Central nervous system herpesvirus infections

Philip Britton

Cheryl Jones

Abstract

The *herpesviridae* family are important causes of central nervous system disease in children. We review the spectrum of disease caused by the viruses in the context of a brief description of their epidemiology and transmission. *Herpesviridae* establish lifelong latency following primary infection and we clearly categorize those diseases associated with primary infection and those associated with reactivation with a particular emphasis on the immunocompromised child. Though a causal association with neurological disease in children is established for HSV and VZV syndromes, we identify the ongoing challenge of establishing causation for other viruses because of the rarity of presentations and viral latency. We review the diagnosis, management and outcome issues with recognition that more research is required.

Keywords central nervous system; children; diagnosis; encephalitis; epidemiology; herpesviruses; pathogenesis; treatment

Introduction

The *herpesviridae* family of DNA viruses includes eight distinct viruses within three sub-families (Table 1). *Herpesviridae* are characterized by high rates of primary infection that are often asymptomatic or produce only mild symptoms, but with the potential for severe disease. They establish long-term latency in the host, characterized by persistence of viral genome with limited gene expression, and can reactivate to produce infectious virus in response to a variety of triggers including immunosuppression, causing subclinical infection or recurrent disease. Save for human herpesvirus 8 (HHV-8 or Kaposi's sarcoma-associated herpesvirus) all the herpesviruses cause central nervous system (CNS) disease in children, with a wide variety of clinical syndromes (Table 1).

Herpes simplex virus (HSV)

HSV-1 and HSV-2 primarily infect muco-epithelial cells and establish latency within ganglia of sensory neurons. They are transmitted by close contact with mucous membrane secretions. Two forms of CNS disease predominate in the young; sporadic encephalitis that is primarily caused by HSV-1 in older infants and children and encephalitis associated with neonatal HSV infection that can be caused by either HSV serotype.

Sporadic HSV encephalitis (HSE)

Herpes simplex encephalitis (HSE) is the most common worldwide cause of sporadic viral encephalitis with an incidence of 1–4 per million population per year. It occurs in a bimodal distribution with peaks between 6 months and 20 years age and the highest incidence over 50 years. In most encephalitis studies, including a recent large prospective study in the United Kingdom, HSV is the most common infectious cause of encephalitis (approximately 20%). Approximately a third of cases occur in the less than 20 years age group, the majority in children 1–4 years of age. Over 90% of HSE is caused by HSV-1 and the majority of disease occurs in immunocompetent hosts. Recently, genetic defects in innate immunity, including the toll like receptor interferon signalling pathways have been identified in some children with HSE. HSE does not occur with increased frequency in immunocompromised hosts however the disease itself may be more severe.

In children with HSE, approximately half have primary HSV infection and half HSV reactivation. This contrasts with adults who develop HSE mostly from reactivation. The pathogenesis of HSE has not been clearly established. Damage to CNS tissues is primarily due to direct viral killing of infected tissues, although the inflammatory response may also contribute to the pathology. For primary infection the virus is thought to enter the CNS directly via the olfactory and trigeminal nerves, whereas it has been postulated that there is retrograde neuronal spread of virus from the trigeminal ganglion in reactivation disease. Alternatively there may be reactivation of latent virus within the CNS itself, although this notion remains unproven.

Our understanding of the breadth of clinical manifestations of HSE has changed with the availability of molecular techniques for diagnosis. The classical HSE fronto-temporal syndrome of fever, personality or behavioural change, aphasia with or without hallucinations occurs in only a minority of children with HSE. Over 90% will present with non-specific features early in the course, including fever, lethargy and/or altered level of consciousness with or without behavioural change. More characteristic features including seizures and focal neurological signs are reported in a minority of children and may not be present early in the illness. Children with HSE report headache with similar frequency to older age groups (about 50%). Occasionally, features of meningitis may be present (photophobia and neck stiffness). Rarely neurological manifestations of childhood HSE include opercular syndrome (facial palsy, dysarthria and dysphasisa).

Laboratory confirmation of HSE is by cerebrospinal fluid (CSF) examination and polymerase chain reaction (PCR) for HSV DNA if lumbar puncture is not contraindicated. The CSF is abnormal in over 90% of HSE cases, most commonly with a monocytic pleocytosis, although total white cell counts (WCC) are usually less than 1000 cells/mm^3. The CSF in HSE can be haemorrhagic, and may contain large numbers of red blood cells

Philip Britton ***B.Med.Sci MBBS DipCH*** *is a Paediatric infectious diseases fellow in the Department of Infectious Diseases and Microbiology, The Children's Hospital at Westmead, and a PhD student with the University of Sydney, NSW, Australia. Conflicts of interest: none.*

Cheryl Jones ***MBBS (Hons) PhD FRACP*** *is a Professor of Paediatrics with Sydney Medical school, University of Sydney, Paediatric Infectious Diseases Physician in the Department of Infectious Diseases and Microbiology, the Children's Hospital at Westmead, NSW, Australia. Conflicts of interest: none.*

Categorization of the herpesviruses and CNS disease in children

	HSV-1 (HHV-1)	HSV-2 (HHV-2)	VZV (HHV-3)	EBV (HHV-4)	CMV (HHV-5)	HHV-6	HHV-7
Sub-family	α	α	α	γ	β	β	β
Sites of latency	Sensory and cranial nerve ganglia	Sensory and cranial nerve ganglia	Sensory and cranial nerve ganglia	B cell	Monocyte, macrophage	Monocyte, macrophage, CNS	CD4 T cell
CNS disease							
More frequent	Encephalitis; Neonatal CNS disease	Neonatal CNS disease	Cerebellitis	Encephalitis	Congenital CMV	Febrile seizures; IAE	Febrile seizures; IAE
Less frequent	ADEM; TM; GBS; Brainstem encephalitis	Mollaret meningitis	Vasculopathy/ Vasculitis; Myelitis; Congenital varicella; ADEM; GBS; Optic neuritis	ADEM; TM; GBS; AIWS	Encephalitis	Encephalitis	Encephalitis
Age	All childhood	Neonates	All childhood	Adolescence	All childhood	All childhood	? Adolescence
Associated with immune-suppression	No	Age-related	Yes and no	No	Yes	Yes	?
Treatment	Aciclovir ?steroids	Aciclovir ?steroids	Aciclovir + steroids Transverse Or nil	?Nil	Ganciclovir foscarnet, cidofovir	Ganciclovir, foscarnet	?

Abbreviations: HHV = Human Herpesvirus, HSV = Herpes Simplex virus, VZV = Varicella-Zoster virus, EBV = Epstein–Barr virus, CMV = Cytomegalovirus, CNS = central nervous system, ADEM = Acute disseminated encephalomyelitis, TM = Transverse myelitis, GBS = Guillain–Barre Syndrome, AIWS = Alice in Wonderland Syndrome; IAE = infection associated encephalopathy.

Table 1

without there being traumatic sampling. The CSF protein is elevated in 80% and CSF glucose usually normal. HSV DNA PCR is highly sensitive and specific (>95%), however, false negative results can occur early in the course of the illness, so repeat testing should be pursued if clinical features are suggestive of HSE. Antiviral treatment may render the PCR negative, but is unlikely to so in the first 5–7 days of therapy. The presence of PCR inhibitors in the CSF (e.g. from blood) can also give a negative PCR result in true disease. The detection of elevated CSF HSV IgG can be used to make a retrospective diagnosis of HSE (i.e. 3 weeks after the onset of signs). The test requires simultaneous detection of blood and CSF HSV IgG and another protein (e.g. albumin) to show integrity of the blood brain barrier.

HSE causes characteristic findings on brain neuroimaging but findings vary with modality, age and duration of illness. MRI is the most sensitive modality for HSE, with newer diffusion weighted sequences associated with the highest sensitivity early in the disease. Imaging most often shows medial temporal lobe and inferior frontal cortex involvement and lesions may be unilateral or bilateral. HSE has been associated with many atypical appearances including multifocal cortical changes and involvement of the cerebellum and brainstem. Atypical appearances are more common in younger children. CT can be normal in up to half of HSE cases in the first 5–6 days, but then will become abnormal in the majority, often showing haemorrhage. EEG was once thought to be specific for HSE through the demonstration of temporal paroxysmal lateralizing epileptiform discharges (PLEDs). However recent studies suggest that although EEG is highly sensitive, features are often non-specific, with temporal lobe changes present late, and in only a small proportion of cases.

HSE is a medical emergency that requires hospitalization and high dose intravenous acyclovir (most experts recommend 15–20 mg/kg/dose or 500 mg/m^2 every 8 hours). There is evidence of better outcomes in those patients for whom antiviral treatment was commenced within 72 hours of symptom onset. The duration of treatment should be at least 14 days, with some authors advocating for 21 days to reduce early relapse. CSF HSV PCR should be performed towards the end of the course to monitor response and the antiviral course prolonged if it remains positive. Case-control studies have suggested that adjunctive corticosteroids to reduce associated immunopathology may be associated with improved outcomes and this is currently being evaluated in a randomized controlled trial.

Prior to the availability of antiviral agents, the mortality of HSE was 70% with almost universal sequelae in survivors. Acyclovir therapy has reduced the mortality of HSE in children to less that 20%, however the incidence of neurological disability in survivors remains high (more than 60%). Many children with HSE require high level supportive care including seizure control. Children with HSE should have paediatric neurology follow up and assessment by a rehabilitation specialist. Rehabilitation is best delivered using brain injury models of care, with recognition that cognitive deficits may become more evident with over time.