Herpesviruses: from the cradle to the grave

Paul D. Griffiths

Herpesviruses are prime contenders for inclusion in the microbiological ages of man since they infect humans at all life stages.

How many herpesviruses are there?

We now have eight human members of the herpesvirus family, grouped into three subfamilies (Table 1), which tend to share biological characteristics. The more recently described viruses are numbered systematically, while the older ones retain their colloquial names.

How do we know that they are herpesviruses?

The characteristics which define members of the herpesvirus family are listed in Table 2. An important common feature is that they can all establish latency so that they are not eradicated from the host following initial infection. Hence, the aphorism, '*What is the difference between love and herpes? Answer: herpes is forever!*' Periodic reactivations from the latent state allow these viruses to transmit to other individuals, e.g. VZV is infectious both when it causes chickenpox and when it reactivates decades later to cause zoster (shingles).

At what age do we acquire them?

Table 3 relates appearance of herpesviruses according to the 'Seven Ages of Man' (with apologies to W. Shakespeare). Some can infect a fetus *in utero* and many transmit to neonates/toddlers. Individuals not infected during childhood become exposed as adolescents and/or adults through salivary and/or sexual contact. Indeed, changing sexual practices mean that most first episodes of genital herpes are now caused by HSV 1 (Clinton–Lewinsky syndrome).

Most adults are infected with several herpesviruses (Fig. 1). Remarkably, most of these infections do not cause symptoms. They are either entirely asymptomatic or produce only mild, self-limiting discomfort which is not brought to medical attention. The only exception to this rule is VZV, which regularly produces symptoms in the form of the familiar chickenpox in the majority of children who acquire it (see Fig. 2).

How do herpesviruses make us sick?

Herpesviruses are normally kept in check by the immune system and so they have evolved a series of mechanisms to evade such responses. The net result is a balance between the virus and its host immune system leading to transmission of virus without (usually) producing disease. When diseases do develop, they are caused by a variety of mechanisms (Table 4).

In those with normal immunity

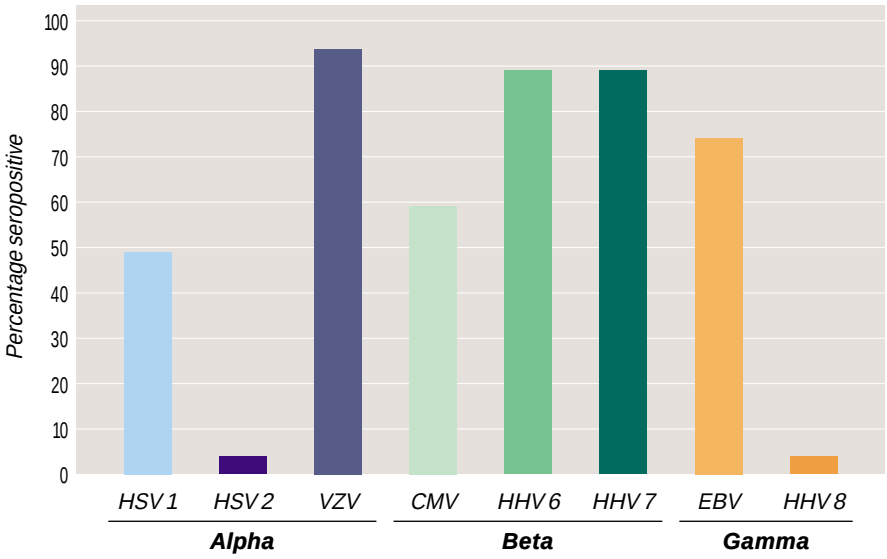
Herpesviruses are very important medically because they are common and produce disease in a substantial minority of cases. Some individuals develop overt disease, such as glandular fever following EBV, probably because they acquire large amounts of virus through the salivary–salivary route (kissing). Some unlucky people develop HSV encephalitis for reasons which are not understood. In the case of genital herpes, many reactivations are clinically silent, but others cause local ulceration which is painful and affects psychosexual well-being. The ulcers (even those which do not produce symptoms) reduce an important barrier of

Table 1. The human herpesviruses

Subfamilies	Common names	Systematic nomenclature	Major diseases
Alphaherpesviruses			
	Herpes simplex virus type 1 (HSV 1)	HHV 1	Cold sores, encephalitis
	Herpes simplex virus type 2 (HSV 2)	HHV 2	Genital infection, *erythema multiforme*
	Varicella zoster virus (VZV)	HHV 3	Chickenpox, zoster
Betaherpesviruses			
	Human cytomegalovirus (CMV)	HHV 5	Hearing loss, retinitis
	Human herpesvirus type 6 (HHV 6)	HHV 6	*Exanthem subitum*, febrile fits
	Human herpesvirus type 7 (HHV 7)	HHV 7	*Exanthem subitum*
Gammaherpesviruses			
	Epstein–Barr virus (EBV)	HHV 4	Glandular fever, Burkitt's lymphoma
	Human herpesvirus type 8 (HHV 8)	HHV 8	Kaposi's sarcoma

Table 2. Characteristics of herpesviruses

- Look similar by electron microscopy
- Initial infection usually gives no symptoms
- Establish latency, persist for life of individual
- Reactivate from latency, so transmitting to others
- Most of these reactivations also give no symptoms
- Re-infections with other strains also occur
- Each herpesvirus causes more than one disease
- Interfere with immune responses
- Important component of multi-factorial complex diseases



LEFT (TOP):
Fig. 1. Proportion of adults in the UK infected with each of the eight herpesviruses. Data are from multiple papers providing estimates of the proportion of adults aged 30–40 years who have IgG antibodies specific for each virus.

LEFT (BOTTOM):
Fig. 2. Chickenpox in the author's children. Number two son (aged 4) acquired chickenpox from school. Fourteen days later, number one son (age 6) acquired it from his brother, prompting this photograph which uses number three son (age 2) as an uninfected control. (He developed chickenpox 14 days after the photograph was taken.) All recovered without treatment or complications.
PHOTO PAUL GRIFFITHS

protection against acquiring HIV infection. CMV and HHV 6 also play a role by activating HIV replication, so increasing the risk of HIV trans-mission to sexual partners.

It is now known that herpesviruses also play a role in complex medical conditions which were not previously thought to have an infectious component. Thus, HSV is the cause of Bell's palsy (paralysis of the nerve on one side of the face) and is also the cause of *erythema multiforme*, a recurrent, painful, nodular rash caused by an immune response to reactivations of HSV.

In those who are immunocompromised

If the immune system is immature (fetus), or is compromised by immuno-suppressive drugs required to prevent graft rejection (transplant) or by HIV infection (AIDS), the delicate balance between virus and host is lost. Uncontrolled herpesvirus replication leads to local disease and/or widespread dissemination of virus, with life-threatening consequences. HSV and VZV cause extensive skin vesiculation; HSV, VZV and CMV cause pneumonitis, hepatitis or encephalitis; CMV frequently causes gut ulceration or retinitis. Furthermore, CMV triggers the immune system of transplant patients to cause rejection of the transplanted organ. Meanwhile, the oncogenic potential of the gammaherpesviruses is increased where EBV induces B-cell lymphomas and HHV 8 induces Kaposi's sarcoma or multi-centric Castleman's disease. In the fetus, the main pathogen is CMV, which causes mental retardation and/or hearing loss.

What can be done about herpesvirus diseases?

Treatment

Fortunately, antiviral agents able to control the worst ravages of herpesviruses have been developed over the last 20 years.

The symptoms of initial genital herpes resolve more rapidly and are less severe when patients are given acyclovir, valaciclovir or famciclovir. Patients with frequently recurring genital herpes have dramatic benefit from long-term prophylaxis, usually with acyclovir or valaciclovir. The chronic pain which follows shingles is also reduced significantly if treatment is begun in the acute phase.

The effects of HSV in transplant patients are routinely prevented by acyclovir prophylaxis given from the time of transplant onwards. Extension of prophylaxis to 6 months also protects against zoster. High-dose acyclovir reduces CMV disease in bone marrow transplant patients. Valaciclovir is potent enough to prevent CMV disease in renal transplant patients and also significantly reduces the graft

Table 3. Infection with herpesviruses during the 'seven ages of man'

Age	Source of virus	HSV	VZV	CMV	HHV 6	HHV 7	EBV	HHV 8
Fetus	Mother		+	+	+			
Newborn baby	Mother/family	+	+	+				
Toddler	Other toddlers	+	+	+	+	+		
Child	Other children	+	+	+			+	+
Adolescent	Kissing	+		+			+	+
Adult	Sex	+		+			+	+
Elderly	Self		+					

Table 4. How herpes viruses make us sick

Mechanism	HSV	VZV	CMV	HHV 6	EBV	HHV 8
Destroy cells	+	+	+			
Cause the immune system to over-react			+		+	
Act as component of complex disease	+		+			
Interact with HIV	+		+	+		+
Cause cancer					+	+

rejection caused by this virus. Ganciclovir prophylaxis reduces CMV disease in liver, cardiac and bone marrow transplant patients, but its marrow toxicity limits its overall benefit in the latter group. A recent report shows that the hearing loss caused by CMV can be reduced significantly if babies with symptoms at birth are treated with ganciclovir.

Even after 20 years of use, HSV resistance to acyclovir has not become a clinical problem in the general population because the viruses which escape from control of this drug are profoundly debilitated. Nevertheless, these 'puny' viruses can still cause diseases in patients with damaged immune systems. Thus, resistance is a small but significant management problem in transplant and AIDS patients, and the number of treatment options is severely limited.

Although these are examples of success, we need to do more. Drugs with better safety profiles, improved potency and the ability to treat resistant strains are required, particularly for CMV, and we need treatments able to control EBV.

Vaccines

A live, attenuated vaccine is being used in the USA to prevent chickenpox. Trial results show that a recombinant HSV vaccine can reduce (but not abolish) acquisition of genital herpes in women, although it has no effect in men. This result is disappointing because as much as one-third of HIV transmission in Africa might be reduced if the ulceration caused by genital herpes could be eliminated.

No other vaccine with proven efficacy against a human herpesvirus has been identified. A recent report from the Institute of Medicine shows that such vaccines should be highly cost-effective, and a CMV vaccine was put in its top priority category. This should stimulate an area held back more by neglect than by overwhelmingly complex scientific problems. Thus, once people realize the full clinical impact of herpesviruses, they will be more willing to invest in the development of vaccines with the eradication of herpesviruses from the human population being the ultimate target.

Further reading

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