Management and outcome in viral meningo-encephalitis

Louise Hartley
Jennifer Evans
Nathalie Emma MacDermott

Abstract

Viruses are the most common infectious cause of meningitis and encephalitis. There are a large number of viruses which may cause meningo-encephalitis either through primary infection or through secondary immune-mediated processes. The presentation of both viral meningitis and encephalitis is described along with features which may help identify the aetiology. Viral meningitis is most commonly caused by enteroviruses notably coxsackie viruses and usually follows a self-limiting course with significantly better outcomes than encephalitis. The most common form of viral encephalitis in the developed world is Herpes simplex encephalitis. This carries a poor prognosis particularly if treatment is delayed, with mortality rates of 70% if left untreated. The importance of testing for Herpes simplex virus on two separate occasions separated by at least 72 h is highlighted, alongside the importance of prompt initiation of intravenous aciclovir and a guide as to when it is appropriate to stop aciclovir. A comprehensive description of neuroimaging findings and management of other viral aetiologies is also included.

Keywords aciclovir; CSF parameters; meningo-encephalitis; neuroimaging; outcomes; viral encephalitis; viral meningitis

Introduction

Meningo-encephalitis is an inflammatory process of the meninges (meningitis), and/or the brain parenchyma (encephalitis). Meningo-encephalitis may be caused by direct primary invasion or by immune-mediated inflammation or demyelination. The majority of cases are caused by infectious agents, mainly viruses, and the viral meningo-encephalitides are the focus of this article. Table 1 incorporates the majority of viruses causing meningo-encephalitis.

We will illustrate the management and outcome of these conditions via clinical cases.

Louise Hartley *MA MRCPCH is a Consultant Paediatric Neurologist in the Department of Paediatric Neurology at the Children's Hospital for Wales, Heath Park, Cardiff, UK. Conflict of interest: none declared.*

Jennifer Evans *MD MRCPCH is a Consultant Paediatrician in the Department of General Paediatrics at the Children's Hospital for Wales, Heath Park, Cardiff, UK. Conflict of interest: none declared.*

Nathalie Emma MacDermott *BSc MRCPCH Department of Paediatric Neurology at the Children's Hospital for Wales, Heath Park, UK. Conflict of interest: none declared.*

Viral meningitis

Clinical case

A 12-year-old girl with fever, sore throat, and headache, subsequently develops nausea, photophobia, and neck pain. Examination reveals a temperature of 39 °C and neck stiffness with an otherwise normal neurological examination. One week previously her 7-year-old brother presented with fever, sore throat, and a vesicular rash on the hands and feet and in the mouth. CT scan of her brain is normal. A lumbar puncture reveals a pressure of 35 cm of water, white blood cells of 102 cells/mm^3 with 90% mononuclear cells, a protein of 0.66 g/L, and a plasma:cerebrospinal fluid (CSF) glucose ratio >0.6. She is started on broad spectrum antibiotics. Throat, stool, blood, and CSF samples are sent for virus isolation, and serum and CSF sent for antibody testing and polymerase chain reaction (PCR). Immunofluorescence staining of tissue cultures reveal a coxsackie group A virus. Antibiotics are stopped. The patient requires intravenous fluids for hydration, analgesics for headache, and antipyretics. Over the next 5 days, she improves and is discharged home.

Aetiology

Enteroviruses account for 85–95% of viral meningitis cases in the developed world. The non-polio enteroviruses, notably coxsackievirus and echovirus, as well as enteroviruses 70 and 71, are by far the most common causes of viral meningitis.

Clinical diagnosis

Systemic manifestations may provide clues to the underlying viral aetiology. The enteroviruses may cause diffuse rashes and the group A coxsackieviruses often cause hand-foot-and-mouth disease and herpangina, whereas the group B coxsackieviruses characteristically cause pleurodynia and myocarditis or pericarditis. Both coxsackieviruses and echoviruses can also cause conjunctivitis and myopathies. In neonates, central nervous system (CNS) enterovirus infection may be accompanied by multiorgan involvement including hepatic necrosis, myocarditis, and necrotizing enterocolitis. Parotitis occurs in approximately half of patients with mumps meningitis.

Pathogenesis and pathophysiology

The pathogenesis of each family of viruses causing viral meningitis varies. Viruses initially enter the host through the respiratory, gastrointestinal or urogenital tracts, or breaks in the skin. Most viruses replicate near the entry site and gain access to the CNS by the haematogenous route, entering across the choroid plexus. These, including the enteroviruses, are more likely to cause meningitis; whereas rabies, Herpes simplex virus (HSV), Varicella-zoster, and poliovirus enter the CNS via peripheral nerves causing encephalitis.

Once the virus reaches the choroid plexus, it spreads throughout the CSF reaching meningeal and ependymal cells where it replicates causing cell destruction and inflammation. The subsequent inflammatory response is responsible for the symptoms of fever, neck stiffness, headache, and photophobia.

Viral causes of acute primary meningo-encephalitis

Type of spread	Virus family	Virus species
Person to person spread	*Adenoviridae*	Human adenovirus
	Hepadnaviridae	Hepatitis B virus
	Herpesviridae	Cytomegalovirus
		Epstein–Barr virus
		Herpes simplex virus 1
		Herpes simplex virus 2
		Human herpes virus 6
		Human herpes virus 7
		Human herpes virus 8
		Varicella-zoster virus
	Orthomyxoviridae	Influenza A virus
		Influenza B virus
	Paramyxoviridae	Measles virus
		Mumps virus
		Parainfluenza virus 1
		Parainfluenza virus 3
		Respiratory syncytial virus
	Parvoviridae	Parvovirus B19
	Picornaviridae	Enteroviruses
		Hepatitis A virus
		Parechovirus
	Polyomaviridae	BK virus
	Poxviridae	Variola virus
	Reoviridae	Reovirus/Rotavirus
	Togaviridae	Rubella virus
Arthropod spread	*Flaviviridae*	Japanese encephalitis B
		Powassan encephalitis
		St. Louis encephalitis virus
		Tick-borne encephalitis virus
		West Nile virus
	Orthomyxoviridae	California encephalitis virus
	Reoviridae	Colorado tick fever virus
	Togaviridae	Eastern equine virus
		Western equine virus
		Venezuelan equine virus
Spread by mammals	*Arenaviridae*	Lymphocytic choriomeningitis virus
	Herpesviridae	Herpesvirus simiae
	Paramyxoviridae	Hendra virus
		Nipah virus
		Vesicular stomatitis virus
	Picornaviridae	Encephalomyocarditis virus
	Rhabdoviridae	Rabies virus

Table 1

This inflammatory response limits viral replication and the length of the meningitic syndrome.

Prognosis and complications

Although the vast majority of patients with viral meningitis recover in 1–2 weeks, about 5% of patients have residual deficits including fatigue, mild cognitive impairments, seizures and cranial nerve palsies. The most severe complications include progression to severe encephalitis, or the development of other organ involvement such as liver necrosis.

Viral meningitis: key points

- The most common symptoms of viral meningitis are headache, fever and neck stiffness.
- Enteroviruses account for 85–95% of viral meningitis cases in the developed world.
- Viral meningitis and bacterial meningitis cannot be reliably differentiated based on clinical grounds and CSF analysis is needed. Antibiotic cover should be continued until bacterial infection excluded or a viral cause identified.
- CSF will classically show a lymphocytic pleocytosis (usually <300 cells/mm^3), a normal glucose, normal or mildly elevated protein and a negative Gram stain and bacterial culture.

Viral encephalitis

Clinical case

A 14-year-old boy presents with a 3-day history of fever, vomiting and headache. He has become increasingly confused over the previous 48 h, with word finding difficulties and inappropriate responses to questions. During the night he becomes more disorientated, unable to understand basic commands and to remember his date of birth or the name of his school. He is pyrexial at 39 °C, but neurological examination is normal. Initial investigations reveal a normal C-reactive protein (CRP) and blood parameters and a normal CT head. Lumbar puncture shows a CSF opening pressure of 29 cm of water, white blood cells of 328 cells/mm^3, with 98% mononuclear cells, red blood cells of 4 cells/mm^3, raised protein of 1.86 g/L and a low plasma:CSF glucose ratio of 0.49. CSF is sent for PCR and he is started on broad spectrum antibiotics and aciclovir.

On day 2 he develops focal seizures, an MRI scan shows swelling of both temporal lobes with extensive swelling of the meninges and leptomeninges. An electroencephalogram (EEG) shows features of encephalopathy. The CSF and blood cultures are negative as is PCR for meningococcus, pneumococcus, enterovirus but PCR for HSV is positive. He is treated with 21 days of intravenous (IV) aciclovir at a dose of 10 mg/kg 8 hourly. Due to the development of raised intracranial pressure he undergoes repeated lumbar punctures.

After 3 weeks of aciclovir treatment he is discharged from hospital. His confusion has settled but he continues to have difficulty with short-term memory. He has persistent epilepsy controlled on carbamazepine. He goes on to leave school at 16 years and works in his father's garage where he is closely supervised, he is unable to consider working independently for a private employer.