

Encyclopedia of Pain

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A–G

With 713 Figures and 211 Tables

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Headache in Aseptic Meningitis

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Synonyms

Viral Meningitis; Serous Meningitis; Abacterial Meningitis; Aseptic Meningitis

Definition

► **Aseptic Meningitis** is the term applied to an acute clinical syndrome that comprises headache, fever, signs of

meningeal inflammation and a predominantly lymphocytic pleocytosis with normal glucose and normal to elevated proteins in the cerebro-spinal fluid (CSF).

Historically, the word 'aseptic' was introduced to denote the nonbacterial aetiology of this syndrome, and included forms of infective meningitis (viral and fungal) that were negative on routine bacteriologic stains and culture. With the introduction of polymerase chain reaction (PCR) based investigations and improved diagnostic techniques, the yield has improved, and the list of conditions that can present with a clinical picture like aseptic meningitis has expanded considerably. Although often used interchangeably, this term is therefore no longer synonymous with ► **Viral Meningitis**.

Characteristics

Introduction

Both infective and noninfective conditions may present with a picture that fits the definition of aseptic meningitis. Infective causes (Table 1) are mostly viral in origin and less commonly of fungal, parasitic, nonpyogenic bacterial, rickettsial or mycoplasmal origin; non-infective causes (Table 2) include tumours of the central nervous system, carcinomas, leukaemias, sarcoidosis, systemic lupus erythematosus (SLE), rheumatoid arthritis, certain drugs, vaccines, immunoglobulins, intrathecal agents and rarely some disorders of unproven aetiology like Behcets syndrome, Vogt-Koyanagi-Harada syndrome.

Aseptic meningitis is common and seen more often in children and young adults, especially during the summer months. Except in the neonatal period, the mortality and morbidity rates are low (Norris et al. 1999; Cherry 1998). Most patients with aseptic meningitis due to viral causes have a benign course and spontaneously improve, while others may run a complicated course unless specifically

Headache in Aseptic Meningitis, Table 1 Viral Conditions that may present with aseptic meningitis

Infectious Etiologies	Non-Infectious Causes
	Drugs:-
Enteroviruses, Polio, coxsackievirus, echovirus	NSAIDs
HSV types 1 and 2	Trimethoprim
Varicella-zoster virus	Azathioprine
Adenovirus	Intravenous immunoglobulin
Epstein-Barr virus	Isoniazid
LCMV	Intrathecal
HIV	Methotrexate
Influenza A and B	Vaccines
	Allopurinol

Headache in Aseptic Meningitis, Table 2 Non-Viral Conditions that may present with aseptic meningitis

Infectious Etiologies	Non-Infectious Causes
Bacteria:-	Other Diseases:-
M.tuberculosis	Sarcoidosis
Borrelia burgdorferi	Leptomeningeal carcinoma
Treponema pallidum	SLE
Brucella	CNS vasculitis
Mycopl.pneumoniae	Behcet disease
Fungi:-	Vogt-Koyanagi-Harada syndrome
Crypto. Neoformans	Migraine
Histo. capsulatum	
Coccidiodes immitis	
Blasto. Dermatitides	
Parasites:-	
Toxoplasma gondii	
Taenia solium	

treated. World-wide prevalence varies depending on geographic factors, seasonal influence, epidemiologic patterns of diseases and vaccination policies.

Clinical Features

Aseptic meningitis is characterized by abrupt onset of headache, fever and neck stiffness. Additional clinical symptomatology may vary depending on the underlying cause. Focal signs and seizures are rarely seen in aseptic meningitis, but mumps, certain arboviruses, and lymphocytic choriomeningitis virus may cause a meningoencephalitis (Rice 2001).

The headache of aseptic meningitis has no typical characteristics. It is severe, most often bilateral and may be associated with fever and vomiting. Lamonte et al. (1995), in their retrospective review of 41 patients with aseptic meningitis, noted that headache was present in all, started or worsened abruptly in 24; in 39 the headache was severe and in 6 it was the worst headache. There was no consistent pattern of location or type of pain. In all cases the headache was different from the usual headache. Systemic prodromal symptoms preceded the onset of headache in 19 patients. Nausea, vomiting, cognitive changes, back pain, blurred vision, phonophobia, photophobia and tinnitus were the associated symptoms seen in their series (Marian et al. 1995).

Migraine headache may mimic aseptic meningitis, but if a patient presents acutely with fever and headache that is bilateral, throbbing not relieved with analgesics and different from their earlier headaches, then aseptic meningitis needs ruling out. Rarely migraine itself can cause

aseptic meningitis. Bartleson et al. (1981) reported a series of patients with complicated migraine and CSF pleocytosis preceded by a viral-like illness (Gomez-Aranda et al. 1997). Other causes of similar headache that may confuse include subarachnoid haemorrhage and other acute headaches.

The cell count in aseptic meningitis is usually less than 1000 per cu. mm, and there may be an early predominance of polymorphonuclear leucocytes. Repeated lumbar puncture in 8-12 hours frequently shows a change from neutrophil to lymphocyte predominance. CSF glucose levels are normal and CSF proteins may be normal or elevated. CSF culture for viruses and PCR studies help in further confirming the diagnosis.

Differential Diagnosis

Viruses are the most common causative agents, but even when all viral diagnostic facilities are available, the causal agent may be difficult to identify in a good proportion of cases. Viral pathogens may enter the CNS through the haematogenous or neural route. Neural penetration is limited to herpes viruses (HSV-1, HSV-2 and varicella zoster virus) and some enteroviruses. Exposure to mosquito or tick vectors is a risk factor for transmission (Adams and Victor 2001). Over 80% of aseptic meningitis are caused by enteroviruses (coxsackie A or B, enterovirus 68 to 71, echovirus and poliovirus), followed by the mumps virus, HSV-2, HIV, and less commonly HSV-1, varicella zoster virus (VZV), Epstein-Barr virus and cytomegalovirus (CMV). Rarely arbovirus, lymphocytic choriomeningitis virus (LCMV) and adenovirus may be responsible for similar symptoms. Influenzal and parainfluenzal illnesses can also cause aseptic meningitis. The incidence of polio and mumps in the vaccination era has decreased significantly in developed countries. In younger people, measles virus may cause aseptic meningitis that is associated with a rash (Waisman et al. 1999).

Human Immunodeficiency Virus (HIV) infection may present with aseptic meningitis, particularly at the time of seroconversion (Levy et al. 1990). Patients may present with CSF pleocytosis, elevated protein level and high intracranial pressure. Besides the usual meningeal signs, patients with HIV infection may have neurological deficits and may need imaging. Adenovirus may be a major cause of meningitis in patients with HIV infections. Varicella zoster virus can affect the immunocompromised.

Arbovirus accounts for approximately 5% of cases of aseptic meningitis in North America, and the incidence varies depending on the life cycle of arthropod vectors, animal reservoirs and their contact with humans. Some of the important viruses include Eastern and Western equine encephalitis viruses, St Louis Encephalitis virus, West Nile virus, Japanese B virus and Colorado tick fever. LCMV affects those at risk who come in contact with rodents or their excreta (Nelsen et al. 1993).

The immediate concern in practice should not be aimed at establishing a particular virus as the cause of the illness, but more importantly to exclude the few conditions with aseptic meningitis like picture, but having another underlying non-viral cause warranting specific management. In every patient with aseptic meningitis one has to look beyond viruses as the causative factor.

Non-viral causes have a more complicated course but can be managed with specific treatment. Tuberculous, fungal, syphilitic, spirochaetal, rickettsial, parasitic and other mycoplasmal infections can cause aseptic meningitis, which should be suspected in the appropriate clinical setting. In the early stages, tuberculous meningitis may appear like aseptic meningitis and can be difficult to diagnose. The glucose levels are reduced only in the later stages and the organism is difficult to find. CSF features of aseptic meningitis, but without fever, may be seen with acute syphilitic meningitis. Cryptococcal infections, other fungal infections, and some rare conditions like *Mycoplasma pneumoniae*, Brucellosis and Q fever can also present like aseptic meningitis. Brucellosis is common in specific geographic locations.

Conjunctival suffusion with transient erythema, severe leg and back pain, pulmonary infiltrates and aseptic meningitis should suggest leptospiral infection. Infection is acquired by contact with soil or water contaminated by the urine of rats, dogs, or cattle. Lyme borreliosis is a common spirochaetal cause of aseptic meningitis and meningoencephalitis. The spirochaete is tick borne, common in north eastern United States from May to July (Eppes et al. 1999).

Leukaemias in children and lymphomas in adults are common sources of meningeal reactions with aseptic meningitis like CSF picture. In these disorders, and in meningeal carcinomatosis, neoplastic cells are found throughout the leptomeninges with additional root involvement. Features of the aseptic meningitis syndrome can also be caused by brain abscess, parameningeal infections and partially treated bacterial meningitis, when it may be mistakenly diagnosed as viral aseptic meningitis. A careful history of previous antibiotic administration must therefore be obtained in all patients with meningitis.

Sarcoidosis, Behcets syndrome, vasculitis and granulomatous angiitis can present with aseptic meningitis syndrome by infiltrating the leptomeninges. These conditions, however, rarely present with a clinical picture of meningitis alone, more often they are seen with other neurological accompaniments (Gullapalli and Phillips 2002; Nelsen et al. 1993). Some chronic diseases like systemic lupus erythematosus, serum sickness and Vogt-Koyanagi-Harada syndrome, may present with aseptic meningitis (Adams and Victor 2001).

Drug induced aseptic meningitis (DIAM), either by: 1) direct irritation of the meninges with intrathecal administration, or by 2) immunological hypersensitivity to the drug, has been reported as an uncommon

adverse reaction with numerous agents (Chaudhry and Cunha 1991). The major categories of causative agents are non-steroidal anti-inflammatory drugs (NSAIDs), antimicrobials, intravenous immunoglobulins, isoniazid, allopurinol and vaccines for measles, mumps and rubella. In addition to headache, there may be signs of a hypersensitivity reaction. Trimethoprim-sulphamethoxazole, azathioprine and intrathecal injections can result in the clinical findings of aseptic meningitis. The association between SLE and ibuprofen as a cause of DIAM is important to recognise. A high index of suspicion is necessary to make the diagnosis. Treatment is to withhold the drug. There are no long-term sequelae of DIAM.

Besides the typical CSF picture, it is essential to isolate the virus in CSF, stool, saliva and throat swabs using PCR and other serologic tests (Jeffery et al. 1997). It is important to enquire about a past history of infectious disease, immunisations, contact with animals, insect bites, recent respiratory or gastro-intestinal infection and recent travel. The season during which the illness occurs and the geographical location are helpful pointers.

Recurrent aseptic meningitis is also known as Mollaret's meningitis and can be a diagnostic dilemma. There is spontaneous remission and no causative agent has been consistently found. It is difficult to identify the virus in the CSF. These patients need detailed investigations with repeat lumbar punctures, cytology or CSF bacterial cultures, PCR, HIV testing and MRI with contrast if necessary. Recurrence in a few cases is caused by HSV-1 and HSV-2 infections (Cohen et al. 1994).

Conclusion

Most patients with aseptic meningitis need only supportive care. It may be prudent to start antibiotics until cultures are shown to be negative, or a second examination of CSF shows a more typical picture. Most patients recover completely and rapidly when the aetiology is viral, unless there is an associated encephalitic component. Precautions should be taken when specific viruses are identified. Effective antiviral therapy is available against HSV-1, varicella and CMV. For HSV-2, acyclovir is the drug of choice. Other causes need appropriate management. Rarely, patients may have persistent headache, mild mental impairment, incoordination or weakness that lasts for months. Although aseptic meningitis is an acute illness, most patients eventually improve.

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