Herpesviruses

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Abstract

Nine herpesviruses from three subfamilies (α, β, γ) are known to infect humans. The hallmark of herpesvirus infection is the ability to establish latency and reactivate when immunosuppressed. While relatively innocuous in young children, α-herpesviruses (herpes simplex virus, varicella-zoster virus) are the cause of significant morbidity and mortality at the extremes of age and in immunosuppressed individuals, with a significant cost to healthcare systems worldwide. Current treatment, although effective, needs improvement; new vaccines and drugs with novel therapeutic targets offer potential to reduce the burden of disease. Within β-herpesviruses, cytomegalovirus (CMV) is the most clinically significant. Congenital CMV infection is the most common infective cause of sensorineural deafness. It is also a common problem after transplantation. Prophylactic or pre-emptive antiviral strategies have been developed for its management. Chromosomal integration of human herpesvirus 6 is a curiosity. Its significance is not clear but it may have clinical implications. γ-Herpesviruses are lymphotropic and can be associated with lymphoproliferative disorders or malignancies. Management options include treating the underlying immune deficiency if present, use of chemotherapy, B cell depletion and adoptive T cell transfer.

Keywords Cytomegalovirus; Epstein–Barr virus; herpes simplex virus type 1; herpes simplex virus type 2; human herpesvirus 6; human herpesvirus 7; human herpesvirus 8; Kaposi sarcoma-associated herpesvirus; varicella-zoster virus

Key points

- Intact cell-mediated immunity is key in the control of herpesvirus reactivation
- Novel drug targets and therapeutic vaccines hold promise for better control of herpes simplex infections
- Varicella-zoster virus can be associated with vasculopathy and increase the risk of stroke
- Postnatal treatment with ganciclovir/valganciclovir can improve the outcome of congenital cytomegalovirus infection
- New therapeutic agents for preventing or treating cytomegalovirus disease are on the horizon
- Epstein–Barr virus is recognized to be associated with a wide range of haematological and non-haematological malignancies

Introduction

Herpesviruses are a group of very ancient viruses that have been infecting many animals for hundreds of millions of years. Species of herpesviruses can be found in mammals, birds, reptiles, fish and even molluscs. Nine herpesviruses are currently known to infect humans (Table 1).

All herpesviruses share a common structure – a lipid envelope that covers an icosahedral protein capsid containing a linear double-stranded DNA genome. The hallmark of herpesviruses infection is the ability to establish latency. After the initial primary infection, herpesviruses are not cleared from the body, but remain latent in cells specific to each herpesvirus type. The presence of an antibody response gives a clue that the infection has taken place, but it is the cell-mediated immune response that is important in keeping the latent virus at bay.

Herpesviruses have developed immune avoidance strategies to prevent recognition by the immune system during the latent infection. When the cell-mediated immunity is weakened, for example by infection with HIV or immunosuppression after transplantation, latent herpesvirus can reactivate. Some herpesviruses are also associated with malignancy.

α-Herpesviruses

Although HSV-2 is the predominant cause of genital herpes, HSV-1 is becoming increasingly important in high-income countries. Neonatal herpes has a high mortality, both untreated (60%) and treated (25%); neonates who survive often have significant long-term sequelae. The major risk factor for neonatal herpes is primary acquisition of genital herpes during the third trimester, owing to the lack of protective maternal HSV-specific antibodies.

The currently available antiviral therapies aciclovir (and its prodrug valaciclovir) and famciclovir are effective at reducing clinical disease; however, they have not been shown to reduce viral shedding. In immunosuppressed patients exposed to long courses of aciclovir, and patients requiring long-term suppressive therapy, resistance to aciclovir can develop, and further potential treatments are limited.

A novel target, the helicase–primase enzyme complex, has been identified with efficacy *in vitro*; Phase II trials have suggested clinical efficacy in patients with symptomatic proven HSV-2 genital herpes as well as a reduction in HSV shedding rate and

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Currently known human herpesviruses showing classification, latency sites and common presentations during primary infection and reactivation

Common name	Commonly used abbreviation	International approved nomenclature	Subfamily	Common presentations during primary infection	Latent sites	Examples of presentations during reactivation
Herpes simplex virus type 1	HSV-1	HHV-1	α	Mucocutaneous lesions (predominantly orofacial)	Sensory ganglia	Recurrent mucocutaneous lesions (predominantly orofacial), encephalitis
Herpes simplex virus type 2	HSV-2	HHV-2	α	Mucocutaneous lesions (predominantly genital)	Sensory ganglia	Recurrent mucocutaneous lesions (predominantly genital), recurrent meningitis
Varicella-zoster virus	VZV	HHV-3	α	Chickenpox	Sensory ganglia	Shingles (zoster)
Cytomegalovirus	CMV	HHV-5	β	Asymptomatic, infectious mononucleosis-like syndrome, congenital infection of fetus	Mononuclear cells, epithelial cells	Non-specific CMV syndrome, retinitis, oesophagitis, colitis, hepatitis, pneumonitis
Human herpesvirus 6A	HHV-6A	HHV-6A	β	Roseola infantum (exanthema subitum)	T cells	Encephalitis
Human herpesvirus 6B	HHV-6B	HHV-6B	β			
Human herpesvirus 7	HHV-7	HHV-7	β	Similar to HHV-6?, pityriasis rosea?	T cells	?
Epstein—Barr virus	EBV	HHV-4	γ	Asymptomatic, infectious mononucleosis (glandular fever)	B cells	Lymphoma (Burkitt's, Hodgkin's, non-Hodgkin's), post-transplant lymphoproliferative disease, nasopharyngeal carcinoma, oral hairy leucoplakia
Human herpesvirus 8/ Kaposi sarcoma-associated herpesvirus	HHV-8/KSHV	HHV-8	γ	Asymptomatic	Lymphocytes	Kaposi's sarcoma, primary effusion lymphoma, multicentric Castleman disease

Table 1

number/recurrence of herpetic lesions compared with placebo at higher dosing schedules.[1]

Numerous HSV-2 vaccines are in development; however, the glycoprotein D subunit vaccine GEN 003 has made the most progress in clinical trials as a therapeutic vaccine. It reduces the rate of lesions and, at higher doses, viral shedding.

In the UK, up to 95% of 10-year-olds have evidence of past exposure to varicella-zoster virus (VZV) not all of whom have had overt chickenpox. In tropical climates, exposure to VZV seems to be delayed until later childhood/adolescence; therefore migrants from these areas to more temperate climates are at risk of developing primary varicella infection in adulthood, with risk of more severe disease.

VZV-associated diseases place a significant burden on hospitals in the UK.[2] Herpes zoster resulted in 3.9 times more annual hospital days and 1.9 times greater total costs than for varicella; in addition, the case fatality rate was higher. However, this may be explained by the age of the population presenting with zoster rather than the disease itself.[2]

Herpes zoster is commonly complicated by chronic pain; however, meningoencephalitis, cerebellitis and VZV vasculopathy are increasingly recognized. VZV vasculopathy can lead to transient ischaemic attacks and stroke as well as cerebral haemorrhagic, multifocal vasculopathy and extracranial vasculopathy. A large UK case study identified an increased risk of stroke during the first 6 months after VZV infection/reactivation. This effect seemed to be reduced by treatment with aciclovir. The severity of these complications provides further evidence for the health and economic benefits of a zoster vaccine, and led to its introduction in the UK in 2013.

A major drawback of the currently available zoster vaccine is that, as a live attenuated vaccine, it is unsuitable for immunosuppressed patients. A subunit vaccine alternative has been pursued and has been evaluated in participants aged 50 or older in Phase III trials. It appears to be highly effective in reducing herpes zoster and postherpetic neuralgia compared with placebo, and was not associated with more significant adverse outcomes or death when comparing the two groups.

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