Viral infections of the central nervous system

Viral infections of the CNS are caused by a broad range of viruses.

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Viral infections of the central nervous system (CNS) include both acute and chronic conditions caused by a broad range of different viruses. It is useful to divide these infections according to the anatomical area affected (Table I).

Table I. Classification of viral infections of the CNS

Anatomical area	Acute	Chronic
Meninges	Viral meningitis	
Brain parenchyma	Viral encephalitis	Measles: SSPE[†]
	ADEM[*]	HIV-associated, e.g.
		HIV-associated neuro-cognitive disorder
		EBV: primary CNS lymphoma
		JC virus: PML[≠]
		Prions: spongiform encephalopathy
Spinal cord	Acute viral myelitis	HIV-1 vacuolar myelopathy
	ADEM*	HTLV-1 myelopathy

[*] Acute disseminated encephalomyelitis
[†] Subacute sclerosing panencephalitis
[≠] Progressive multifocal leucoencephalopathy.

Anatomical proximity may mean that more than one area is affected at the same time. For example, meningoencephalitis describes the occurrence of both meningitis and encephalitis and encephalomyelitis refers to simultaneous encephalitis and myelitis.

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Outcomes of these infections are variable, ranging from generally benign in aseptic meningitis to severe with neurological sequelae and even death in encephalitis.

Acute

Viral meningitis

Acute meningitis is meningeal inflammation that develops over hours to days. Most cases of viral meningitis are caused by enteroviruses (70 - 90%), herpes simplex virus type 2 or mumps. Other viral causes include cytomegalovirus (CMV), Epstein-Barr virus (EBV), varicella-zoster virus (VZV), human immunodeficiency virus (HIV), arboviruses and lymphocytic choriomeningitis (LCM) virus. Patients present with acute fever, headache and signs of meningeal irritation, e.g. photophobia and neck stiffness. The prognosis is usually excellent. Cerebrospinal fluid (CSF) polymerase chain reaction (PCR) testing can be performed for diagnosis. Treatment is largely supportive.[1]

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Viral encephalitis

The majority of pathogens that cause encephalitis are viruses. Table II lists some of the more common viral causes of encephalitis. Encephalitis is inflammation of the brain with clinical evidence of neurological dysfunction. Patients present with fever, headache and altered level of consciousness. Encephalitis differs from meningitis in that there are disturbances in higher mental function, e.g. behavioural changes, seizures, focal paresis or paralysis.[1]

Table II. Viral causes of encephalitis[1]

Worldwide distribution	Limited to a certain geographic area
Herpes viruses	Flavi viruses
• Herpes simplex virus (HSV)	• West Nile virus
• Varicella-zoster virus (VZV)	• Japanese encephalitis virus
• Epstein-Barr virus (EBV)	• St Louis encephalitis
• Cytomegalovirus (CMV)	• Tick-borne encephalitis virus
• Human herpesvirus 6	
Non-polio enteroviruses	Alpha viruses
	• Western equine encephalitis virus
	• Eastern equine encephalitis virus
Rabies virus	
Mumps virus	

Herpes simplex virus type-1 encephalitis (HSE) is the most common cause of sporadic fatal encephalitis worldwide and is a medical emergency.[2] Early, aggressive treatment with intravenous acyclovir is essential to prevent mortality and limit neurological sequelae.

Acute disseminated encephalomyelitis (ADEM)

ADEM is a rare, immune-mediated disorder that is triggered by an environmental stimulus in genetically susceptible individuals.[3] Neurological symptoms and signs start within days to weeks after a viral infection or immunisation. Bacterial and viral meningitis or encephalitis must be ruled out. Patients present with involvement of the white matter and multifocal neurological abnormalities and encephalopathy, e.g. confusion, excessive irritability or altered level of consciousness.[4] Diagnosis is based on clinical and radiological features. There is no specific biological marker or confirmatory test.

Acute viral myelitis (Table III)

Acute viral myelitis includes two distinct clinical syndromes. Viruses may target the grey matter, causing acute flaccid paralysis (AFP), e.g. poliovirus. AFP is due to cytolytic infection of the anterior horn cells.[5] Viruses may also target the white matter, causing asymmetric motor

Table III. Acute viral myelitis

Spinal cord grey matter: acute flaccid paralysis	Spinal cord white matter
Enteroviruses, e.g. Polioviruses 1, 2 and 3 Non-polio enteroviruses, e.g. • Coxsackie A and B virus • Enterovirus 71 Flaviviruses, e.g. • West Nile virus • Japanese encephalitis virus	Herpes viruses, e.g. • Herpes simplex virus (HSV) • Varicella zoster virus (VZV) • Cytomegalovirus (CMV) • Epstein-Barr virus (EBV)

and sensory symptoms. The association between the myelitis and the virus is not always clear. In some cases it may represent an autoimmune response. In others a positive PCR test in the CSF suggests that the myelitis is directly related to the viral infection.

Acute transverse myelitis (ATM) occurs when both halves of the spinal cord are affected, and there is symmetrical weakness, sensory loss and bladder involvement. The yield of several tests appears to be low, and there is no consensus regarding optimal evaluation in terms of cost effectiveness.[6] Data from randomised trials of initial therapy and management are scarce. Corticosteroid therapy is standard first-line treatment for ATM; however, supportive evidence is mainly from case studies or trials involving multiple sclerosis patients.

Chronic

Progressive multifocal leucoencephalopathy (PML)

PML is a demyelinating disease of the CNS caused by JC virus reactivation. It is an opportunistic infection in HIV which has decreased since the use of antiretroviral treatment. Symptoms include weakness, cognitive impairment, visual abnormalities and sensory loss. Signs include hemiparesis, gait disturbance, dysarthria and dysphasia. Brain biopsy is the gold standard for diagnosis but JC virus PCR is increasingly used, as it is less invasive.[7] Sensitivity of JC PCR declines when the patient is on antitretroviral treatment.[8] New or clinical worsening of PML may occur shortly after the initiation of antiretroviral treatment due to the immune reconstitution inflammatory syndrome (IRIS).[8]

HIV-associated neurocognitive disorder (HAND)

HAND comprises HIV-associated dementia (HAD) (also called HIV encephalopathy), mild neurocognitive disorder (MND) and asymptomatic neurocognitive impairment. HAD is a subcortical dementia and AIDS-defining illness. Initial symptoms may be subtle, including short-term memory loss, mental slowing, reading and comprehension difficulties and apathy. Typically there is cognitive, behavioural and motor dysfunction. Other conditions may mimic HIV encephalopathy, e.g. CMV encephalitis or PML. No diagnostic CSF profile has yet entered clinical practice. Treatment consists of suppressing HIV replication by using antiretroviral therapy.[9]

Primary CNS lymphoma (PCNSL)

PCNSL is an AIDS-defining malignancy that is strongly related to EBV infection and immunosuppression. It is a rare B-cell variant of non-Hodgkin's lymphoma. It can present with focal or non-focal signs and symptoms, e.g. confusion, lethargy, memory loss, hemiparesis, aphasia and seizures.[10] The incidence has declined since the use of antiretrovirals. PCNSL needs to be differentiated from other lesions, especially toxoplasmosis. Diagnosis includes imaging, e.g. magnetic resonance imaging (MRI) or computed tomography (CT) scan, CSF EBV PCR and biopsy if necessary.[10]

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Subacute sclerosing panencephalitis (SSPE)

SSPE a rare, chronic, degenerative CNS disease that occurs secondary to persistent infection with a defective measles virus.[11] The prevalence is estimated at 1 per 100 000 cases of measles. Signs and symptoms appear an average of 7 years after the initial infection and include personality changes, myoclonic seizures and motor disturbances. Often, coma and death follow. This condition occurs particularly in those who had measles at a very young age, i.e. before the age of 2 years. Diagnosis includes finding high titres of measles-specific antibody in the serum and CSF.[12]

Prions

Prion diseases are degenerative disorders of the nervous system. They have long incubation periods followed by chronic neurological disease and fatal outcomes.[13] They are caused by transmissible particles that contain a pathogenic isoform of the prion protein, a normal constituent of cell membranes.[13] The most common human prion disease is Creutzfeldt-Jakob disease (CJD); 85% of cases are sporadic, 10 - 15% inherited and 1% transmitted by medical procedures. In 1994, variant CJD emerged in the UK and is associated with consumption of contaminated beef.

HIV-1 vacuolar myelopathy (VM)

VM is a slowly progressive, painless, spastic paraparesis, with sensory ataxia and neurogenic bladder. It is characterised by vacuolar changes, particularly in the thoracic spinal cord. It is symptomatic in 5 - 10% of patients with AIDS. MRIs of the spine are typically normal, or may show nonspecific tract hyperintensities.[14] Treatment with antiretrovirals has not been shown to be effective.

HTLV-1 associated myelopathy/ tropical spastic paraparesis (HAM/ TSP)

HAM/TSP is an immune-mediated disease caused by HTLV-1. The lifetime risk of developing HAM/TSP in HTLV-1 carriers ranges between 0.3% and 4%.[15] It has a slow onset with a chronic and steady progression. Weakness of the lower limbs is usually the first symptom, which progresses to an abnormal spastic gait. Other symptoms include bladder dysfunction, constipation, back pain and paraesthaesias in the lower limbs. The diagnosis is made by HTLV-1 serology on blood and CSF.

Neurological syndromes associated with viral infections: Reye's syndrome

Reye's syndrome is an acquired condition with hepatic and cerebral manifestations. In the late 1970s, Reye's syndrome showed an association with certain viruses, e.g. influenza B and varicella zoster virus in children. By 1988 the incidence had fallen dramatically due to awareness of its association with aspirin. Today this disorder is rare.[16]

Diagnostic approach

Clinical history

It is important to obtain a comprehensive travel and exposure history. Non-viral aetiologies should always be considered. The season of the year can provide important

aetiological clues, e.g. enteroviral meningitis typically occurs during summer and autumn. Clinicians must consider the patient before them, e.g. in children certain viruses are more common or severe. In immunocompromised patients opportunistic viral infections should be kept in mind.[17]

Neuroimaging

Brain CT or MRI scan can be useful to rule out a space-occupying lesion or features of obstructive hydrocephalus which is a contraindication to doing a lumbar puncture. It can also provide nonspecific evidence of an underlying viral process, e.g. changes in the temporal lobe suggestive of HSV. In myelitis it may show cord lesions and inflammation of spinal nerve roots.

Lumbar puncture (LP) and CSF analysis

CSF analysis provides the opportunity to distinguish between viral, bacterial, and fungal causes of meningitis and encephalitis (see Table IV).

CSF polymerase chain reaction (PCR)

PCR testing has revolutionised the diagnosis of viral CNS infections. It can be performed for many viruses including herpes viruses (HSV, VZV, CMV, EBV), enterovirus, JC virus and mumps. False negative and false positive results may occur and results must be correlated with the clinical picture.

Table IV. CSF findings[18]

CNS infection	Opening pressure	Cell count (cells/mm^3)	Glucose	Protein
Bacterial meningitis	Increased	Greatly increased: 100 - 5 000 Neutrophils predominate	Decreased	Increased
Viral meningitis	Normal	Moderately increased: 10 - 500 Lymphocytes predominate	Normal	Normal/ slightly increased
Encephalitis	Increased	Moderately increased: 10 - 500 Lymphocytes predominate	Normal	Normal/ slightly increased

Serology

West Nile CNS infection is diagnosed by detection of West Nile virus-specific IgM in the CSF. Serum antibodies may also be useful in the setting of suspected West Nile virus infections.[17]

Brain biopsy

Brain biopsy should be only be considered where benefits clearly outweigh risk, e.g. serious neurological illness for which a diagnosis is required for either therapeutic or prognostic reasons but remains unidentified by neuroradiological or CSF analysis.[17]

References available at www.cmej.org.za

IN A NUTSHELL

- Viruses can cause a wide range of CNS manifestations.
- Obtaining a thorough travel and exposure history is essential during evaluation.
- Patient characteristics, e.g. age and immune status may assist in narrowing down the list of likely viruses.
- Diagnosis is challenging and aetiology may remain unproven after several investigations.
- Molecular techniques have offered more rapid and accurate diagnosis but clinical correlation is vital when interpreting results.

SINGLE SUTURE

Clean your lungs with broccoli

Not content with helping to prevent cancer, broccoli may also help the immune system to clean harmful bacteria from the lungs. A compound found in the vegetable is now being trailled as a treatment for people with lung disease.

To ensure that the lungs function correctly, macrophages remove debris and bacteria that can build up and cause infection. This cleaning system is defective in smokers and people with chronic obstructive pulmonary disease (COPD). Now, researchers have found that a chemical pathway in the lungs, called NRF2, involved in macrophage activation, is wiped out by smoking. Sulphoraphane, a plant chemical that is made by broccoli and other cruciferous vegetables, can restore this pathway.

Shyam Biswal at Johns Hopkins University in Baltimore, Maryland, and colleagues, exposed defective macrophages from the lungs of 43 people with COPD to two bacterial strains that are common causes of COPD-associated infections. In the presence of sulphoraphane, the NRF2 pathway was boosted and the macrophages' ability to engulf bacteria was restored.

The sulphoraphane in broccoli is activated by enzymes in saliva that vary between people, so the dose obtained by eating it would also likely vary. Biswal's team has now started phase 2 clinical trials to test the compound in people with COPD to see if it improves lung function.

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