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Herpesvirus Infections of the Central Nervous System

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Abstract

There are over 200 herpes viruses species, of which 10 affect humans. Each of these 10 herpesviruses has a unique clinical syndrome, but common to all is their ability to cause infection and pathology in the central nervous system. In this article, we disucss the epidemiology, clinical presentation, diagnostic modalities, treatment, sequelae and avaibility of vaccination of each of the following herpesviruses: Herpes simplex virus 1 (HSV-1) and 2 (HSV-2), Varicella zoster virus (VZV), Human Cytomegalovirus (HCMV), Human Herpesvirus 6A (HHV-6A), 6B (HHV-6B) and 7 (HHV-7), Epstein Barr virus (EBV), Human Herpesvirus 8 (HHV-8), and Simian Herpesvirus B.

Keywords

neurological infections

herpersviruses

virology

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Hippocrates described lesions which "crawl" on the skin, illustrating the derivation of the term herpesvirus from the Greek "to creep." Herpesviruses are widely disseminated in nature, and encompass over 200 species, of which 10 affect humans.[1] The broader Herpesviridae family was originally categorized into subfamilies in the 1970s, according to their distinct biological properties, as Alpha-, Beta- and Gamma-herpesviruses. In spite of knowledge

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gained from nucleotide and amino-acid sequencing, this classification is still applicable. The Alphaherpesviruses include Herpes simplex virus 1 (HSV-1) and 2 (HSV-2), and Varicella zoster virus (VZV); the Betaherpesviruses include Human Cytomegalovirus (HCMV), Human Herpesvirus 6A (HHV-6A), 6B (HHV-6B) and 7 (HHV-7); and the Gammaherpesviruses, Epstein Barr virus (EBV) and Human Herpesvirus 8 (HHV-8). All nine human herpesviruses cause neurological disease.[2] Additionally, a virus associated with non-human primates, B virus/ Simian herpesvirus B/ *Cercopithecine herpesvirus type 1*, is notable for causing disease in humans. The ten herpesviruses are discussed individually, in sections below.

All the Herpesviruses consist of a core containing linear double-stranded DNA, 124–295Kb in length, an icosahedral capsid, with a surrounding amorphous tegmentum and envelope.[1] The mature virions are relatively large, between 120–360 nm, and in the case of HCMV this is the largest viral genome known to infect humans. The genome includes 70 to 200 protein coding genes, and nucleic acid synthesis occurs in the nucleus.

The eminent British Scientist, James Lovelock, is known for remarking that "An inefficient virus kills its host. A clever virus stays with it."[3] The statement pertained to the intriguing property of all herpesviruses to maintain their genome in a host for a lifetime. This is termed latency, and may lead to periodic reactivations that may be entirely asymptomatic or lead to clinical disease. The most common example of this is 'cold sores,' oral lesions that may represent Herpes simplex virus 1 or 2 reactivation. Neurological disease may be seen in the context of both primary infection and reactivation. An understanding of herpesvirus latency is essential to interpreting diagnostic testing as part of the management of cases.

This paper provides a practical approach to the evaluation, diagnosis and treatment of neurological herpesvirus infections. There is also reference to the future direction of research.

Human Herpesvirus 1/ Herpes Simplex Virus 1

Human herpesvirus 1 or Herpes simplex virus 1 (HSV-1) is a leading cause of neurological infections worldwide, and the chief identified etiology of sporadic encephalitis in the western world.[4,5] The virus is ubiquitous, and highly neurotropic, with devastating consequences in affected patients.[2] This section focuses on clinical aspects in immunocompetent adults, although other patient groups are discussed.

Key messages:

- HSV-1 CNS infection can have a non-specific presentation and therefore requires a high index of suspicion, with early commencement of intravenous acyclovir [6].
- Clinicians should consider a repeat lumbar puncture (LP) for HSV-1 PCR if the first PCR is negative, as there may be a false negative result early in the course of the disease [7]

HSV-1 and -2 were the first human herpesviruses to be discovered.[1] In 1968, Nahmias and Dowdle identified two viral antigenic subtypes, serotypes, of Herpes simplex virus, distinguishing HSV-1 and -2 with contrasting biological properties and susceptibility 'above and below the belt,' respectively.[8] Nonetheless, to date, several questions remain to be answered. In particular, the impressive capacity of the virus for latency and neurovirulence remains the subject of considerable research.[1]

Current estimates suggest that 3.7 billion people (67%) worldwide between the ages of 0–49 years are infected with HSV-1.[9] Seroprevalence studies suggest that infection is associated with increasing age, lower socio-economic status and geographic location.[10] Deep-sequencing approaches have facilitated the study of genetic polymorphisms, and confirmed

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that rarely it is possible for a person to be infected by multiple strains of the virus.[1] In Western countries, HSV encephalitis affects 1 in 250,000 to 1,000,000 per year.[4] It has a bimodal age distribution affecting young children and older adults, with no gender imbalance. In the small subset of patients that develop CNS infection, this may be associated with both primary infection and reactivation, typically differentiated by the presence of detectable HSV IgG in the serum in the context of reactivation.[2] Nonetheless, only 10% have evidence of recurrent herpes labialis, and conversely CNS invasion is very uncommon in patients with recurrent herpes labialis.

HSV-1 enters through mucosal membranes or skin abrasions from respiratory droplets or direct contact with a person excreting HSV-1, largely through the mouth in early childhood.[11] After initially replicating in epithelial cells, it may fuse with axon terminals of sensory nerve fibers of the peripheral nervous system (PNS), with subsequent retrograde transport to the sensory ganglion.[1,12] It is understood that there may be further replication in the sensory ganglion, and then host immune repression of the lytic or productive infection, to establish latent infection. Latent infection refers to a quiescent state in which gene expression is repressed and there is no detectable HSV-1 DNA. In a subset of neurons infected by HSV-1, there may be periodic reactivation, and this may lead to anterograde transport of the virus to the periphery, which may lead to asymptomatic shedding or visible lesions. The route of entry continues to be debated, with evidence to implicate direct entry through olfactory nerves consistent with pathology seen in the limbic system, and through the trigeminal ganglia. It is notable that recent evidence suggests that CNS invasion is associated with genetic defects, and is more common in immunosuppressed patients.[13] These patients may present atypically and demonstrate progressive deterioration.

The considerable individual variability in the natural history of HSV-1 infection is likely due to differences in the virus, the environment, and the host. Host suceptibility is clear from individual reports and case series of HSV-1 in patients with immunodeficiency syndromes, or treated with immunosupressive therapy such as Natalizumab and TNF Alpha inhibitors.[14,15] Studies of gene mutations implicate impairments in interferon signaling, such as STAT1 and NEMO.[16,17] Further, in apparently immunocompetent individuals, HSV-1 encephalitis has been associated with defective responses in Toll-like receptors. Humans are the primary host and reservoir for HSV-1; however, mice share several cell receptors, and mice models have been useful for studying disease. Knockout or supression models have confirmed genetic predispositions (e.g., Tlr3, Trif, Stat1), identified others (e.g., Myd88, Irf3, Irf7, Tlr9) and also improved understanding of the pathogenesis of disease.[18]

There has also been increasing acknowledgment of individual variation in infecting viral strains, ~2–4%.[19] Sequencing studies suggest there are at least three major clades, with suggested geographic clustering and recombination. Metagenomic approaches will improve our understanding of pathogenesis of infection, and response to treatment.

The classic clinical presentation of HSV-1 is an encephalitis, or meningoencephalitis. Patients present acutely (<1 week) with fever, headache, confusion and/or altered consciousness. They may also exhibit a variety of focal neurological deficits, including hemiparesis, dysphasia, aphasia and focal cranial nerve palsies.[20] Autonomic features, such as urinary and fecal incontinence are also seen.[2] Patients may also experience respiratory and gastrointestinal symptoms. HSV-1 is acknowledged to have a predilection for the frontal and temporal lobes, particularly the mesial temporal lobe, leading to emotional and behavioral manefestations. This has a range of presentations, including hypomania, amnesia and Kluver Bucy syndrome.[21,22] Rarely, a brainstem encephalitis has been described, with neuro-opthalmological features and focal cranial nerve palsies.[23] None of the described clinical

presentations are perfectly sensitive or specific, and there are frequently delays in diagnosis and instigation of appropriate treatment. Equally, front-line clinicians responsible for the initial management may never have seen a case before.

HSV-2 is more commonly associated with a meningitis syndrome. However, it is increasingly acknowledged that HSV-1 may rarely present as both acute and recurrent 'Mollaret's syndrome.'[24] These are discussed further in the section on HSV-2. Lastly, HSV-1-associated myelitis is a rare presentation, and has been described in case reports.[25,26] The reports suggest that infection of the thoracic cord is more frequently seen, and that initial HSV-1 PCR may be negative.[25,27]

CSF examination typically demonstrates a lymphocytic pleocytosis, with a slightly raised protein and normal glucose. CSF testing for HSV-1 DNA by PCR is the mainstay of diagnosis of HSV-1, and is highly sensitive and specific.[20] Nonetheless, false negatives are seen early in the disease process, and if there is high suspicion, a repeat LP should be performed. Skin lesions are rarely seen, but should also be tested if present. Brain biopsy should be considered in cases that remain undiagnosed, and recent case reports have demonstrated a role for unbiased next generation sequencing.[28,29] EEG findings include spike and slow-wave activity, and periodic lateralised epileptiform discharges. These findings are no longer considered pathognomonic for HSV-1 encephalitis, but may have a role in unidentified patients who have subtle motor or non-convulsive status epilepticus. Lastly, an HIV test should be performed in all patients.

Brain imaging is essential for multiple reasons: to assist with the diagnosis, to survey the extent of damage to inform prognostic information and neurorehabilitation, and also to establish a baseline. It is generally acknowledged that CT is ~50% sensitive, and MRI almost 100%. In contrast, one study reported inter-rater agreement between CT and MRI; however, this may be related to the patient group included.[30] MRI with diffusion-weighted imaging (DWI) remains the imaging modality of choice. Findings typically include assymetrical frontotemporal changes, sometimes with associated mass effect, and leptomeningeal enhancement.[30,31] More diffuse patchy areas of diffusion restriction are also seen, suggesting cytotoxic injury, and more advanced cases exhibit necrosis and parenchymal hemorrhage.

The mainstay of treatment is intravenous acyclovir, and this should be administered as soon as possible, at a dose of 10mg/kg three times a day.[6] Penetration of acyclovir across the blood-brain-barrier (BBB) is not entirely clear, although it is suggested to be improved in HSV-1 encephalitis due to increased permeability. Ideally, treatment should be delayed until after an LP has been performed; however, if not done within 6 hours of presentation then acyclovir should be started. Acyclovir reduces mortality to less than 20%; however, delays in administration continue to be seen. If the diagnosis is confirmed, treatment should continue for 2–3 weeks. Guidelines recommend repeating the LP at day 14–21; however, this is a contentious issue and is not always considered necessary. An RCT evaluating the role of an extended 3-month course of Valacyclovir did not demonstrate a improvement in outcome.[32] A multi-centered clinical study evaluating the role of adjuvant steroids is currently ongoing in the UK (https://doi.org/10.1186/ISRCTN11774734).

Resistance to acyclovir is rare, and is more frequent in immunocompromised patients. In these cases, gancivloir or foscarnet may be used.[33,34] These drugs are known to inhibit HSV-1 in vitro; however, their efficacy against HSV-1 neurological infections is less clear.

A fundamental gap in our armamentarium against HSV-1 is the availability of a vaccine. In view of the challenges in diagnosing and managing the disease and the associated

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poor outcomes, it is a vaccine that will have the greatest effect on the devastating corollaries of the disease.[35]

Human Herpesvirus 2/ Herpes simplex virus 2

In contrast to many texts, HSV-2 is presented here as a separate section. While the two viruses are very similar, with 83% genetic homology and significant antigenic cross-reaction, there are important differences in their clinical presentation.[1] HSV-2 infects an estimated 417 million people aged 15–49 years (11.3%) worldwide, with ~19 million new cases in 2012 (11.3%).[36] Evidence suggests that primary HSV-2 infection is associated with the advent of sexual activity.[37] The highest prevalence is recorded in Africa, followed by Asia, and it is consistently higher in females compared with males.[36] The burden of disease is largely genital herpes, however the virus may infect 'above the belt' and there are notable CNS manifestations.

Our knowledge of neurological disease has advanced with type-specific molecular assays.[33] Approximately 5–10% of cases of herpes simplex encephalitis are caused by HSV-2. Additionally, a recent nested cross-sectional viral genotyping study suggests that 7% of HSV-2 infection involves dual-strains.[38] The virus typically presents as a meningitis, either acutely or as a recurrent 'Mollaret syndrome.'[2,24] HSV-2 acquisition is usually the result of transmission by genital contact, with infection of epithelial cells in the anogenital region, and then retrograde transport to the sensory ganglia.[1] In contrast to HSV-1, sacral ganglia are the main site of latency. CNS disease may be a result of either primary infection or reactivation.

Host susceptibility to HSV-associated CNS infections have been studied more extensively for HSV-1. Studies of HSV-2 genital infection have implicated similar pathways as those for HSV-1, such as the activation of NK cell and the type 1 interferon response.[39,40]

CNS complications of HSV-2 infection are more frequently described in immunocompromised individuals, particularly in the context of HIV infection.[41–43] Presentations include recurrent headache, acute or recurrent meningitis, and rarely, meningoencephalitis, encephalitis or transverse myelitis.[2,24,33] These findings are confirmed in mouse models, in which neurovirulent strains of HSV-1 cause encephalitis, and HSV-2 causes meningitis.[18]

Cases of meningitis present with characteristic features including fever, headache, back-pain, photophobia, neck stiffness nausea and vomiting. Only 10–20% of cases have visible genital lesions at presentation, although it is notable that genital examinations are frequently omitted during the clinical assessment of patients.[44,45] It is difficult to accurately study the risk of recurrence, but it is suggested that recurrences are less frequent with increasing time from the primary infection. HSV-2 infection is rarely associated with an encephalitis or meningioencephalitis syndrome, and a variety of presentations have been published in case reports and case series.[46] It is notable that there have been inconsistencies in the literature due to lack of clear case definitions of the syndrome. Evidence from case reports also suggests an association of HSV-2 with strokes.[47]

The diagnosis and treatment of encephalitis or meningoencephalitis is the same as that for HSV-1. In the context of HSV-2-associated meningitis, imaging in adult cases typically demonstrates leptomeningeal enhancement; however, there may be no abnormality detected.[48] The evidence for the treatment of meningitis is scant, but acyclovir is still the mainstay of management.

Meningitis has typically been considered benign, although there is now clear evidence of long-term morbidity. A recent multicenter study demonstrated a reduction in scores

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reflecting quality of life and disability, and this was worse for HSV-associated meningitis compared with other viral etiologies.[24]

Varicella Zoster Virus

Key messages:

- VZV is associated with vascular pathology, both during acute infection and in the 6 months following infection.
- Acute primary VZV or reactivation of VZV can cause encephalitis, particularly of the cerebellum. Diagnosis is through imaging and the detection of VZV DNA in the CSF.

Varicella Zoster Virus (VZV) is an alphaherpesvirus, in the genus Varicellovirus. VZV causes two distinct clinical syndromes: primary infection causes varicella (chicken pox), whereas reactivation leads to herpes zoster (HZ) (shingles). VZV establishes latency in dorsal root ganglia and cranial nerve root ganglia, and waning cell-mediated immunity allows viral reactivation which manifests as lesions in a dermatomal distribution. It was this presentation that facilitated the mapping of cutaneous dermatomes in the early 20th century[1]

VZV is predominantly transmitted via the inhalation of aerosolized virus particles, with some transmission occurring through contact with the skin lesions of varicella or HZ. Varicella is a seasonal disease in temperate climates, with the highest incidence seen in winter and spring, and cycles of outbreaks occur every 2–5 years. In temperate climates with no vaccination, over 90% of individuals are infected before 12-years-old, which contrasts with tropical climates where the proportion of seropositive individuals only reaches this level in adulthood.[49] In HZ, latent VZV in the dorsal root ganglia reactivates and travels along the sensory nerve. It shows no seasonal pattern, but clearly demonstrates age as a major risk factor, reflecting declining cell-medicated immunity. The probability of HZ before the age of 45 years is 10.5% for women and 8.6% for men, increasing to a lifetime risk in individuals over 45 years of 22% for men and 32% for women.[50] In addition to sex and age, other risk factors for HZ include immunosuppression: HIV-infected individuals, those with cancer, and transplant recipients have a 3 times higher HZ incidence than those without these conditions.[51] Diabetes, female gender, psychological stress, genetic polymorphisms, physical trauma and white ethnicity are additional risk factors.[52] Recently, mutations in genes that code for the subunits of RNA polymease III have been identified as being associated with severe VZV infection.[53]

In children, the most common CNS complications of varicella are encephalitis and cerebellitis, occurring in 1:1000 cases of pediatric varicella.[54] VZV was the leading cause of viral encephalitis in immunocompetent children in two large studies, in which there were no fatalities.[54] Cerebellitis in children usually occurs around 1 week after the onset of the rash, but can also occur several weeks later. Children present with a wide-based gait, dysarthria, headache and vomiting and, less commonly, meningeal irritation. MRI findings in children with cerebellitis most often include bihemispheric bright signal on FLAIR or T2-weighted imaging with diffuse parenchymal swelling. Leptomeningeal enhancement is seen in severe cases, with additional signs of hemorrhage and restricted diffusion.[55] Confirmation is through the identification of VZV DNA by PCR in the CSF. CSF usually also demonstrates a pleocytosis and elevated protein. Debates persist about whether this syndrome is immune-mediated or viral-driven, but treatment with acyclovir is standard. A complete recovery is usual, although behavioral disorders and hearing impairment in children have been reported.[54] There is a 4-fold increased risk of stroke in children in the 6 months after chicken pox.[56] In adults, VZV encephalitis in the immunocompetent is rare but has been described.[57]

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Long term neurocognitive impairment or behavioral changes have also been reported. Sequencing of VZV isolates from immunocompromised and immunocompetent adults with zoster, meningitis and encephalitis revealed that zoster and meningitis, which are considered benign conditions, arise from single or few virions. Encephalitis, a condition with more long-term sequelae, arises from primary infection with, or reactivation of, multiple virions.[57] The risk of stroke after varicella in adults is increased, although not to the same extent as seen in children.[56]

HZ most commonly occurs in the thoracic and lumbar dermatomes, and manifests as erythematous papules which progress to vesicles or bullae over 3–4 days. Occasionally, these vesicles appear pustular or hemorrhagic, including in immunocompetent hosts, but most resolve and crust over by day 7–10. Prodromal pain ("burning," "throbbing," or "stabbing") in the affected dermatome occurs in 75% of patients, and can occur days to weeks before the rash.[58] Occasionally, allodynia or itching are described.[58] Systemic symptoms (headache, fever, malaise) occur in fewer that 20%. Usually a single dermatome is affected, with occasional signs in one or two surrounding dermatomes. In immunocompromised patients, multiple dermatomes can be affected with more severe lesions and organ involvement (pneumonitis and hepatitis), and is associated with a higher mortality. The presentation with only pain but no rash is called "zoster since herpericum." Muscle weakness occurs rarely with HZ, and is isolated to the region of the affected dermatome, explained by a myelitis at the same level: leg weakness in the case of HZ in the lumbosacral region, arm weakness in cervical HZ, neurogenic bladder and anal sphincter weakness in sacral HZ.[59]

In cranial nerve HZ, the trigeminal ganglion is most commonly involved, and symptoms depend on the branch of the trigeminal nerve involved. Herpes Zoster Opthalmicus (HZO) often presents with a prodromal illness of fever, headache and unilateral eye pain, with pain or hyperesthesia of the forehead. Lesions appearing on the tip or side of the nose (Hutchinson Sign) indicate that the nasocilliary branch of the trigeminal nerve, which innervates the cornea, is involved. These patients often have keratitis, which can scar leading to long term visual impairment: prompt recognition and treatment of HZO are necessary. Ramsay Hunt Syndrome (RHS) describes the triad of ipsilateral facial paralysis, ear pain and vesicles in the auditory canal. RHS has been attributed to reactivation in the geniculate ganglion and involvement, predominantly, of the 7^{th} and 8^{th} cranial nerves, although the 5^{th}, 9^{th} and 10^{th} are frequently also involved. Consequences of RHS can include deafness and Bell's palsy. Pain from HZ after the rash has disappeared is the most common complication, termed post-herpetic neuralgia (PHN). PHN lasts for longer than 3 months in 15% of patients, and is more severe in the immunocompromised and with advancing age.[52] An increased risk of stroke for up to a year after HZ has been demonstrated in multiple studies, has been summarized in a systematic review.[60]

Acute retinal necrosis (ARN) caused by VZV presents with eye pain, reduced vision and photophobia. Progressive outer retinal necrosis (PORN) presents with sudden painless loss of vision, or floaters and constricted visual fields. Both, if untreated, can lead to blindness from retinal scarring, optic atrophy or, in the case of PORN, retinal detachment. Examination of the fundus reveals peripheral whitening and central vasculitis with optic nerve edema and "vitreous haze" indicating vitritis. Intra-ocular ganciclovir and intravenous acyclovir are treatments of choice for both; without treatment, the other eye is affected within a month in one-third of patients.

In addition to the increased risk of stroke after chicken pox or HZ mentioned above, vasculopathies associated with varicella have been recognized for 50 years. In CNS VZV vasculitis, older patients commonly present with fever, headache and altered mental status

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after a recent episode of HZ. CSF reveals both red and white blood cell pleocytosis (usually <100 cells/cm^3), and MR or CT angiography demonstrate vasculitis (focal arterial stenosis or bleeding) and/or infarcts in the white and/or gray matter. These patients are often treated for autoimmune vasculitis because of a lack of rash or other features indicting primary or reactivation of varicella.[61] Spinal cord infarction, aneurysm, subarachnoid or intracerebral hemorrhage, arterial dissection, peripheral arterial vasculopathy, and temporal arteritis have been described as complications of primary VZV infection or reactivation.[7]

Congenital varicella syndrome (CVS) manifests as an infant born with hypoplastic limbs, chorioretinitis, cataracts, limb scarring and neurological abnormalities (microcephaly, hydrocephaly, developmental delay). CVS occurs in 0.4–2% of infants born to mothers with primary varicella in the first 20 weeks of pregnancy, although there is no evidence that HZ during pregnancy leads to CVS. Varicella immunoglobulin (VZIG) is used as post-exposure prophylaxis (see section on treatment)

Guillain-Barré Syndrome is a rare complication of VZV infection, occurring predominantly after an episode of HZ, and less frequently after acute varicella.[62]

The diagnosis of varicella can be confirmed by a vesicle swab which is tested for VZV DNA by PCR. Similarly, HZ can be diagnosed by a vesicle swab for VZV DNA. Complicated infections such as CNS presentations can be diagnosed by collection of CSF which is tested for VZV DNA by PCR, where the CSF often shows a lymphocytic pleocytosis and elevated protein. VZV CSF viral load is associated with the severity of the neurological symptoms.[54] In encephalitis or cerebellitis, testing the CSF for VZV DNA has a high sensitivity. In vasculitis, the sensitivity is as low as 30%. The detection of intrathecal VZV antibodies can be used when the PCR is negative (e.g., in late diagnosis). The use of Reiber's formula allows correction of blood brain barrier disruption during an acute infection by using contemporanous VZV antibodies and total albumin in serum and CSF to calculate an index.[63] Serological diagnosis of primary varicella or reactivation is not useful, except potentially in primary infection in children. For ophthalmic involvement, such as in ARN, vitreal sampling can reveal VZV DNA, but a lesion swab or tear sample can confirm the less localized syndrome HZO.

Primary varicella in immunocompetent children is often a self-limiting condition and does not require treatment. Immunocompromised children and adults, as well as immunocompetent adults, are more likely to suffer complications, and anti-viral medication is recommended. Patients with CNS involvement (myelitis, cerebellitis, infarction, encephalitis) are treated with IV acyclovir, the duration of which may depend on clinical response, usually a minimum of 14 days.[64] Higher doses of acyclovir are used, since the virus is less sensitive to acyclovir than HSV is. IV therapy is preferred over oral therapy since oral bioavailability of acyclovir is poor, and CNS levels are only 50% of plasma levels.[54] Oral valacyclovir, the pro-drug of acyclovir, reportedly achieves equivalent serum levels IV acyclovir, however there is a lack of evidence of its efficacy as an acyclovir alternative in CNS infections. Oral valacyclovir is commonly used to treat HZ since it can be taken three times a day rather than acyclovir's five times a day. Acyclovir resistance is rare, but has been seen in immunocompromised patients in whom the antiviral drug foscarnet (given IV) has been used as an alternative. Famciclovir (a pro drug of pencilovir which has a similar mechanism of action to acyclovir) is another alternative with excellent bioavailability but limited evidence to support its use.

VZIG is recommended by the CDC and Royal College Obstetrics and Gynecology (RCOG) as post-exposure prophylaxis for individuals at risk of severe infection or sequelae. Pregnant women with no evidence of immunity, immunocompromised individuals, and

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newborns of mothers with varicella immediately before or after delivery are offered VZIG. VZIG is only used as prevention and has no efficacy as treatment for varicella or HZ. Vaccination in childhood to prevent primary varicella is routine in several countries, and utilizes the live attenuated Oka vaccine. This live vaccine has caused severe infection in immunocompromised children to whom it was erroneously administered. To prevent HZ in older adults, the same Oka live attenuated strain is used but with a 14 times larger dose, reducing the incidence of HZ by 51% after 3 years. In countries where the vaccine is routine, hospitalization, morbidity and mortality from all forms of VZV infection has been reduced significantly.[54] Treatment of HZ with antivirals improves acute neuritis and duration of lesions, although there is little evidence to show a reduced risk of PHN. Antivirals include acyclovir, valacyclovir or famiciclovir; the latter two are often preferred due to a lower tablet burden, attributed to higher bioavailability. PHN requires treatment with tricyclic antidepressants (amytriptyline), antiepileptics (gabapentin, its prodrug pregabalin, carbamazepine, levetiracetam), topical analgesics (lignocaine patches, capsaicin) or opioid analgesia. Meta-analyses have shown that there is no evidence to support the use of steroids in preventing PHN, and that use of antivirals during acute HZ do not reduce the risk of PHN.[65]

Epstein-Barr Virus

Key messages:

- EBV encephilitis is thought to be a more benign syndrome than other herpes virus encephalitides. The infection is self-resolving with no reported sequelae.
- Primary CNS lymphoma is associated with EBV infection. This can present with symptoms of a space occupying lesion.

The disease infectious mononucleosis (IM) was first named in 1920, and the causative agent was identified by Anthony Epstein and Yvonne Barr in 1964 when they identified viral particles in cultured cells from a patient with Burkitt's lymphoma.[1] These viral particles were named Epstein-Barr virus (EBV) and were later noted to infect and immortalize human B lymphocytes in culture, adding to the theory that EBV caused Burkitt's lymphoma. EBV was the first tumor virus identified, and has subsequently been associated with several B cell lymphomas; Hodgkin lymphoma, X-linked lymphopfoliferative disease type-1, diffuse large B cell lymphoma, post-transplant lymphoproliferative disease (PTLD), and epithelial cancers; nasopharyngeal cancer and gastric cancer.[66] It is also the most common persistent and asymptomatic infection in humans; an estimated 90–95% of adults are seropositive.

Two main types of EBV circulate, type-1 and type-2. Through airborne and intimate contact (i.e., kissing) EBV infects epithelial cells with a predominantly lytic infection before establishing non-cytopathic latency in B cells. Most patients recover completely from acute primary EBV infection, or IM, although around 10% will have fatigue that persists for 6 months or more. It has been suggested that an aseptic meningitis is a common and predominantly undiagnosed self-resolving complication of IM.[67] Acute infection leading to encephalitis occurs in 0.05 cases per 1,000,000 per year,[68] and has been identified as the cause of acute encephalitis in 5% of patients.[69] EBV-encephalitis is thought to be a more benign encephalitis than that of the other herpesviruses. The pathophysiology is unclear; direct viral invastion, immune complex deposition or post-infectious autoimmune response have been suggested. The presentation is most commonly that of fever with altered metal status, although case studies have also described atypical presentations, including a slow onset focal neurological deficit with behavioral change, or an opsoclonus-myoclonus syndrome which, in one case, followed 10 days after the classic sore throat, fever and rash of

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Volume Number: 39; Issue Number: 3
IM.[67] Acute cerebellar ataxia and acute disseminated encephalomyelitis have been described in both acute primary EBV infection (diagnosed serologically with EBV DNA as well as in the CSF), and chronic relapsing EBV infection signified by high EBV DNA levels detected in the CSF.[68] Post-mortem studies have confirmed EBV as the cause of encephalitis, describing diffuse parenchymal white matter infiltrates with EBV-infected B- and some T-cells, though the pathophysiology of most of these cases remains unclear. The vast majority of patients with EBV encepalitis presented in case series have a complete resolution of neurological symptoms.[70] In the few cases reported, poor outcomes have occurred due to brain edema causing raised intracranial pressure.[71] In one case series of 10 patients with EBV encephalitis, 4 had persistent neurological morbidity; most of these were behavioral issues or developmental delay, and one was upper limb paresis.[70] Treatment modalities for EBV encephalitis are controversial. Corticosteroids and acyclovir have been used, but since acyclovir has no effect on the clinical and virological outcomes of IM, their use is likely to be of limited value in neurological presentations.[72]

In patients who have undergone stem cell or bone marrow transplant, EBV can lead to PTLD. CNS-specific PTLD can occur in ~4% of stem cell transplant recipients.[73] Definitive criteria are through biopsy of any CNS lesion but, if not available, one can use a combination of EBV DNA detected in the CSF, CSF cells revealing monoclonality or morphology consistent with PTLD, abnormal (or normal) imaging, and the absence of an alternative diagnosis.[73] Treatments include a reduction in immunosuppression, rituximab, chemotherapy and an infusion of donor lymphocytes or EBV-specific cytotoxic lymphocytes.

In HIV-infected individuals, primary CNS lymphomas (PCL) are almost always EBV-positive. Patients with PCL commonly present with symptoms of a mass lesion (focal neurology, neuropsychiatric symptoms, signs of raised intracranial pressure or seizures), and less commonly with the “B-symptoms” of lymphoma. Neuroimaging will reveal a well-defined lesion which is usually isodense or hypodense and enhances with contrast. PCLs rarely involve the posterior fossa. Diagnosis is ideally through biopsy, though in HIV-infected individuals the presence of EBV in the CSF combined with classic imaging and a low CD4 count can be sufficient.[74] Treatment of HIV-infected individuals is with high-dose methotrexate, corticosteroids and in some situations radiotherapy, alongside antiretroviral therapy.[74] EBV is not usually involved in the pathology of PCL in HIV-negative patients.[75]

There is clear evidence of an epidemiological association between Multiple Sclerosis (MS) and EBV infection; however, pathological evidence which explains this is unclear and the role of EBV in MS remains and controversial.[67] As with several other herpes viruses, acute EBV has an association with the development of GBS.

Human Herpesvirus 5/ Human Cytomegalovirus (HCMV)

Human herpesvirus 5/ Human cytomegalovirus (HCMV) is a ubiquitous Betaherpesvirus with the largest genome of viruses known to infect humans. It is the leading infectious cause of congenital disease, with intrauterine transmission in around 0.7% of pregnancies worldwide, with 12–25% of infections resulting in sensorineural hearing loss.[76] This section will focus on neurological disease, and how this relates to the ability of the virus to cause opportunistic infections in the face of poor T cell function.[1]

Humans are the only reservoir for HCMV, and the seroprevalence is ~60% in adults in developed countries, and 100% in developing countries.[2] This high prevalence poses a particular problem for immunocompromised individuals, for whom HCMV infection ranges from asymptomatic to life threatening. This became apparent during the AIDS epidemic, when one third of brain autopsies were noted to demonstrate HCMV infection. However

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Volume Number: 39; Issue Number: 3
currently, in clinical practice, this is most relevant in solid organ and hemopoietic cell transplant recipients.

HCMV neurological infection typically results in a subacute or chronic encephalitis; however, there are no pathognomonic features of disease.[2] Patients may present with confusion, disorientation, seizures and focal neurological signs. A rapidly fatal course has been reported, with necrotizing periventricular encephalitis.[77]

HMCV serology (CMV IgM and IgG) should be performed in immunocompetent patients, and as screening prior to transplant. The mainstay of diagnosis is quantitative HCMV PCR.[2,78] However positive results should be interpreted with caution, used in the context of the clinical presentation, repeat HCMV DNA levels, and other investigation results such as imaging. It is not uncommon for patients to have a low level HCMV viremia in the context of immunosuppression.[79] Detection of CMV DNA in the CSF is more specific for CNS involvement. Lastly, end-organ damage may be detected on biopsy, demonstrating the classic owl's eye inclusion bodies on histopathology (Fig. 1), HMCV DNA detection by PCR or antigen staining. MRI may identify ventriculitis,[80] through evidence of subependymal curvilinear hyperintense lesions on FLAIR imaging,[81] white matter nodular signal abnormalities or focal atrophy.[82,83]

Management requires a multidisciplinary approach, with consideration of reducing immunosuppression or starting HAART, starting antivirals and monitoring HCMV viremia. For this reason, patients should ideally be referred to appropriate specialist centers. Currently liscensed antivirals have suboptimal CSF penetration, and the decision to treat may be affected by predicted side effects. Ganciclovir is typically first-line, but this may cause bone marrow suppression. Equally, foscarnet causes nephrotoxicity, and may result in electrolyte imbalances that predispose to seizures. Unfortunately, there is limited data that these treatments improve outcome. In patients who do not respond to treatment, it is important to consider investigating for treatment resistance.[84] Options in treatment resistant cases are minimal. Cidofovir is sometimes used in refractory cases, as is the potent immunosupressant Leflunomide, but these have poor CNS penetration[85,86] and there is limited evidence of efficacy.[87,88]

There has been a considerable amount of research focusing on novel therapeutics and vaccines. Letermovir was licensed last year for prophylaxis in stem cell transplant patients.[89] A vaccine administered to patients on a transplant list would represent a paradigm shift. Research has moved to 'second generation' vaccines, involving both humoral and cell-mediated immunity.[90]

Human Herpesvirus 6

Human herpesvirus 6 was first identified in 1986, cultured from peripheral blood mononuclear cells of patients with lymphoproliferative disorders and AIDS.[91] It was only in 2011 that the two variants, HHV-6A and -6B, were formally recognized as two distinct viruses.[1] HHV-6A and 6B have 90% nucleotide conservation, and 25–75% amino acid conservation.[1] The viruses are Betaherpesviruses, within the genus Roseolovirus, and primarily cause disease in young children and severely immunosuppressed adults.[92]

Several aspects of the viruses have complicated our understanding of their role in neurological disease. These include their ubiquitous nature, lack of distinction between HHV-6A and -6B on laboratory tests, their capacity to develop latency, reactivate asymptomatically, and integrate into the germ line.[92–94] It is for these reasons that there

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Journal ISSN: 0271-8235; Article ID Number: SIN-18-0092
Volume Number: 39; Issue Number: 3
should be considerable caution in the interpretation of 'positive' results. This is increasingly important with the use of multiplex PCR assays in clinical testing.[94]

Seroprevalence studies suggest that 70–100% of children worldwide are infected with HHV-6B by the age of 2 years. In contrast, HHV-6A has a low prevalence in developed countries, with a higher prevalence reported in Africa, and its role in disease remains unclear.[93,95] However, a recent study incorporating metagenomic next-generation sequencing (mNGS) suggests that HHV-6A may be underdiagnosed by current molecular methods.[96]

HHV-6 may be transmitted through respiratory secretions or saliva. As with other herpesviruses, HHV-6A and -6B are seen to result in latent infection, and therefore infection may be considered lifelong. Importantly, both viruses demonstrate a remarkable phenomenon of chromosomal integration. This involves the covalent incorporation of the viral genome into the subtelomeric region of human chromosomes (ciHHV-6). Studies in the UK and USA suggest that ciHHV-6 is seen in 0.2–1% of the general population, and 1% of live births.[92,97] HHV-6 DNA may be detected in these patients in any sample tested; however, there is no good evidence for risk of disease.

In young children, primary infection is largely asymptomatic, but children may develop a febrile illness with the sudden onset of a rash, Erythema Subitum or Sixth disease, and Roseola Infantum. In this age group, in most countries, infection may result in febrile seizures, with or without the onset of rash. These are predominantly benign, although there is some evidence that this is rarely associated with epilepsy.[93] In contrast, in Japan, HHV-6 infection is recognized to produce encephalitis in children, with almost half developing neurological sequelae.[98] Research suggests this may be due to a genetic predisposition.

The second group of patients at risk of HHV-6 encephalitis or meningoencephalitis are the severely immunocompromised, specifically human stem cell transplant patients, with higher risk in those receiving cord blood. These are considered reactivation of HHV-6 infection, since primary infection is rare in adults.[99] Characteristically, this involves a limbic encephalitis, but other presentations have been noted.[93] Notably, patients may also develop myocarditis, hepatitis, thrombocytopaenia and hemophagocytic syndrome.

Early in the course of infection, neuroimaging does not usually demonstrate any abnormality.[31,100] Later, the typical changes include mesial temporal and limbic T2 hyperintensitites,[31] and these may resemble HSV.[101]

Evidence of the effect of antivirals is limited to in vitro studies, and case reports.[102,103] First-line treatment involves lowering immunosuppression if possible, and administration of ganciclovir or foscarnet. However, this may be limited by side effects of the drugs, and the prognosis is poor.

Lastly, with the increasing use of immunosuppression, as well as improved diagnostic technology such as mNGS, it is expected that there will be an associated rise in HHV-6 neurological disease. It is likely that we will also soon be in a better position to recognize and treat the disease.

Human Herpesvirus 7

Key messages:

- HHV-7 is predominantly a self-resolving childhood infection; over 90% of adults have serological evidence of previous infection.

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Journal ISSN: 0271-8235; Article ID Number: SIN-18-0092
Volume Number: 39; Issue Number: 3

- Seizures, and less commonly hemiplegia, meningitis and encephalitis, have been described in HHV-7 encephalitis.
- HHV-7 encephalitis can be caused by reactivation in immunocompromised adult patients.

Human herpesvirus 7 (HHV-7) was first identified in 1990.[1] Its genome is closely related to that of HHV-6. Unsurprisingly, HHV-6 and 7 share other similarities; both are ubiquitous, both lead to the clinical syndrome exanthema subitum (ES), and both cause cell lysis during initial infection before establishing life-long latency. HHV-7 infects epithelial cells in the salivary gland before establishing latency in CD4+ T-lymphocytes.[1] Around 90% of adults have serological evidence of HHV-7 infection, and healthy adults secrete HHV-7 in saliva, leading to the most common transmission being from adults to children in the same household. The majority of seroconversion occurs in children aged between 6 months and 2 years,[104] and often occurs after HHV-6 seroconversion. Approximately 30% of individuals acquire HHV-7 later in life.[105] ES classically presents as fever followed by rash. Neurological presentations in the setting of acute HHV-7 in children have been described in case reports, predominantly including simple or persistent seizures, and less commonly hemiplegia, meningitis and encephalitis.[106] A recent summary of immunocompetent adults with acute HHV-7 and neurological signs included the following presentations: encephalitis with or without flaccid paralysis, acute myeloradiculopathy, encephaloradiculomyelitis, and acute myelitis.[107] In these patients, the diagnosis was made based on the absence of alternative diagnoses and the presence of HHV-7 DNA identified by PCR of CSF or, in two cases, a rise in HHV-7 antibody titers in the CSF, indicating intrathecal production.[107] The authors postulated that the illness was due to HHV-7 reactivation rather than primary infection in around half of patients. The challenge for diagnosing encephalitis or myelitis through the presence of HHV-7 in the CSF is that the virus has been detected in normal brain tissue from patients who died of unrelated causes in one autopsy series.[108] This finding requires further clarification since HHV-7 was thought to only establish latency in CD4 T-cells and not neural cells, indicating a potential tropism in alternative cell types. Focal neurological signs in HHV-7 CNS infections are usually consistent with focal findings on MRI, including signal hyperintensity on T1-weighted imaging and STIR sequences which enhance with gadolinium contrast.[109]

Acute primary HHV-7 infection can be diagnosed serologically. Seroconversion from HHV-7 IgG negative prior to the infection to HHV-7 IgG positive a week or more after the onset of the illness could indicate acute HHV-7 infection ;however, the preceding serum sample is rarely available. Testing the avidity of HHV-7 has been used; a low HHV-7 IgG avidity indicates an immature antibody and therefore primary infection which has likely occurred in the past 3 months.[106] Intra-thecal antibody production can be used to indicate an acute or reactivation of infection localized to the CSF.

Due to the rarity of serious or fatal HHV-7 infection in the CNS, there have been no randomized controlled trials of antivirals or adjunt medications. Treatment for HHV-7 CNS infections usually includes ganciclovir and / or intravenous immunoglobulin and methylprednisolone. In immunocompromised individuals, a reduction in immunosuppressant medication may be important in controlling a reactivation.

Human Herpesvirus 8

Human herpesvirus 8 (HHV-8) was the most recent herpesvirus to be identified and is associated with the development of the muco-cutaneous malignancy Kaposi’s Sacroma (KS) and the lymphoproliferatice diseases Castleman’s and Primary Effusion Lymphoma (PEL).

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Volume Number: 39; Issue Number: 3

KS was first identified in the late 19th century by Moritz Kaposi,[1] but it was not until 1994 that Chang et al identified a novel viral sequence from KS lesions in HIV-infected patients with advanced immunosuppression.[110] There are 4 major forms of KS: classic KS which affects elderly Mediterranean or eastern European individuals; endemic KS which causes disseminated lymphadenopathy in children in central/east Africa; iatrogenic KS which develops after immunosuppression treatment; or the most recognized epidemic KS due to advanced HIV or AIDS. HHV-8 can infect multiple cell types and causes either a lytic or latent infection. Latent infection with HHV-8 in B-cells in the setting of immunosuppression can lead to two B cell lymphoproliferative disorders; PEL and Castleman's disease. Both are rare diseases, and occur in patients with advanced HIV or other forms of immunosuppression. Castleman's disease can manifest as a single lymph node (in unicentric disease) or multiple lymph nodes (in multicentric disease (MCD)). Half of the cases of MCD are clearly associated with HHV-8 latent infection; the pathophysiology of HHV-8 negative MCD is not well understood.

The epidemiology of HHV-8 varies with geographical region, but seroprevalence overall increases gradually with age, leading to ~50% of the population being seropositive by age 50.[1] HHV-8 is detected in saliva and breast milk, and is horizontally transmitted within families. It is also sexually transmitted and has been iatrogenically transmitted in solid organ transplants.[111]

Rare cases of multicentric Castleman's disease affecting the brain have been reported. These lesions have predominantly been leptomeningeal, enhancing with contrast and difficult to differentiate from meningiomas.[112] Confirmation through biopsy is essential for these lesions, and treatment universally involves antiretroviral therapy for patients with HIV, if this has not already been instituted. Additional treatments include rituximab or chemotherapy with doxorubicin or etoposide.

Cases of KS in the brain have also been described in single case reports, and only in patients who are HIV-infected. KS lesions of the CNS can be single or multiple, and usually enhance with contrast, with surrounding edema.[113] Cases are predominantly diagnosed post-mortem. Treatment for KS usually involves antiretroviral therapy, with the addition of chemotherapy such as doxorubicin or danorubicin.

B Virus/ Simian Herpesvirus B/ Cercopithecine Herpesvirus Type 1

"Dr. W. B., 29 years old was engaged in experimental work on poliomyelitis. On Oct 22nd 1932 he was bitten on the dorsum of the left ring and little fingers at the terminal phalangeal joints by an apparently normal Macacus rhesus monkey. 3 days later, Dr. B. noticed pain, redness, and slight swelling at the sites of the bites. A lymphangitis developed and soon there was enlargement and tenderness of the left epitrochlear and axillary lymph nodes. In the afternoon of Oct. 28, he was admitted to the Third Surgical Service of Bellevue Hospital. His temperature was 101.4°F., the pulse was 90; physical examination revealed only the superficial redness and slight induration over the dorsum of the terminal phalanges of the left little and ring: fingers with an associated regional lymphangitis and epitrochlear and axillary lymphadenitis. In the course of the next few days he appeared to improve considerably.

On Nov. 1, 7 days after the first signs of infection of the: fingers appeared, he developed generalized abdominal cramps, which lasted for 2 days and were not associated with tenderness, rigidity, nausea, vomiting, or diarrhea. On Nov. 4, he developed marked hyperesthesia of the lower extremities associated with urinary retention. Physical examination at that time revealed a generalized hyperalgesia below the level of the umbilicus; the knee jerks and abdominal reflexes were absent; the ankle jerks and cremasterics were present. The Babinski sign was negative; there were no signs of meningeal irritation; the upper extremities were not involved. The following day, Nov. 5, there was flaccid paralysis of both lower extremities. A spinal puncture performed that day yielded a clear fluid under slightly increased pressure with no evidence of block. Microscopic examination showed 112 cells per c. mm., all monocytes, albumen +, globulin +, reducing body 75.9 mg. per 100 cc.; smears and culture of the fluid were negative.

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Volume Number: 39; Issue Number: 3

> On Nov. 5, after a neurological consultation by Drs. F. Kennedy and E. D. Friedman, the latter made the following note: "…There is a level at about D 7 to D 8 below which pain and temperature senses are diminished. Tactile and posterior column sense not seriously altered. Bladder retention..." During the next day, Nov. 6, the sensory level had ascended to D3, the ankle jerks were still present, and the upper extremities remained normal. On Nov. 7, …the temperature rose to 104.8°F. The following morning, Nov. 8, the temperature dropped to 99°F., but the patient looked very ill and complained of pain in the upper extremities. During the course of the day, hiccoughing developed and the respirations became slow and irregular. During the evening the respiratory rate diminished to six a minute; he became quite cyanotic, and was put into a respirator. About 75 minutes later he had a convulsion, with apparently laryngeal spasm, and lost consciousness. Pulmonary edema developed, the frothy fluid being pumped out through the mouth and nose. Despite partial aspiration of the fluid, and the application of supportive measures, he lived only 5 more hours."
>
> - Reproduced with permission from Sabin and Wright's original paper in 1932[114]

Following the tragic demise of Dr. B, pathologists set on identifying the presumed infectious cause.[114] Systematic investigation ensued, involving histopathology, filtration, cell culture and animal inoculation. A filterable virus obtained from his brain tissue was immunologically linked to HSV, and produced a similar disease in rabbits and a select species of monkeys.[2]

B virus is now known to be an alphaherpesvirus, endemic in macaque monkeys (e.g., rhesus macaques and cynomolgus monkeys), and the only simian herpesvirus species that is highly pathogenic for humans.[1] There is high seroprevalence in macaques by the age of 2.5 years.[115] For these reasons, it is an important occupational hazard for people working with monkeys. It must be suspected after exposure to macaques, either by a scratch/ bite or laboratory accident. Nonetheless, infection with B virus is exceedingly rare, and there have been ~50 documented human cases worldwide, of which 21 have been fatal.[116]

The incubation period in humans has been reported to be 2 to 35 days, and is typically within 21 days. Infection may present as a vesicular rash at the site of inoculation, ipsilateral lymphadenopathy, and progressive neurological symptoms.[117] Patients develop ascending myelitis, encephalomyelitis or encephalitis. Alternatively, a subset of patients develop a recurrent rash akin to herpes zoster.

Laboratory diagnosis involves serology and molecular detection, but these are usually only available in reference laboratories.[1,2] Immediate post-exposure management involves thorough cleaning, as well as consideration of treatment for rabies, tetanus and the adminstration of antibiotics. Prophylaxis should be considered with 14 days with valacyclovir 1 g three times a day or Aciclvoir 800mg five times a day. High risk exposures are those that involve deep punctures, lacerations to the head, neck or torso, or any contact with skin or mucous membranes if the monkey is unwell or confirmed to be shedding B virus. Patients that develop symptoms are treated with high dose intravenous acyclovir or ganciclovir for 2–3 weeks or until symptoms resolve. It is recognized that prophylaxis and treatment are based on in vitro antiviral activity, in vivo animal models, and case reports in humans.[117]

In summary, it should be kept in mind that there is a simian herpesvirus that causes potentially fatal encephalomyelitis in humans. This is rare but important, as it may be prevented and treated with antivirals.

Conclusion

Herpesviruses have co-evolved with humans for centuries. Most herpesviruses establish life-long latency and periodically reactivate, allowing onwards transmission but occasionally leading to an acute severe illness. Several herpesviruses infect neural tissue, leading to severe CNS disease or significant congenital damage. The challenge of diagnosing illnesses associated with herpesviruses lies in their latency: the presence of a herpes virus does not necessarily indicate that the herpesvirus is responsible for current illness presentation. In this

review, we have highlighted the main presentations, diagnosis and prevention methods for herpesviruses, with a specific focus on the central nervous system. Although there is a significant body of research available to understand the pathophysiology of herpesvirus infections, evidence-based treatment guidelines for the majority are lacking, and diagnostic modalities are limited. A combination of serological and virological diagnostics with personalized genomic medicine may provide a better understanding of this complex area in the future.

Conflicts of Interest

None of the authors have any conflicts of interest to declare.

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Fig. 1 (a and b) Brain biopsy from an adult male with advanced HIV and CMV encephalitis. Arrows highlight the typical "owl's eye" appearance of CMV inclusion bodies. (c) Brain biopsy from a neonate with CMV encephalitis.

Table 1 Herpesviruses with key clinical presentations, diagnosis and treatments

Virus	Common clinical presentation or syndrome	CNS disease or CNS complication	Diagnosis of CNS disease	Treatment	Vaccine or prevention
HHV-1/HSV-1	Oral stomatitis	Encephalitis or Meningoencephalitis	Clinical syndrome with HSV-1 DNA detected in CSF	Acyclovir or Valacyclovir	No
HHV2 / HSV-2	Genital ulcers	Encephalitis or Meningoencephalitis	Clinical syndrome with HSV-2 DNA detected in CSF	Acyclovir or Valacyclovir	No
Varicella Zoster	Chicken pox (varicella)	Cerebellitis or encephalitis. Note: increased risk of stroke for 6 months, particularly in children.	Clinical syndrome with presence of VZV DNA in CSF	Acyclovir can be used in cerebellitis but predominantly self-resolving. High-dose acyclovir for encephalitis.	Live vaccine available, licensed in some countries for children to prevent primary varicella.
	Shingles (herpes zoster)	Post-herpetic neuralgia (PHN), Ramsay Hunt Syndrome (RHS), Herpes Zoster Opthalmicus (HZO). Note: increased risk of stroke for 6 months.	Clinical diagnosis. Lesion swab for VZV DNA PCR	Anticonvulsants or tri-cyclic antidepressants. IV Acyclovir for RHS / HZO	Live vaccine available, licensed in some countries for children to prevent HZ in older adults.
	Congenital varicella syndrome (CVS)	Developmental delay, microcephaly / hydrocephalus	Varicella in pregnancy diagnose	No treatment for infants with CVS.	Prevention with varicella zoster immunoglob

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		multiple optic abnormalities	d clinically, serologically or lesion swab for VZV DNA PCR		ulin.
Epstein-Barr Virus	Glandular fever, infectious mononucleosis	EBV-encephalitis Post-transplant lymphoproliferative disease (PTLD), Primary CNS lymphoma (PCL)	• Imaging in PTLD or PCL • CSF cell morphology for PTLD • Presence of EBV DNA in CSF.	• Rituximab/lymphocyte infusion and reduce immunosuppression for PTLD • Methotrexate, steroids and radiotherapy for PCL (+/– ART if HIV positive) • Possible use of acyclovir in EBV-encephalitis	No vaccine or prevention
HHV-5/HCMV	Congenital disease	Encephalitis or meningoencephalitis	HCMV DNA detected in CSF	Ganciclovir or Foscarnet	Vaccine in development
HHV-6a/HHV-6b	CNS disease in imunosupressed patients	Encephalitis or meningoencephalitis	HHV 6 DNA detected in CSF	None	No vaccine or prevention
HHV-7	Erythema subitum	HHV-7 encephalitis / myelitis	HHV-7 in CSF, imaging, serology (peripheral and intrathecal)	• Ganciclovir • Methylprednisolone • Intravenous immunoglobulin	No vaccine or prevention
HHV-8/KSHV	Kaposi's Sarcoma Primary effusion	CNS KS lesions CNS lesion of multicentric	Biopsy	• Antiretroviral therapy if HIV-infected. • Chemotherapy	No vaccine or prevention

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	lymphoma Castleman's disease (multi or unicentric)	castleman's disease			
Herpes-B	Rare cause of CNS infection in a returning traveler	Encephalitis and Meningoencephalitis	Herpes B DNA detected in CSF	• Acyclovir	No vaccine or prevention