Chapter 4
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 usually has a benign course, in some patients, it needs hospitalization. The development of the polymerase chain reaction (PCR) has enabled detection of viral genomes, facilitated a rapid diagnosis, and enabled the use of antiviral treatment when needed.

The prognosis is usually favorable.

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

Acute Viral Meningitis Outline

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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 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 decreased state 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 a 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. 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.

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

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. The 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.

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 [2].

Etiology

Enteroviruses account for 85–90 % of aseptic meningitis cases in most series (see Table 4.1). 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 [2].

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

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	>1,000/μl
Neutrophils	–	<50 %	>50 %
Protein (mg/dl)	<30–40	<100	>100
Glucose (mg/dl)	>50	>50	<40
Gram's stain	Negative	Negative	Positive (60 %)

(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 [3].

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 [2]. 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 [4].

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 [2].

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 VEB, for which the prevalence of

Table 4.3 Performance of the main methods for microbiological diagnosis of viral meningitis [4]

	CSF			Other sources		
Microorganisms	PCR	Culture	Serology	PCR	Culture	Serology
Enteroviruses	+++	++	–	+++ (throat, feces)	+++ (throat, feces)	+
Herpesviridae						
VHS	+++	–	+	–	–	–
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

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) [4, 5].

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.

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 [3]:

- 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 pre-existing 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.
- Some medications (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 [6].

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. 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, 2, 7].

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.

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 [3]. 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. Meningitis appears in 36 % of women and 13 % of men at the time of an initial (primary) episode of genital herpes [1].

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.

Of these patients, 20 % will develop a few or up to ten episodes of meningitis lasting 2–5 days followed by spontaneous recovery [8]. 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 [9]. Diagnosis depends on amplification of HSV DNA from CSF by PCR.

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 [10].

Epstein-Barr Virus (EBV) and Cytomegalovirus (CMV)

Both viruses can cause aseptic meningitis in association with mononucleosis syndrome, particularly in the immunocompromised host, but this occurs in less than 5 % of cases. EBV and CMV are almost never cultured from CSF, but DNA can be amplified in some patients [11].

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 [12–14].

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

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. 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, 15]. Hydrocephalus is frequent, particularly in children, and CSF analysis shows lymphocytic pleocytosis and increased proteins; in one-fourth of patients, glucose levels are decreased [16].

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, 2]. Prior to widespread vaccination, mumps was a main cause of aseptic meningitis. The vaccine with live attenuated virus is protective but imperfect, and outbreaks still occur even among vaccinated individuals [17].

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].

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 [19–21].

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 a 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 [18]. 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 % [18–21].

Arbovirus Infections

The term arboviruses refer to viruses that have an arthropod vector, such as mosquitoes or ticks. These viruses are members of the 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 more 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 [22–24].

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). Oral acyclovir (800 mg, five times a day), famciclovir (500 mg, twice a day), or valacyclovir (1,000 mg, twice a day) for the last week of the treatment may be used, although data on efficacy are lacking.

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 [6]. 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. Antiretroviral therapy may be started for HIV meningoencephalitis.

References

1. Tunkel AR, van de Beek D, Scheld WM. Acute meningitis. In: Mandell GL, Bennet JE, Dolin R, editors. Principles and practice of infectious diseases. 7th ed. Philadelphia: Churchill Livingstone/Elsevier; 2010. p. 1189–229.
2. Roos KL, Tyler KL. Meningitis, encephalitis, brain abscess, and empyema. In: Kasper H, Braunwald L, Fauci J. Principles internal medicine. 16th ed. New York: McGraw Hill; 2005. p. 2471–90.
3. Jhekwaba UK, Kudesia G, McKendrick M. Clinical features of viral meningitis in adults: significant differences in cerebrospinal fluid findings among herpes simplex virus, varicella zoster virus, and enterovirus infections. Clin Infect Dis. 2008;47:783–9.
4. Navarro Mari JM, Pérez Ruiz M, Vicente Anza D. Diagnóstico de laboratorio de las meningitis linfocitarias. Enferm Infecc Microbiol Clin. 2010;28 Suppl 1:56–61.
5. Perez-Ruiz M, Vicente D, Navarro-Marí JM. Infecciones agudas del sistema nervioso central (meningitis y encefalitis) virales y bacterianas de origen autóctono. Enferm Infecc Microbiol Clin. 2008;26 Suppl 9:8–14.
6. Desmond RA, Accortt NA, Talley L, Villano SA, Soong SJ, Whitley RJ. Enteroviral meningitis: natural history and outcome of pleconaril therapy. Antimicrob Agents Chemother. 2006;50(7):2409–14.
7. Perez C, Oña M, Ballesteros S, Llaneza J, Lagunilla L, Perez S, Fernández C, Solis G. Meningitis por Enterovirus. Características epidemiológicas, clínicas y de laboratorio en una serie de 60 niños. An Esp Pediatr. 2001;55:11–4.
8. Shalabi M, Whitley RJ. Recurrent benign lymphocytic meningitis. Clin Infect Dis. 2006;43:1194–7.
9. Berger JR, Houff S. Neurological complications of herpes simplex virus type 2 infection. Arch Neurol. 2008;65:596–600.
10. Mueller NH, Gilden DH, Cohrs RJ, Mahalingam R, Nagel MA. Varicella zoster virus infection: clinical features, molecular pathogenesis of disease, and latency. Neurol Clin. 2008;26:675–97.
11. Steiner I, Budka H, Chaudhuri A, Koskiniemi M, Sainio K, Salonen O, Kennedy PGE. Viral meningoencephalitis: a review of diagnostic methods and guidelines for management. Eur J Neurol. 2010;17:999–1009.

12. Hanson KE, Reckleff J, Hicks L, Castellano C, Hicks CB. Unsuspected HIV infection in patients presenting with acute meningitis. Clin Infect Dis. 2008;47:433–4.
13. Schacker T, Coller AC, Hughes J, Shea T, Corey L. Clinical and epidemiological features of primary HIV infection. Ann Intern Med. 1996;125(4):257–64.
14. Zavasky D-M, Gerberding JL, Sande MA. Patients with AIDS. In: Wilson WR, Sande MA. Current diagnosis and treatment in infectious diseases. New York: McGraw Hill; 2001. p. 315–27.
15. Yung CF, Andrews N, Bukasa A, Brown KE, Ramsay M. Mumps complications and effects of mumps vaccination, England and Wales, 2002-2006. Emerg Infect Dis. 2011;17(4):661–7.
16. Escalza-Cortina I, Azkune-Calle I, Rodriguez-Sainz A, Gomez-Beldarrain M, Vicente-Olabarría I, Garcia-Monco JC. Pearls and Oy-sters: chronic mumps meningoencephalitis with low CSF glucose and acute hydrocephalus in an adult. Neurology. 2014;82: e41–3.
17. Hviid A, Rubin S, Muhlemann K. Mumps. Lancet. 2008;371:932–44.
18. Centers for Disease Control and Prevention (CDC). Brief report: lymphocytic choriomeningitis virus transmitted through solid organ transplantation. MMWR Morb Mortal Wkly Rep. 2008;57(29):799–801.
19. Fisher SA, Graham MB, Kuehnert MJ, et al. Transmission of lymphocytic choriomeningitis virus by organ transplantation. N Engl J Med. 2006;354(21):2235–49.
20. Amman BR, Pavlin BI, Albariño CG, et al. Pet rodents and fatal lymphocytic choriomeningitis in transplant meningitis. Emerg Infect Dis. 2007;13(5):719–25.
21. Kotton CN. Zoonosis in solid-organ and hematopoietic stem cell transplant recipients. Clin Infect Dis. 2007;44:857–66.
22. Drew WL. Viral infection of the central nervous system. In: Wilson WR, Sande MA, editors. Current diagnosis and treatment in infectious diseases. New York: McGraw-Hill; 2001. p. 315–27.
23. Solomon T. Flavivirus encephalitis. N Engl J Med. 2004;351:370–8.
24. Sánchez-Seco MP, Navarro JM. Infecciones por el virus de Toscana, el virus del Nilo Occidental y otros Arbovirus de interés en Europa. Enferm Infecc Microbiol Clin. 2005;23(9):560–8.