Herpesvirus Infections of the Central Nervous System

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Abstract

Double-stranded DNA herpesviruses are capable of establishing latency and reactivation. They are subdivided into eight human herpesviruses (HHVs): herpes simplex virus type 1, type 2, varicella-zoster virus, Epstein–Barr virus, cytomegalovirus, HHV-6, HHV-7, and Kaposi sarcoma virus. Most HHVs have the potential to cause serious neurological disease, which may be acute, chronic, monophasic, or recurrent; clinical features vary depending on the herpesvirus involved. During the course of primary infections, or even during reactivations or re-infections, neurological disease in the form of encephalitis, cerebellitis, meningitis, or myelitis may occur. Herpes simplex encephalitis is life-threatening, whereas herpes simplex virus type 2-associated recurrent aseptic meningitis is self-limited, presenting with headache, episodic fever, and meningismus. Polymerase chain reaction testing of cerebrospinal fluid is the method of choice for diagnosis, along with supplementary clinical findings and magnetic resonance imaging (MRI). Cerebrospinal fluid-polymerase chain reaction analysis has brought about an upgrade in the diagnosis of central nervous system (CNS) viral infections, especially those caused by herpesviruses, replacing aggressive brain biopsy techniques. Additionally, quantitating viral DNA levels in the cerebrospinal fluid (CSF) allows prognosis determination. Treatment modalities often involve starting the patient on empiric acyclovir; discontinued only when herpesvirus is ruled out.

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5.1 Herpesviruses in Central Nervous System Infections

5.1.1 Introduction

Infections affecting the central nervous system (CNS) in humans may be a result of bacteria, viruses, fungi, or parasites. Viruses can affect the CNS in one of many ways.

(a) By directly infecting the central nervous system, viruses may replicate and destroy the cells, as seen in encephalitis. Common etiological pathogens linked to viral encephalitis are herpes viruses (chiefly, herpes simplex virus) and arboviruses, (example, West Nile virus).
(b) By infection limited to the meninges, i.e., meningitis.
(c) Infections elsewhere in the body may trigger the immune system to attack and damage cells around the nerves, leading to a CNS infection; acute disseminated encephalomyelitis, for example.

The inflammatory changes that occur following neuroinfections can affect one or more anatomical regions. Accordingly, meningitis occurs if the meninges are involved, encephalitis in case of brain parenchyma involvement and myelitis if the spinal cord is involved. Multiple regions may also be involved simultaneously, such as meningoencephalitis or encephalomyelitis (Swanson and McGavern 2015).

Encephalitis is parenchymal inflammation of the brain, resulting from either non-infective, infective, or post-infective causes, accompanied by neurologic dysfunction. Approximately, 50% are due to infectious causes (Bradshaw and Venkatesan 2016).

Common encephalitic viruses are: Herpes simplex virus type 1 (HSV-1) and 2 (HSV-2), the non-polio enteroviruses, and arboviruses. Apart from these, the cytomegalovirus (CMV), Epstein–Barr virus (EBV), human herpesvirus 6 (HHV-6), and influenza viruses are also relevant. Humans are the only reservoirs for Herpesviruses. Once infected by herpesviruses, reactivation is possible, especially in immunocompromised individuals, because these viruses remain latent in the host. It is important to diagnose the various herpes virus infections, both clinically and radiologically, at the earliest, because most of them, if treated early and efficiently, have a favorable outcome.

Human herpes viruses (HHV) are a group of viruses that come under the family of Herpesviridae and entail eight species relevant to human infections. The human herpesviruses are mostly neurotropic and cause serious disease of the CNS, with acute or chronic presentations. All eight herpes viruses are capable of establishing

Table 5.1 Classification of viruses in the family-herpesviridae

Subfamily	Common name	Official designation of the virus
Alphaherpesvirinae	Herpes simplex virus-type-1 (HSV-1)	Human herpes Virus-1 (HHV-1)
Alphaherpesvirinae	Herpes simplex virus-type-2 (HSV-2)	Human herpes Virus-2 (HHV-2)
Alphaherpesvirinae	Varicella zoster virus (VZV)	Human herpes Virus-3 (HHV-3)
Gammaherpesvirinae	Epstein-Barr virus (EBV)	Human herpes Virus-4 (HHV-4)
Betaherpesvirinae	Human cytomegalovirus (HCMV)	Human herpes Virus-5 (HHV-5)
Betaherpesvirinae	Human herpes virus −6	Human herpes Virus-6 (HHV-6)
Betaherpesvirinae	Human herpes virus −7	Human herpes Virus-7 (HHV-7)
Gammaherpesvirinae	Kaposi sarcoma-associated herpes virus (KSHV)	Human herpes Virus-8 (HHV-8)

latency after primary infection in the natural host. Latency can be reactivated after varying periods of time, in accordance with the molecular nature of latency in the virus, as well as its type. The herpesviruses can affect the CNS by presenting as cerebellitis, encephalitis, meningitis, or even myelitis. Furthermore, these presentations may be linked to a fallout of primary infection or as an occurrence of viral re-infection or reactivation (Meyding-Lamadé and Strank 2012).

Over the past few decades, considerable importance has been given to herpesviruses, mainly due to their possible role in Alzheimer's disease (AD) and other neuro-degenerative disorders. These ailments are thought of as being linked to not only HSV-1 but also HHV-6 and EBV (Duarte et al. 2019).

The family Herpesviridae along with its subfamilies (Table 5.1) include DNA viruses with icosahedral capsids and a host nuclear-membrane-derived envelope (Muralidhar and Chawla 2019). The genomic constitution is that of a single, linear, double-stranded DNA, encoding 70–200 proteins, which depends on the species. There are three subfamilies in the family Herpesviridae.

5.1.2 General Features for Herpetic CNS Infections

An extensive clinical history along with physical examination are important in making an accurate diagnosis of herpesvirus-associated neuroinfections (Table 5.2). A viral etiology is implicated when there are classic signs and symptoms of meningeal inflammation (including Brudzinski sign, fever, headache, Kernig sign, neck rigidity, photophobia, etc.), along with any characteristic findings pointing toward viral involvement (e.g., vague abdominal symptoms of diarrhea or vomiting, conjunctivitis, herpangina, pharyngitis, rash/s, specific skin lesions, etc.). Focal

Table 5.2 General features and characteristics of human herpes viruses (HHV) of family herpesviridae

Sl. No.	Human herpes virus	Latency site	Primary infection	CNS infection	Laboratory diagnosis	Management
1.	HHV-1	Trigeminal ganglion	Herpes labialis	Encephalitis, meningitis, and myelitis	(specific serology HSV-1), viral culture, and PCR of CSF sample	Acyclovir and foscarnet
2.	HHV-2	Sacral and lumbar ganglia	Herpes labialis	Encephalitis, meningitis, and myelitis	(specific serology HSV-2), viral culture, and PCR of CSF sample	Acyclovir and foscarnet
3.	HHV-3	Trigeminal and dorsal root ganglion	Varicella (chickenpox)	Encephalitis, meningitis, cerebellitis, myelitis, Vasculitis, Reye's syndrome, acute cerebellar ataxia, and neuropathy	PCR of CSF sample	Acyclovir and valacyclovir
4.	HHV-4	B cells and epithelial cells	Infectious mononucleosis	Meningitis, encephalitis, ADEM, acute cerebellar ataxia, polyradiculomyelitis, transverse myelitis, GB syndrome, cranial, and peripheral neuropathies	PCR of CSF sample	Acyclovir and ganciclovir
5.	HHV-5	Cells of myeloid lineage	Pneumonitis myocarditis	Meningo-encephalitis, myelitis, and polyradiculopathy	Virus isolation and PCR of CSF sample	Ganciclovir and cidofovir
6.	HHV-6	Monocytes and macrophages and brain tissue	Exanthema subitum	Meningoencephalitis, myelopathy, temporal lobe epilepsy, post-transplant acute limbic encephalitis (PALE), multiple sclerosis, and aseptic meningitis	PCR of CSF sample	Ganciclovir and foscarnet
7.	HHV-7	CD4+ lymphocytes and salivary glands	Exanthema subitum and rubella like illness	Encephalitis and PALE	PCR of CSF sample	Foscarnet and cidofovir
8.	HHV-8		Kaposi's sarcoma	Encephalitis, AIDS-dementia complex, amyotrophic lateral	Serologic assays, immunofluorescence, ELISA,	Cidofovir, foscarnet,

HHV8 genome is bound to cell DNA in an episome form	sclerosis (ALS), and primary CNS lymphoma.	and Western blot. PCR of CSF sample	ganciclovir, and valganciclovir

PCR polymerase chain reaction, *ELISA* enzyme linked immuno sorbent assay

sensory impairments or motor deficits typically indicate encephalitis of viral etiology. Also, when there is a history of exposure to diseased contacts, mosquitoes, rats, and ticks or there are seasonal viral outbreaks, a diagnosis of CNS infection by herpesvirus should be suspected (Autore et al. 2021).

(Note: *There is a difference between Encephalitis and Encephalopathy. Encephalopathy is a broad terminology, referring to a clinical state, defined by changes in behavior, confusion, disorientation, and further cognitive impairments. These changes may be seen not only in encephalitis but also in various other non-inflammatory conditions*).

The presentation of encephalitis can be misleading, with prodromal symptoms favoring a diagnosis of upper respiratory infections. The clinical manifestations of encephalitis may then evolve over a period of days, presenting with fever, headache, seizures, and sometimes focal neurological deficits, which are all common features occurring in many conditions, and not specific to any one disease.

5.1.3 Diagnosis of Herpetic Encephalitis

In general, when investigating a case of suspected herpetic encephalitis in adults, the following tests should be performed:

– Cerebrospinal fluid (CSF) (at least 5 ml to be collected)—bands, cell count with differential count, glucose, Gram's stain, immunoglobulin G index, India ink staining for Cryptococcus lactose, opening pressure, and protein concentration.
– Bacterial cultures as relevant.
– Blood culture.
– Serology (acute and convalescent serum to be tested with titers) VDRL, ELISA for IgM and IgG of relevant organisms (HSV, EBV, etc.)
– Polymerase chain reaction (PCR) test for HSV-1/HSV-2, VZV, enteroviruses, and other possible pathogens.
– For non-neurologic findings, added syndrome-oriented testing ought to be carried out, accordingly (e.g., bronchoalveolar lavage, endobronchial biopsy, skin biopsy, throat swab PCR/culture, etc.).
– Brain MRI may be normal or with specific findings.
– More than 80% of viral encephalitic cases exhibit an abnormal electroencephalogram (EEG) with diffuse slow waves of high amplitude, with or without focal epileptiform activity. It is often necessary to continuously monitor EEG, especially to identify non-convulsive status (da Costa and Sato 2020).
– Blood tests—Blood gas analysis, complete blood count (CBC), differential white blood cell (WBC) count, platelet count, CRP, procalcitonin, serum electrolytes, kidney function test (KFT), liver function tests (LFT), international normalized ratio for prothrombin time (INR), and partial thromboplastin time (PTT).

There are several indications for performing imaging before a lumbar puncture (Autore et al. 2021)

(a) Severe case of depressed mental status.
(b) Papilledema.
(c) Hydrocephalus.
(d) Trauma history or CSF shunt procedure.
(e) Focal CNS impairments.

5.1.4   Treatment of Herpetic Infections of CNS

5.1.4.1 Initial Management

When an emergency case presents with alterations in consciousness, it is of utmost importance to recognize and treat emergency issues first, including hemodynamic and respiratory insufficiency. A quick assessment of other potential reversible associations in encephalopathy should be made, like electrolyte disturbances, hypoglycemic conditions, and so forth, which can be executed easily in an emergency setting. Once these irregularities are handled and the patient is stabilized, proper triaging and assessing for intensive care unit admission should be carried out. A neurological ICU, with a multi-disciplinary team, if available, is recommended, especially for patients with comorbidities, autonomic dysfunctions, or in a coma (Bradshaw and Venkatesan 2016).

5.1.4.2 Empirical Treatment of Encephalitis

Empirical treatment, in all encephalitis cases, must be started right away, while relevant investigations may be carried out alongside. Intravenous acyclovir should be started early at 10 mg/kg eighth hourly and continued for 14–21 days, along with a broad-spectrum antibiotic for bacterial causes, till a definitive diagnosis is made, when it may have to be stopped. This is because bacterial meningoencephalitis is often indistinguishable from herpes virus encephalitis. Till a definite diagnosis is established, the patient has to be followed up very closely (Bradshaw and Venkatesan 2016).

Although there exists an extensive list of different viruses associated with CNS infections, most of them follow similar cascades of pathogenic events. More or less, they involve events such as the infringement of the blood–brain barrier, as well as the release of glutamate, interferon-1, reactive oxygen species, tumor necrosis factor-alpha, and other potentially neurotoxic mediators. It should be noted that these universal mediators may just as well serve as current or future targets for therapeutic agents (Autore et al. 2021).

5.2   Emphasis on Individual HHV Types Causing Infections of the CNS

5.2.1   HHV-1 Also Known as Herpes Simplex Virus Type-1 (HSV-1)

5.2.1.1 Introduction

As a neurotropic agent, HSV-1 exhibits a wide array of medical disorders, ranging from oral and facial skin manifestations to serious infection of the CNS. In adults, it remains the most common reason for severe, life-threatening sporadic, necrotizing encephalitis (85%). The CNS infections of HSV-1 may be labeled as "neonatal HSV neuro-infection," in neonates, or "herpes simplex encephalitis" (HSE) in age groups outside the neonatal age. Apart from this, HSV-1 is implicated as a cause of blinding keratitis, as well as a cause of neonatal disseminated herpes (Mielcarska et al. 2022). Almost 90% of encephalitis in children and adults is due to HSV-1, with a worldwide incidence of 2 and 4 cases/1,000,000, and the majority of these infections occur in over 50-year-olds (Bradshaw and Venkatesan 2016; Shoji et al. 2002).

5.2.1.2 Pathogenesis

Following infection in an uninfected individual, HSV-1 becomes latent in peripheral sensory neurons of the trigeminal or dorsal root ganglion, and the vestibular and facial ganglion, where it remains latent and causes changes in the cellular processes essential for the normal functioning of neuronal cells (Mielcarska et al. 2022). The asymptomatic individuals with HSV-1 infection serve as important reservoirs of the virus, contributing to transmission via means of viral shedding. Recent studies suggest that HSV-1 neuro-infection may be contributory to Alzheimer's disease, wherein it damages the neurons and glial cells and also affects the homeostatic and immune functions. This hypothesis is backed by various incidences involving the detection of AD-linked biomarkers in HSV-1 neuro-infection cases. In addition, advanced age predisposes to HSV-1 reactivation and its entry into the brain (Mielcarska et al. 2022).

The various known routes for HSV-1 to reach the central nervous system include the following:

(a) Olfactory tract via the olfactory epithelium and neurons to the olfactory bulb.
(b) Trigeminal tract—Viral particles can also undergo CNS migration through the anterograde route (along trigeminal neurons) (Swanson and McGavern 2015).
(c) Vertical transmission is also possible after the previous infection of the mother and subsequent HSV-1 infection through the hematogenous route.
(d) After a recurrent HSV-1-orofacial infection, peripheral ganglia reactivation can occur, followed by axonal migration to the CNS.

HSV-1 virions, when present in the CNS, are able to trigger a continuous microglial activation, leading to the emission of large amounts of cytokines and chemokines, as well as substantial neuro-inflammatory events (Campos et al. 2021). These biochemical and morphological changes in the neurons may ultimately end in

glial cell and neuronal loss. Acute herpes simplex type 1 encephalitis causes apoptotic or necrotic neuronal cell loss. It involves the frontal lobes, temporal lobes, and certain areas of the cerebral hemispheres (i.e., insular cortex). The immune system clears any virus at the infection site, while those residing within the neurons enter a latent phase, with their DNA existing as episomes. Here, the viral protein is not expressed, except for limited genes (latency-associated transcripts, i.e., LAT) (Mielcarska et al. 2022).

The virus can be reactivated by several stress factors, such as emotional stress, trauma, fever, immunosuppression, ultraviolet rays, hormonal changes, dental operations, etc. (Duarte et al. 2019). It is clear that the immune system serves a crucial part in preventing the reactivation of the virus because the latent virus enters a lytic replication cycle when the immune system is suppressed.

Pathology—Herpes simplex virus enters host tissues via broken skin barriers or mucous membranes, and journeys toward the dorsal root neurons (retrograde axonal transport). It interacts with glycosaminoglycans at cell surfaces, for example, heparan sulfate and cell-adhesion molecules like nectin-I (da Costa and Sato 2020).

Histopathological examination of brain tissue, within 7 days, reveals areas of mononuclear inflammation, and necrotizing processes, characteristically in the frontal and/or temporal lobes, with perivascular inflammation, edema in the affected neurons, as well as microglial engulfment of neurons (Swanson and McGavern 2015).

Associated frontal and temporal lesions may be necrotic, inflammatory, or hemorrhagic. Intracerebral hemorrhage and infarction are both pathologically distinct HSV-associated neuro-infection findings. Infection-associated intracerebral hemorrhage occurring in the temporal region is almost exclusively linked to HSV-1, with morbid consequences (Hauer et al. 2019).

Eosinophilic, intranuclear inclusion bodies are present in the neuron and glial cells. Inclusions containing viral antigen and herpesvirus particles are seen on immunohistochemistry and electron microscopic examination, respectively. Latent states of HSV by PCR analysis have been found in parts of the limbic system such as in the cerebellar amygdala and hippocampus (Shoji et al. 2002; Bradshaw and Venkatesan 2016).

5.2.1.3 Clinical Features

Primary HSE is seen in 30% of cases, while 70% of cases are recurrent infections, with almost all cases due to HSV-1. HSV-1 is highly invasive and capable of accumulation in the dorsal root nerve ganglia (DRG). It is also capable of cerebral cortex, hippocampal, insular, mesial temporal, and orbitofrontal migration. These cases are highly vulnerable to Alzheimer's disease. The majority of adult encephalitic cases are due to HSV-1 infection (Campos et al. 2021). Primary HSV-1 infections usually have a subclinical presentation. When symptomatic, the infections may be gingivostomatitis in younger age groups, or tonsillitis and pharyngitis in adult populations. Eye infections in the form of keratoconjunctivitis are also of importance, as they can lead to corneal scarring and blindness. Herpetic lesions typically begin as vesicles that eventually become shallow ulcers, many a time

accompanied by systemic findings of fever, malaise, and myalgia (Muralidhar and Chawla 2019).

HSE has a non-specific clinical picture, with a transitory influenza-like illness or with an abrupt onset. Encephalitis must clinically be suspected once indicators of CNS dysfunction present acutely (in 24–72 h), in the form of headache, seizures, behavioral abnormalities, focal deficits, or coma, along with common systemic manifestations or known risk factors (da Costa and Sato 2020; Meyding-Lamadé and Strank 2012; Shoji et al. 2002).

Complications of HSE—Imperative complications of acute encephalitis, apart from respiratory and circulatory insufficiencies, include cerebral edema, herniation, raised intracranial pressure, and seizures (Bradshaw and Venkatesan 2016).

Differential Diagnosis of HSE—Several clinical conditions have to be actively looked for and ruled out when making a diagnosis of HSE. These include the following:

(a) **Vascular causes**—cerebral venous sinus thrombosis, intracerebral hemorrhage, ischemic stroke, posterior reversible encephalopathy syndrome, reversible vaso-constriction syndrome, subarachnoid hemorrhage, and vasculitis.
(b) **Metabolic disturbances**—electrolyte imbalances, hepatic/renal encephalopathies, hypoglycemic states, mitochondrial encephalopathy-lactic acidosis-stroke-like episodes (MELAS), septic encephalopathy, and Wernicke's encephalopathy.
(c) **Toxic causes**—Alcohol, drugs and lactic acidosis.
(d) **Trauma.**
(e) **Malignancy**—Primary brain tumor with cerebral metastases.
(f) **Epileptic causes**—Status epilepticus (non-convulsive).
(g) **Infective causes**—Other viral encephalitis, other post-infectious encephalitis, bacterial, mycobacterial, and fungal meningitis (Shoji et al. 2002).

5.2.1.4 Laboratory Diagnosis of HSV-1 Encephalitis

(a) Serology—four-fold elevation of HSV antibody (ELISA for IgG and IgM).
(b) Serum/CSF antibody ratio < 20; antibody index >/= 1.91.
(c) Polymerase chain reaction—HSV-DNA detection by CSF-PCR is the current gold standard diagnostic test, which is highly reliable and avoids the invasive procedure of brain biopsy. For HSV, it has 100% specificity, along with a sensitivity of more than 95%. In cases with a negative primary test despite high clinical suspicion, the recommendation is to test an additional sample in 2–7 days' time. In view of situations where there is a negative CSF-PCR for HSV initially, which later turns out to be positive, it is always required to give importance to clinical suspicion (James et al. 2009; Shoji et al. 2002).
(d) Viral culture—HSV isolation from CSF.
(e) Chemi-luminescence immune-assay (CLIA).
(f) Cerebrospinal fluid examination—CSF may be hemorrhagic and shows pleocytosis (≥5 nucleated cells/ml) with pressure moderately or greatly increased. There may or may not be pleocytosis in the CSF, but lymphocytes

are predominant, and RBCs are frequently seen. The usual HSE-CSF findings comprise (1) moderate lymphocytic pleocytosis of 10–200 cells per mm^3, (2) mildly raised red blood cells, (3) moderately elevated protein (50–100 mg/dl), and (4) mostly normal glucose levels (Shoji et al. 2002).

(g) Electroencephalogram (EEG) studies—Electroencephalography should ideally be executed in all suspected individuals to perceive any generalized/focal epileptiform activities. It might correspondingly aid in distinguishing the origin of specific behavioral alterations, primarily involving psychiatric states or encephalopathy (da Costa and Sato 2020). EEGs might indicate non-specific, slowing periodic lateralizing epileptiform discharges known as PLEDS (da Costa and Sato 2020). The changes in EEG usually involve one side initially and subsequently progress toward the contralateral temporal region.

(h) Brain imaging techniques.
  – Brain computed tomography (CT) scans—CT changes in 80% of patients with HSV show decreased attenuation in the temporal lobe/s or hyper-intensified regions. Whenever there are signs of increased intracranial pressure, a non-contrast CT scan is generally suggested before lumbar puncture (Meyding-Lamadé and Strank 2012).
  – Magnetic resonance imaging (MRI)—MRI is considered the most sensitive/specific radiological investigation in HSE, especially in its initial course, and provides a great account of parenchymal inflammation, demonstrates focal, contrast-enhancing lesions, and helps in recognizing idiopathic inflammatory neurological findings. Brain MRI shows hyperintensity regions on fluid-attenuated inversion recovery (FLAIR) images, T2-weighted (T2W) images, diffusion-weighted images, and T1W images, which may show gadolinium-enhanced cingulate gyrus, insular cortex, orbitofrontal, and/or gadolinium-enhanced temporal lobes (Shoji et al. 2002).

(i) Brain biopsy, although rarely performed these days, is designated for postmortem cases or for highly suspicious, unresponsive cases (Meyding-Lamadé and Strank 2012).

The vital way for early identification and management of HSE includes attaining familiarity with the clinical syndromes and features associated with it. It must also be remembered here that in immunosuppressed patients (e.g., those on chemotherapy, those taking corticosteroids, transplant recipients, or those with human immunodeficiency virus (HIV) infection or other immune-suppressing ailments), the atypical presentations may occur, further complicating the diagnosis, thus needing a strong sense of suspicion (Meyding-Lamadé and Strank 2012).

5.2.2 Treatment

HSE if left untreated has a mortality of 70%, and those who do survive end up with significant neurological deficits, nearly 97%. The first antiviral agent used to treat HSE was idoxuridine, but it was both toxic and ineffective. The next drug to counter

HSE was vidarabine, which was better tolerated and brought down the mortality to 54%, although 86% of the survivors had residual neurologic deficits. Acyclovir is presently the usual treatment of HSE in most parts of the world. It is a guanine analog, acycloguanosine, given in a 3-week course of 30 mg/kg/day (3 divided doses) (James et al. 2009). Empiric treatment with acyclovir for suspected cases (until ruling out of HSE) still remains the recommendation (Autore et al. 2021). However, it is also vital to be mindful of the fact that none of the anti-herpetic drugs can actually cure a latent infection or prevent symptom recurrence and asymptomatic viral shedding.

5.2.3 Human Herpes Virus (HHV)-2 Also Known as Herpes Simplex Virus Type-2

5.2.3.1 Introduction
About 80% of neonatal encephalitis cases transmitted from mothers to newborns are due to HSV-2, which reduces to less than 10% after the neonatal period. Thereafter, the acquisition of HSV-2 infection is mostly through the sexual route. HSE in neonates typically presents clinically around 2 weeks after delivery. In adults, it is the most common cause of uncomplicated genital herpes, although it can occasionally affect the CNS and cause meningitis, radiculomyelitis, and rarely encephalitis (Meyding-Lamadé and Strank 2012). Determination of adult HSV-2 infection is made by various history points, e.g., age of sexual debut, race, sexual partners, female gender, positivity for other sexually transmitted infections, and the presence of HIV or other infections.

5.2.3.2 Pathogenesis
Primary infection often begins at mucocutaneous surfaces with retrograde viral migration and latency of its genome in peripheral sensory ganglia. Subsequently, episodic reactivation occurs when there is antegrade communication to nerve endings and mucocutaneous surfaces. HSV-2 affects several parts of the CNS, including brain matter, brainstem, cranial nerves, nerve roots, retina, spinal column, and other parts of the neuroaxis. Primary HSV-2 associated aseptic meningitis cases may be seen in 13% males and 36% females (Hauer et al. 2019). Serious cerebrovascular-related consequences of HSV neuroinfections can occur, which are mostly comorbidities, irrespective of gender, age, and immunosuppression status.

5.2.3.3 Clinical Features
Herpes simplex encephalitis due to HSV-2 accounts for 1.6–6.5% in adults, especially in immunocompromised hosts. HSV-1 affects the orbitofrontal and/or temporal lobes, but HSV-2 prefers to infect the brainstem. It remains latent in the sacral and lumbar ganglia. HSV-2 encephalitis can occur without features of meningitis. Alterations in awareness, cranial neuropathies, hemiparesis, as well as hemisensory loss, are some of the CNS manifestations. Lumbosacral or thoracic ascending

myelitis may occur in immunocompromised hosts. Acute retinal necrosis, which is characterized by red eyes, periorbital pain, decreased vision, episcleritis, keratotic precipitates, retinal vasculitis, and retinal detachment, is one of the eye syndromes that meningoencephalitis can afflict. In infants and neonates, the HSV-2 infection may present in a localized or disseminated form, either of which can lead to encephalitis, with a more serious prognosis than HSE due to HSV-1. Meningitis and myelitis linked to genital herpes are more prevalent in adults, and HSV-2 as an opportunistic infection accompanying AIDS can cause acute encephalitis and acute necrotizing myelopathy. HSV-2 causes Mollaret's meningitis, which is a type of recurrent aseptic meningitis, although benign, and characterized by recurrent, 2- to 5-day meningitis bouts, which may occur several weeks to years apart.

5.2.3.4 Diagnosis

(a) Tzanck smear—To check for multinucleated giant cells, a swab is obtained from a lesion's base and stained with Giemsa.
(b) Immunofluorescence and immunoperoxidase stains—Here, antibodies to early viral proteins are detected. This is more sensitive than the Tzanck smear.
(c) Viral culture—specimens used for HSV-2 culture include vesicle scraping, genital swabs, or fluid. The virus is grown on human tissue culture; syncytia development and intranuclear Cowdry type A inclusion bodies in host cells are signs of viral growth. Though specific, this is not a very sensitive method of diagnosis.
(d) Serology—Intrathecal monitoring of HSV-2 antibodies is useful after the acute infection stage. In general, the serological tests are not very sensitive and are useful only in differentiating between HSV-1 and 2.
(e) Brain imaging—In the early stages of HSE, CT and MRI scans of the head reveal diffuse edema, while later stages show calcifications, cystic encephalomalacia, and cerebral atrophy.
(f) Electroencephalography (EEG)—There is slow background and paroxysmal discharges in the EEG.
(g) Cerebrospinal fluid—As in all CNS infections of viral etiology, CSF analysis shows normal glucose, raised protein levels, and lymphocytic pleocytosis, which is not quite specific.
(h) PCR—It can detect HSV-2 in cerebrospinal fluid, serum, and other tissues. It is currently the gold standard for the identification of HSV neuroinfections since it is quick, specific, and sensitive for herpes simplex virus type 1 and 2.

5.2.3.5 Treatment

Currently, intravenous administration of acyclovir sodium at a dose of 10 mg/kg every 8 h for 2–3 weeks is advised for treating HSE in adults and children older than three months. Neonatal patients receive a dose of 20 mg/kg, 8 hourly, for a 2–3 week course.

Age, level of awareness at presentation, duration, severity of encephalitis, and HSV load are some of the variables that influence HSE therapy and prognosis. If HSV-2 DNA is still present in the CSF post 3 weeks of treatment, acyclovir

(intravenous) medication is given for an additional 2 weeks. PCR of a cerebrospinal fluid sample is done again for HSV-DNA. Acyclovir sodium is used as therapy for HSV-2 meningitis at 5–10 mg/kg three times per day. Acyclovir is used to manage myelitis or radiculitis in a similar manner (10 mg/kg three times each day). In patients with HSV-2 myelitis, it is recommended that glucocorticosteroid be given in high-dose IV therapy along with acyclovir, to decrease the risk of ascending myelitis, as a complication (Shoji et al. 2002). Drug resistance to acyclovir in HSV-1 and -2 can occur due to thymidine kinase mutations and can be treated with valacyclovir. Acyclovir-resistant HSV also responds to cidofovir and foscarnet sodium (Berger and Houff 2008).

5.2.4 Human Herpes Virus (HHV)-3 Varicella Zoster Virus

5.2.4.1 Introduction

Varicella zoster virus (VZV) in the young (as varicella infection) has decreased considerably since there is a reliable vaccination available. VZV CNS infections occur in about 1% of varicella cases, a few days or weeks before or after the appearance of rash. These CNS infections may follow the cranial nerve dermatome or may present as cerebellar ataxia or encephalitis. Immunocompromised patients are clearly at increased risk.

5.2.4.2 Clinical Features

Among the CNS infections caused by VZV, VZV meningitis is the most common, followed by encephalitis, myelitis, Reye's syndrome, acute cerebellar ataxia, and neuropathy (Shoji et al. 2002). Clinically, VZV Encephalitis often presents as an acute or subacute delirium and generally non-specific features, such as fever, headache, meningism, ataxia, and seizures. There is a lot of variation regarding the areas of the brain that are impacted, the extent of the CNS impairment, and the cognitive functions that are involved (Meyding-Lamadé and Strank 2012). Postherpetic neuralgia, which lingers long after the cutaneous signs have disappeared, is the major consequence. The peripheral and central nervous systems are both susceptible to acute neurological problems (Meyding-Lamadé and Strank 2012). In HIV-positive individuals, there may be difficulty in diagnosis because the CNS infections may be a part of the opportunistic infections, in the absence of the typical skin eruptions (zoster sine herpete).

5.2.4.3 Diagnosis

The clinical diagnosis of varicella is relatively easy when typical skin lesions are present. Laboratory diagnosis involves cerebrospinal fluid analysis, which exposes a slight mononuclear pleocytosis along with normal glucose and protein levels.

As in HSV infections, real-time PCR is the favored test, for use in the diagnosis of VZV DNA in CSF. Quantitative PCR is more useful than qualitative PCR. Compared to individuals with other VZV-related CNS disorders, those suffering from encephalitis or meningitis generally have greater viral loads. This might be useful for

anticipating the course of VZV-meningoencephalitis in HIV-infected persons as well as evaluating therapeutic efficacy (Meyding-Lamadé and Strank 2012).

Massive and minor ischemic infarcts or hemorrhagic infarcts are visible on brain MRI, in cortical or subcortical grey and white matter. The likelihood of VZV involvement is highly considered when abnormalities, particularly at the gray-white matter junctions, are noted.

5.2.4.4 Treatment

Routine vaccination of children aged 12–15 months, and healthy persons aged 13 years and above, is known to minimize infections of CNS and complications in later life. Treatment of varicella is essentially symptomatic. Herpes zoster management involves antiviral therapy, which should be started within 72 h of the rash's emergence. Valacyclovir, which is known to be superior to acyclovir (8 days: per oral 800 mg 5 times a day), is advised for 1 week, per orally as 1 g three times a day (Meyding-Lamadé and Strank 2012). If steroid treatment is indicated, it should be for a short duration of 3–5 days, only to minimize side effects (Meyding-Lamadé and Strank 2012).

5.2.5 Human Herpes Virus (HHV)-4 Also Known as Epstein–Barr Virus (EBV)

5.2.5.1 Introduction

Epstein–Barr virus is responsible for infectious mononucleosis (IM) as well as neuroinfections. Among the most prolific viruses, it affects over 90% of people within the first 10 years of life and lasts the entire person's lifetime. Primary infection is usually asymptomatic and occurs through infected saliva, in childhood, as well as up to 40% of adults and teenagers, leading to infectious mononucleosis. Meningitis is a rare but serious side effect of EBV infection and typically develops during the initial illness.

5.2.5.2 Pathogenesis

Unlike CNS infections caused by HSV, neurological diseases caused by EBV have distinct etiology. Brain biopsies of EBV-encephalitis cases fail to reveal EBV-proteins or nucleic acids, unlike the presence of HSV proteins in encephalitic brain tissue of HSVE cases. Thus, an autoimmune mechanism has been attributed to EBV-associated CNS disease (Meyding-Lamadé and Strank 2012).

It is important to note that EBV establishes latency only in lymphoid cells and not in neurons. Hence, upon reactivation, the extra-neural locations are likely to become infected with the virus, and infected lymphocytes will then disseminate the EBV to the CNS (Meyding-Lamadé and Strank 2012).

5.2.5.3 Clinical Features

A sore throat with fever and adenopathy, or even splenomegaly, are common symptoms of infection with Epstein–Barr virus, which is typically a self-limiting,

lymphoproliferative condition. The CNS infections may occur before, during, or after IM and can be grouped into two categories—CNS infections occurring with primary or reactivated EBV, and occurrence of a chronic-active EBV involvement. Acute cerebellar ataxia, acute disseminated encephalomyelitis (ADEM), cranial/peripheral neuropathy, encephalitis, Guillain–Barré syndrome, meningitis, polyradiculomyelitis, and transverse myelitis are among the medical conditions that may affect the central nervous system (Meyding-Lamadé and Strank 2012). The involvement of the cerebellum is more common in EBV CNS infections. Other presentations, although uncommon, include gait abnormalities, extrapyramidal involvement, Reye syndrome, improper antidiuretic hormone secretion, or acute fatty liver disease along with encephalopathy. Cases of chronic encephalitis or recurrent meningitis have also been described (Shoji et al. 2002; Meyding-Lamadé and Strank 2012).

5.2.5.4 Diagnosis and Treatment

Traditional diagnosis of EBV infections involves serological tests to detect both specific and non-specific antibodies to the virus. The heterophile antibody detection by the conventional Paul-Bunnel test, along with clinical features and the presence of atypical lymphocytes, is fairly diagnostic for Epstein–Barr virus involvement.

In addition to alterations in serology that are indicative of acute EBV infection, PCR analysis for CSF-DNA can be used to identify neurological disorders associated with EBV. While CT scans may be normal, MRI may nevertheless detect lesions since it is so sensitive, especially on T2W imaging. With brain-MRI, basal ganglia can display focal abnormalities that could aid in differential diagnosis. In cases of encephalitis, EEGs usually reveal generalized slowness with sporadic episodes (Meyding-Lamadé and Strank 2012).

Treatment—For the treatment of EBV infections of CNS, acyclovir and corticosteroids are recommended. Some groups recommend acyclovir usage, or ganciclovir, for managing EBV-encephalitis (da Costa and Sato 2020).

5.2.6 Human Herpes Virus (HHV)-5 Also Known as Human Cytomegalovirus (HCMV)

5.2.6.1 Introduction

CMV is known to cause congenital maternal–fetal infection, with asymptomatic maternal infection leading to symptomatic cases in newborns. CMV causing acquired CNS infection is rare in healthy children but can cause severe disease and complications in immunocompromised hosts, with high residual adverse effects and mortality.

5.2.6.2 Pathogenesis and Clinical Features

Congenital cytomegalovirus infection's neuropathogenesis is due to the dissemination of CMV through the CSF, including the brain's endothelial cells, the contiguous astrocytes, and the choroidal epithelial cells. Viral replication in these cells leads to

intranuclear inclusion bodies, like all herpes viruses and lysis of cells. Immune-mediated damage is also implicated in the antigen–antibody complex deposition (James et al. 2009).

Clinical Features—CMV infection rarely causes CNS infections in adults. However, when it does affect the CNS, the cases may present as myelitis, encephalitis (CMVE), or radiculopathies. Diagnosis of CMVE is very difficult because there are no clinical features unique to this condition, and it may present with non-specific signs, such as confusion, seizures, or disorientation. In addition, it may be clinically indistinguishable from HIV dementia (Meyding-Lamadé and Strank 2012). Ventriculoencephalitis or encephalopathy is seen in immunocompromised hosts, such as AIDS patients. Cases of CMV lumbosacral radiculoneuritis have also been reported, which include progressive flaccid paralysis of limbs, areflexia, and recto-urinary impairment.

5.2.6.3 Diagnosis and Treatment

No typical laboratory or neuroimaging finding exists for CMVE. Once cerebral fluid pleocytosis and CMV-PCR test are confirmed, the condition is diagnosed.

Treatment—CMV infections are treated with IV ganciclovir at 15 mg/kg per day every 12 h, for 6 weeks (Shoji et al. 2002). As CMV infection is self-limited and usually tends to resolve, antiviral treatment is generally not recommended for immunocompetent children. However, a 12-month maintenance therapy with valganciclovir 15 mg/kg/dose twice a day, per orally, is advised for immunocompetent kids with severe symptomatic infections (Autore et al. 2021). With this course, hearing outcomes are improved in neonates having symptomatic congenital cytomegalovirus neuroinfections, presenting as aberrant CSF for age, chorioretinitis, hearing loss, intracranial calcifications, and/or microcephaly. One of the limitations of antiviral treatment of congenital CMV infection is that the damage to CNS has already been done in utero before the condition is recognized. That is why, preventive efforts are of paramount importance (James et al. 2009).

5.2.7 Human Herpes Virus (HHV)-6 Also Known as HHV-6

5.2.7.1 Introduction

Among the most pervasive herpes viruses, HHV-6 infects humans at a prevalence of close to 100%. HHV-6 type A (HHV-6A) and type B (HHV-6B) are the two different types that make up this virus. Although HHV-6A is not linked to any serious human illnesses, HHV-6B is the source of the widespread childhood illness, exanthema subitum, often known as the sixth disease, or as roseola infantum. It often affects children between the ages of 1 and 2. It is characterized by a fever of 2–3 days and, in 25–30% of newborns, a non-vesicular, cutaneous rash that is primarily on the trunk and back. Via saliva from mother to child, or among children, is the most likely method of transmission.

5.2.7.2 Pathogenesis and Clinical Features

HHV-6 is also known to establish latency, like all other herpes viruses, which is in monocytes or macrophages, as well as in brain tissue. Reactivation commonly occurs in immunocompromised patients but may also be seen in immunocompetent hosts.

Clinical Features—The primary infection with HHV-6B, exanthema subitum, usually presents with fever and rash. The CNS is affected as a complication of this primary infection, which may present as encephalopathy, meningitis, meningoencephalitis, seizures, or even hemiplegia. A seemingly rare complication of exanthema subitum in healthy children is aseptic meningitis, which generally has a good prognosis (Autore et al. 2021).

In adults and elderly patients, HHV-6 may affect the CNS and cause epilepsy, myelopathy, temporal lobe epilepsy, post-transplant acute limbic encephalitis (PALE), and multiple sclerosis without skin lesions (Shoji et al. 2002). HHV-6 virus establishes latency in the cells of medial temporal lobes, and hence, the clinical features of PALE include abnormal temporal lobe EEG readings, significant anterograde amnesia, or even seizures (Meyding-Lamadé and Strank 2012).

Differential diagnosis—On MRI, HHV-6 CNS infections have to be differentiated from HSVE, other viral encephalopathies, lymphoproliferative disorders affecting the CNS, and drug-induced encephalopathies. Radiological findings of mesial temporal lobe region association along with an immunocompromised state, particularly in post-transplant recipients on prophylactic acyclovir maintenance, are the distinguishing features that allow for a definitive diagnosis of HHV-6 involvement (Meyding-Lamadé and Strank 2012).

5.2.7.3 Diagnosis

CSF, in HHV-6 infections of CNS, shows mild pleocytosis. MRI abnormalities include bilateral, non-enhancing, medial temporal lobe T2W, or FLAIR hyperintensity images, sharply defined by para-hippocampal gyrus sparing. A major diagnostic tool, however, is CSF-PCR for HHV-6-DNA detection, although the findings of this test have to be interpreted with caution. This is because the HHV-6 virus is known to get integrated into host chromosomes; hence, this chromosomal integration has to be distinguished from primary infection and reactivation of the virus (Meyding-Lamadé and Strank 2012). Verifying that CSF-PCR positivity is followed by a negative serum PCR result will help to solve this issue (da Costa and Sato 2020).

5.2.7.4 Treatment

In immunocompetent children, there is really no need to treat HHV-6 infections, as these are self-limiting and recovery is the norm. However, in immunocompromised hosts, there can be life-threatening complications of CNS infections, which need immediate action. Acyclovir is not effective in treating this condition, due to the absence of the thymidine kinase enzyme. Therefore, ganciclovir is utilized as first-line, in HHV-6-encephalitis, either by itself or in synergistic combination with foscarnet (da Costa and Sato 2020). It should be noted that acyclovir/ganciclovir

as a prophylaxis is already given to individuals receiving immunosuppressive medication to stop any reactivation of HSV and CMV, respectively. In these circumstances, ganciclovir may also work as prophylaxis to stop HHV-6 reactivation (Meyding-Lamadé and Strank 2012). There is no effective vaccine available for the prevention of HHV-6 infections.

5.2.8 Human Herpes Virus (HHV)-7 Also Known as HHV-7

5.2.8.1 Introduction
HHV-7 is a ubiquitous virus, present worldwide, mostly acquired in infancy. Seventy percent of youngsters get the illness via droplets or breast milk, by the age of four. Due to its amino acid resemblance with that of several HHV-6 proteins and properties, the clinical features and pathogenicity are similar in both these viral infections. This virus reactivates in around 20% of recipients of solid-organ transplants, resulting in infection.

5.2.8.2 Pathogenesis
In CD4+ T cells, HHV-7 develops both active and latent infection. It very easily creates continuing infection within the salivary glands. Other tissues implicated in the latency of this virus are the tonsils, skin, mammary glands, lungs, kidneys, and liver. It partakes a narrower tissue tropism as compared to HHV-6. In immunocompromised patients, it can reactivate either alone or with HHV-6B and CMV viruses. Human herpesvirus 7 infects, yet does not multiply in macrophages and monocytes in vitro. In Kaposi sarcoma lesions, HHV-7 has been found to affect CD34+ hematopoietic progenitor cells, CD68+ macrophages, and monocytes. Additionally, it can be present in breast milk.

5.2.8.3 Clinical Features
Sporadic viral encephalitis is known to occur with HHV-7, HHV-6A, as well as HHV-6B, especially in immunocompromised individuals, when serious encephalitis and generalized symptoms can be present. Risk factors for reactivation of HHV-7 leading to encephalitis comprise repeated hematopoietic stem cell transplantations, unmatched cord blood transfusions, immune suppression, and cytotoxic drugs. The condition of post-transplantation acute limbic encephalitis (PALE), which is linked to significant morbidity, is perhaps the most severe symptom. Occasionally, primary HHV-7 infection can invade the brain and induce febrile convulsions. HHV-7 is also known to cause infantile hemiplegia together with skin rash (Shoji et al. 2002).

5.2.8.4 Diagnosis and Treatment
Both HHV-7 and HHV-6 have similar growth characteristics, notably their cytopathic outcomes in cell culture, which include the production of refractile, ballooned, multinucleated giant cells. In comparison to HHV-6, HHV-7 tends to grow at a slower pace and is not as cytopathic.

To culture human herpesvirus 7 from a continuous CD4+ lymphoblastic cell line, peripheral blood mononuclear cells, or cord blood, primary phytohemagglutinin-stimulated CD4+ T cells are needed.

Enzyme-linked immunosorbent assays (ELISA) or indirect immunofluorescence assays are used to identify antibodies in serological screening for Human herpesvirus 7 in children. The absence of antibodies makes it more likely that the existence of the viral-DNA in blood will be indicative of an acute HHV-7 infection. In adults, the recognition of viral protein appears to be considerably more specific than viral DNA, in determining the cause of encephalitis to be due to HHV-7.

Treatment—Treatment of HHV-7 is best accomplished with cidofovir and foscarnet in vitro, although ganciclovir inhibits viral replication.

5.2.9   Human Herpes Virus 8 (HHV-8) Also Known as Kaposi Sarcoma-Associated Herpes Virus (KSHV)

5.2.9.1 Introduction
All types of Kaposi sarcoma (KS), classic, AIDS related, endemic, transplant related, primary effusion lymphoma (PEL), even solid organ variants, and lymphoproliferative, multicentric Castleman's disease (MCD), are etiologically linked to HHV-8. In general, HHV-8 does not cause CNS infections, except when there is immunosuppression in the host, wherein several complications can occur.

5.2.9.2 Pathogenesis and Clinical Features
In the latent state, the HHV8 genome is tethered to the cellular DNA as an episome.

Clinical Features—KSHV infection is prevalent in individuals all over the world and is associated with a rare cancer called Kaposi sarcoma. The lesions of this malignancy may involve the skin, nose, throat, or other body tissues. KSHV also causes certain types of lymphoma.

In terms of neurological syndromes, HHV-8 is linked to primary CNS lymphomas, amyotrophic lateral sclerosis, and AIDS–dementia complex. As a part of any differential diagnosis for unexplained viral encephalitis, this virus should always be taken into consideration, especially in immunocompromised persons (Shoji et al. 2002).

5.2.9.3 Diagnosis and Treatment
The majority of the time, serologic analyses like immunofluorescence, ELISA, and Western blots are used in laboratories to determine whether a patient has HHV-8 infection. PCR of CSF samples is the test of choice for diagnosing HHV-8 encephalitis. Minimal KSHV titers, as determined by PCR, do not always imply that a condition is linked to KSHV infection (Meyding-Lamadé and Strank 2012).

Treatment—Anti-HSV agents that are known to be effective against KSHV are cidofovir, foscarnet, ganciclovir, and valganciclovir. They act by reducing HHV8 viremia and thus contribute to controlling diseases presenting with high levels of KSHV replication.

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