents and the movement of mice into homes and barns during cold weather. Most LCMV infections occur among young adults, although persons of all ages have been affected [1].

LCMV illness occurs in most infected individuals usually 8–13 days after being exposed to the virus, and it is usually nonspecific or influenza-like. Thirty-five percent of infected persons exhibit clinical evidence of CNS infection in the second phase (following a few days of recovery). There is an especially severe form of the disease in immunosuppressed patients because of solid organ or hematopoietic stem cell transplantation, in which LCMV may result in serious systemic infections and death [20]. The overall case fatality rate is less than 1%, and people with complications including meningitis almost always recover completely. A more severe disease is likely to occur in people who are immunosuppressed. Mortality in these patients may be as high as 75% [20–23].

Arbovirus Infections

The term arboviruses refer to viruses that have an arthropod vector, such as mosquitoes or ticks. These viruses are members of togavirus (Eastern equine encephalitis, Western equine encephalitis, Venezuelan equine encephalitis, etc.), flavivirus (St. Louis encephalitis, West Nile viruses, Japanese encephalitis, Murray Valley encephalitis, dengue and yellow fever viruses), and bunyavirus families (California encephalitis virus group, hantaviruses, Toscana virus).

For some arboviruses, distribution is universal, while for others, it is geographically restricted since it is determined in large part by the range of their arthropod vectors. These infections appear most often during the summer and early autumn in temperate climates.

Most infections are asymptomatic, and the clinical picture, when it occurs, can range from a self-limited febrile syndrome to severe symptoms (meningitis or meningoencephalitis).

For the diagnosis, it is especially relevant to collect data about recent travel or insect bites; in the laboratory, the use of direct detection techniques such as CSF culture and/or PCR usually warrants etiologic diagnosis [24–26].

Treatment

Patients with a clinical picture suggestive of meningitis should be investigated for the possibility of bacterial and viral causes for the purpose of establishing the diagnosis and potential avoidance of unnecessary hospitalization and/or antibiotic treatment.

In the usual case of viral meningitis, treatment is symptomatic and hospitalization is not required.

Intravenous acyclovir may be of benefit in patients with meningitis caused by HSV-1 or HSV-2 (10 mg/kg per day in three divided doses for 14–21 days) and VZV (10–15 mg/kg per day in three divided doses for 10–14 days). VZV is less sensitive to acyclovir than HSV, and a higher dose may be used in younger patients without renal impairment [2]. Oral acyclovir (800 mg, five times a day), famciclovir

(500 mg, twice a day), or valacyclovir (1000 mg, twice a day) for the last week of the treatment may be used, although data on efficacy are lacking [2].

There are no controlled trials of antiviral treatment of CNS infection caused by CMV, EBV, or HHV-6, and most of the results described are in immunocompromised patients. Ganciclovir and foscarnet are sometimes recommended in CMV [2]. Ganciclovir is ten times more potent in vitro against CMV and EBV than acyclovir and is equally effective against HSV-1, HSV-2, and VZV [2].

Antiviral therapy of enteroviral meningitis is limited. Pleconaril prevents viral replication by inhibiting viral uncoating and blocking viral attachment to host cell receptors. Pleconaril was tested in two placebo-controlled clinical trials and in both shortened the course of illness compared to placebo recipients, especially when given early in the course of the disease. However, the benefits were only modestly achieved in the subgroup of patients with more severe disease after adjusting for confounding variables [2, 8]. Pleconaril has not achieved approval by the US Food and Drug Administration (FDA) because it induces CYP3A enzyme activity and has the potential for drug interactions. Ribavirin appears to be effective in animal models, but clinical experience is lacking. Treatment with intravenous immunoglobulin and milrinone has been used in patients with severe neurological complications. A recent prospective, open-label, randomized controlled study has demonstrated that both can reduce morbidity and mortality [2, 27].

Antiretroviral therapy should be started without delay for HIV meningoencephalitis [14, 16].

Corticosteroids are often administered in the acute phase of HSV encephalitis, in patients with clinical signs of increased intracranial pressure, but this situation is not frequent in the meningitis. The pathogenesis in VZV meningitis has not been elucidated, and the value of additional corticoids has not been studied. A short duration, such as 3–5 days, is generally recommended to avoid adverse effects [2].

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