Central nervous system herpesvirus infections

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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 categorise those diseases associated with primary infection and those associated with reactivation with a particular emphasis on the immunocompromised child. Although 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 3 sub-families (Table 1). *Herpesviridae* are characterised by high rates of primary infection — often asymptomatic or produce only mild symptoms — with the potential for severe disease. These viruses establish long-term latency in humans, characterised by persistence of viral genome with limited gene expression, but can periodically reactivate to produce infectious virus in response to a variety of triggers including immunosuppression, causing subclinical virus shedding or recurrent disease. Except for human herpesvirus 8 (HHV-8 or Kaposi's sarcoma-associated herpesvirus) all the herpesviruses cause or have been associated with 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 a leading 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 six months and 20 years age and the highest incidence over 50 years. In most encephalitis studies amongst adults, 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. 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. Damage to CNS tissues is mostly due to direct viral killing of infected tissues, although the inflammatory response may also contribute to the pathology.

Our understanding of the breadth of clinical manifestations of HSE has changed with the availability of molecular techniques (namely polymerase chain reaction — PCR) 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).

Laboratory confirmation of HSE is by cerebrospinal fluid (CSF) examination and 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. HSE can cause haemorrhagic necrosis and the CSF may contain large numbers of red blood cells 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 early in the course of the illness, so repeat testing should be pursued if clinical features are suggestive of HSE. The presence of PCR inhibitors in the CSF (e.g. from blood) can also give a negative PCR

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Categorisation 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	Febrile seizures; IAE	Febrile seizures
Less frequent	ADEM; TM; GBS; Brainstem encephalitis	Mollaret meningitis	Vasculopathy/Vasculitis; Myelitis; Congenital varicella ADEM; GBS; Optic neuritis	ADEM; TM; GBS; AIWS	CMV; 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 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

result in true disease. Anti-viral treatment may render the PCR negative, but is unlikely to so in the first 5–7 days of therapy. 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.

Magnetic resonance imaging (MRI) is the most sensitive modality for detecting HSE, with newer diffusion weighted sequences showing the highest sensitivity early in the disease. Characteristic HSE findings on brain neuroimaging are medial temporal lobe and inferior frontal cortex involvement and lesions may be unilateral or bilateral. However, HSE has been associated with many atypical appearances including multi-focal 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). 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 hospitalisation and high dose intravenous acyclovir (most experts recommend 15–20 mg/kg/dose or 500mg/m^2 every 8 hours). There is evidence of better outcomes in those patients for whom antiviral treatment was commenced within 72hrs of symptom onset. The duration of treatment should be at least 14 days, with some authors advocating for 21 days to reduce early relapse. Some advocate for CSR HSV PCR to be performed towards the end of the treatment 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 an ongoing randomised controlled trial.

Prior to the availability of antiviral agents, the mortality of HSE was 70% with almost universal sequalae in survivors. Acyclovir therapy has reduced the mortality of HSE in children to less than 20%, however the incidence of neurological disability in survivors remains high (>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 with brain injury models of care, with recognition that cognitive deficits may become more evident with over time.

Clinical relapse is described in a third of childhood HSE cases. However, only a small proportion of these children have proven CSF HSV recurrence. In cases of virological relapse full re-treatment is required and consideration of lifelong prophylactic oral antiviral therapy (in addition to a search for underlying genetic deficiencies). Most other relapses occur in the absence of viral detection in CSF. Historically, a post-HSE choreiform disorder was a feature of these 'relapses'.

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