Viral Encephalitis

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Abstract

Viral encephalitis is a rare disorder by caused by numerous viruses. Herpes simplex virus 1 causes more cases of encephalitis than other viruses. Additional viruses that can cause encephalitis are Varicella zoster virus, human cytomegalovirus, and several RNA viruses, including West Nile virus. These viruses have novel properties with respect to epidemiology, pathogenesis, clinical features and therapeutic approaches. All viruses that cause encephalitis have the ability to induce inflammation in brain tissue (cerebral edema). Encephalitis, in general, destroys neurons, causes bleeding in the brain (intracerebral hemorrhage), and brain damage. This chapter discusses the clinical features, productive infection, latent infection, epidemiology, pathogenesis, and animal models used to examine encephalitis. Furthermore, therapeutic strategies used to treat encephalitis for many of the viruses that can cause encephalitis are discussed. The major antiviral agents used to treat herpes encephalitis are acyclovir, valacyclovir, ganciclovir, cidofovir and foscarnet. For each of these drugs, we discuss the pharmacology, mechanism of action and adverse effects.

Keywords

Arboviruses • Herpesviruses • Inflammation • Viral infection of brain

29.1 Introduction

Encephalitis is an acute inflammation of the brain that can be caused by several viruses. Members of the Herpesviridae family cause most cases of encephalitis: for example, herpes simplex virus 1, varicella zoster virus, human cytomegalovirus, human herpesvirus 6, and Epstein Barr virus. In addition, several arboviruses, including West Nile virus, Saint Louis encephalitis, Eastern encephaltic virus, Western equine encephalitic virus, La Crosse virus, and Colorado Tick Fever can cause encephalitis. Arboviruses are RNA viruses transmitted by arthropod vectors: mosquitoes, ticks, and sandflies for example. Additional RNA viruses that are not arboviruses can cause encephalitis, and these include Mumps virus, Measles, Rubella, Henipah, and Enteroviruses. The only other DNA virus known to cause encephalitis is the JC virus, which belongs to the Polymavirinae subfamily. Although these viruses have very different biological properties, they can all enter the central nervous system, replicate in neurons, promote inflammation in the brain, and consequently cause encephalitis. In general, patients with encephalitis suffer from fever, headache, seizures, and photophobia. Less commonly, stiffness of the neck can occur with rare cases of patients also suffering from stiffness of the limbs, slowness in movement and clumsiness depending on which part of the brain is involved. Encephalitis is not a typical outcome of viral infections, but it is life threatening and

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difficult to treat. This chapter discusses the properties of viruses that cause encephalitis, how they cause clinical disease, and available therapeutic that are available.

29.2 Herpesvirus Mediated Encephalitis

The Herpesviridae family is divided into three subfamilies: α-herpesviriane, β-herpesvirinae, and γ-herpesvirinae. Each subfamily member contains a human virus that can cause encephalitis and these viruses are discussed below.

29.2.1 Herpes Simplex Virus 1 (HSV-1) Mediated Encephalitis

29.2.1.1 Epidemiology of HSV-1

Approximately 90 % of the population is infected with herpes simplex virus 1 (HSV-1), and at least 10 % with HSV-2 (Whitley 1997; Nahmias and Roizman 1973). Humans are the only natural reservoir for this infection and no vector is needed for virus transmission (Stanberry 2004). HSV-1 primary infection occurs mainly in childhood and HSV-2 infection occurs predominantly in sexually active adolescents and young adults. HSV encephalitis (HSE) is the most common causative agent of encephalitis of the herpesviruses.

29.2.1.2 Pathogenesis and Clinical Symptoms of HSE

HSV is the most commonly identified cause of acute, sporadic viral encephalitis in the U.S. accounting for 10–20 % of all cases (Corey 2005). It is estimated that there are approximately 2000 new diagnosed HSE cases per year in the U.S. There are peaks at 5–30 years of age, and at more than 50 years of age. Since the 1940s, HSV-1 and HSV-2 have been implicated in the causation of acute necrotizing encephalitis in infants, children and adults. Encephalitis due to HSV 2 in newborn infants is a widespread disease in the brain and commonly involves a variety of other organs in the body including the skin, eyes and lungs (Stanberry et al. 2004). HSE is typically associated with necrotic cell death resulting from virus replication and inflammatory changes secondary to virus-induced immune response (DeBiasi et al. 2002). However, there is not a perfect correlation between virus burden in the brain and the severity of histological changes and neurological symptoms. Deficiency of a cellular gene, UNC-93B, was identified in a family that had a high incidence of encephalitis (Casrouge et al. 2006). The UNC-93B gene apparently plays a role in interferon signaling indicating the importance of controlling virus replication in the CNS of infected individuals.

Two recognizable groups of symptoms are seen in most patients. There are nonspecific clinical symptoms that include fever, headache, meningeal irritation, nausea, vomiting, confusion, generalized seizures, and alteration of consciousness. The second group of changes is referred to as focal necrosis of the orbitofrontal and temporal cortexes and the limbic system, and includes anosmia, memory loss, peculiar behavior, speech defects, hallucinations (particularly olfactory and gustatory) and focal seizures. There is rapid progression in some cases with the appearance of reflex asymmetry, focal paralysis, hemiparesis and coma. Cerebral edema contributes to these symptoms and plays an important role in the outcome (Stanberry et al. 2004).

HSE is characterized by severe destruction of temporal and frontal lobe structures, including limbic mesocortices, amygdala, and hippocampus. Without antiviral therapy, the mortality rate is as high as 70 %; but even after antiviral therapy 20 % of these patients die. Despite early treatment, chronic progressive tissue damage in magnetic resonance imaging (MRI) can be found up to 6 months following the onset of symptoms. Approximately 2/3 of HSE cases occur because of reactivation from latency (Yamada et al. 2002), which explains why there is high morbidity and long-term complications despite antiviral treatment (Lahat et al. 1999; McGrath et al. 1997; Skoldenberg 1991).

29.2.1.3 Summary of Productive Infection

HSV-1 and HSV-2 are double stranded DNA viruses with a genome size of 152 kb, and they encode at least 84 proteins. Binding and entry of HSV-1 into permissive cells is mediated by viral proteins interacting with cellular receptors (Spear 1993). After uncoating, the viral genome is present in the nucleus and viral gene expression ensues. HSV gene expression is temporally regulated in three distinct phases: immediate early (IE), early (E), or late (L) (Honess and Roizman 1974). IE gene expression does not require protein synthesis and is stimulated by VP16 (O'Hare 1993). In general, proteins encoded by IE genes regulate viral gene expression, and as such are important for productive infection. E gene expression is dependent on at least one IE protein, and generally E genes encode nonstructural proteins that control viral DNA synthesis. L gene expression is maximal after viral DNA replication, requires IE protein expression, and L proteins comprise the virion particle.

29.2.1.4 Summary of Latent Infection

Acute infection is typically initiated in mucosal epithelium, and then HSV-1 establishes latency in sensory neurons located in trigeminal ganglia (TG) or sacral dorsal root ganglia. Despite a vigorous immune response during acute infection, latency is established. As many as 20–30 % of sensory neurons are latently infected [reviewed in (Jones 2003; 1998)]. As a consequence of primary infection, HSV-1 genomic DNA is also present in the central nervous system (CNS) of a significant proportion of the adult human population (Fraser et al. 1981).

The latency associated transcript (LAT) is abundantly transcribed in latently infected neurons [reviewed in (Jones 2003; 1998)]. Mice, rabbits, or humans latently infected with HSV-1 express LAT. In productively infected cells or latently infected rabbits, an 8.3 kb transcript is expressed that has the same sense as LAT. Splicing of the 8.3 kb transcript yields an abundant 2 kb LAT and an unstable 6.3 kb LAT. The majority of LAT is not capped, is poly A-, appears to be circular, and is designated as a stable intron. In small animal models, LAT is important but not required for the latency-reactivation cycle [reviewed in (Jones 2003; 1998)]. The first 1.5 kb of LAT coding sequences are important for reactivation from latency. A study by (Umbach et al. 2008) concluded LAT is a micro-RNA (miRNA) precursor that encodes four miRNAs plus two within LAT promoter sequences. The various LAT encoded micro-RNAs inhibit expression of key viral transcriptional regulatory proteins (ICP4 and ICP0) and the neurovirulence protein ICP34.5 (Tang et al. 2008; 2009). The miRNAs that are abundantly expressed during latency do not appear to be essential for latency using a mouse model of infection (Kramer et al. 2011).

LAT interferes with apoptosis in transiently transfected cells, and in TG of infected rabbits or mice (Jones 2003). Inhibiting apoptosis may be the most important function of LAT because two anti-apoptosis genes, the bovine herpesvirus 1 LAT homologue (Mott et al. 2003; Perng et al. 2002) and the baculovirus IAP gene (Jin et al. 2005) restores wild-type levels of spontaneous reactivation to a LAT null mutant. Two additional small RNAs (s-RNAs) encoded within the first 1.5 kb of LAT coding sequences (Peng et al. 2008) inhibit apoptosis as well as productive infection (Shen et al. 2009). These LAT s-RNAs are not miRNAs because they lack Dicer cleavage sites and a mature miRNA band that migrates between 21–23 nucleotides is not detected.

29.2.1.5 Animal Models for Studying HSE

HSE occurs in a certain percentage of mice or rabbits following infection. The frequency of HSE in experimental infections is dependent on the pathogenic potential of HSV-1, and the mouse strain used for experimental infection. For HSE to occur after ocular infection, the virus must enter the TG, and then spread to the CNS, or the virus directly gains access into the brain via the optic nerve. Models have also been developed in which HSV is directly inoculated into the brain. In this model, transport from the peripheral tissue → peripheral nervous system → CNS is not important. Thus, viral genes necessary for neuronal transport and spread are not as important if the brain is inoculated.

Viral genes necessary for productive infection, inhibiting apoptosis, or inhibiting immune recognition play a significant role in the potential of HSV to initiate encephalitis. Innate immune responses play a significant role in lethal encephalitis because HSV-1 interactions with toll-like receptor 2 contributes to HSE (Kurt-Jones et al. 2004). LAT, although not important for productive infection, enhances the frequency of encephalitis in male Balb/C mice (Jones et al. 2005). These studies add support to the concept that viral and host factors regulate the frequency of HSE.

29.2.2 Varicella Zoster Virus (VZV) Induced Encephalitis

29.2.2.1 Epidemiology of VZV

Humans are the only known reservoir for VZV, and VZV is a ubiquitous human pathogen. A serologic study of 1201 US military trainees indicated that 95.8 % of the population has been exposed to virus (Jerant et al. 1998). Chickenpox is common in childhood and affects both genders equally as well as people of all races. VSV is spread by droplet or airborne transmission and is highly contagious. Primary infection produces varicella (chickenpox), after which VZV becomes latent in neurons of TG, cranial nerve, dorsal root, and autonomic ganglia along the entire neuro-axis. Reactivation can occur decades later resulting in zoster (shingles). The details of latency and neuropathogenesis are presented below.

29.2.2.2 Clinical Features of VZV

Acute VZV infection leads to chickenpox, which results in an extensive vesicular rash (Abendorth and Arvin 2000). Chickenpox in the immunocompetent child is mostly benign and associated with lassitude and a temperature of 100–103 °F for 1–2 days. Other symptoms include malaise, itching, anorexia, weakness and exhaustion, which gradually resolve as the illness improves. The hallmark of chickenpox is the skin manifestations that consist of maculopapules, vesicles and scabs in varying stages. In general, immunocompromised children have more lesions. Although chickenpox is usually a mild disease, there are exceptions. For example, an epidemic of 292 cases of chickenpox occurred in rural India resulting in 3 deaths (Balraj and John 1994). In the United Kingdom, about 25 people die from chickenpox every year, in part because VZV vaccination is not mandatory (Rawson et al. 2001). VZV vaccine effectively prevents varicella; however breakthrough varicella and virus reactivation can still occur [reviewed by (Arvin and Gershon 1996)].

With chickenpox, the most frequent organ affected other than the skin is the CNS (Liesegang 1999). The neurologic abnormalities are often seen as acute cerebellar ataxia or encephalitis. Encephalitis is the most serious complication of chickenpox and it can be life threatening in adults. It occurs in 0.1–0.2 % of patients with chickenpox (Johnson and Milbourn 1970).

Herpes zoster is characterized by a unilateral vesicular eruption with a dermatome distribution and affects up to one mil-

lion people in the United States each year, reviewed in (Gilden et al. 2007). Since VZV is latent in most ganglia, herpes zoster can occur nearly anywhere on the body. The most common sites are the thoracic and in the cutaneous distribution of the ophthalmic branch of the trigeminal nerve. Postherpetic neuralgia (pain that persists more than 30 days after the onset of rash of after cutaneous healing) is the most serious complication in immunocompetent patients and generally occurs in patients more than 60 years old. Acute retinal necrosis caused by VZV occurs occasionally in immunocompetent patients although more recent reports have focused on ocular disease in HIV-infected patients. In HIV-infected patients, the lesions rapidly increase in size and coalesce. These lesions respond poorly to antiviral therapy and almost inevitably cause blindness in the involved eye. Retinitis is less aggressive in immunocompetent patients and can often be treated with antiviral therapy such as acyclovir. Neurologic complications associated with zoster are diverse, including motor neuropathies of the cranial and peripheral nervous system, encephalitis, meningoencephalitis, myelitis and Guillain-Barre syndrome (Liesegang 1999). Extracutaneous sites of involvement include the CNS as shown by meningoencephalitis or encephalitis. The clinical symptoms are similar to those of other viral infections of the brain. Involvement of the CNS with cutaneous herpes zoster is probably more common than recognized clinically. Classically, VZV infection involves dorsal root ganglia. Motor paralysis can occur as a consequence of the involvement of the anterior horn cells, in a manner similar to that encountered with polio. These patients may have severe pain. Herpes zoster in the immunocompromised patient is more severe than in the normal person but even in these patients disseminated herpes zoster is rarely fatal. Following a zoster outbreak, VZV can spread to blood vessels of the brain, leading to vasculopathy, particularly in immunocompromised patients.

Therapy for herpes zoster is aimed at accelerating healing, limiting the severity and duration of acute or chronic pain, and reducing complications associated with the infection. In patients who are immunocompromised, therapy should be aimed at reducing the risk of viral dissemination. Acyclovir, valacyclovir and famciclovir are all used in the U.S. for the treatment of herpes zoster. Acyclovir is approved in the U.S. for the treatment of both chickenpox and herpes zoster in the normal host. Oral acyclovir therapy in normal children, adolescents and adults shortens the duration of lesion formation by about a day, reduces the total number of new lesions by about 25 % and reduces many of the symptoms in about one-third of patients (Snoeck et al. 1999; Gnann and Whitley 2002).

29.2.2.3 Summary of Productive Infection and Latency

VZV contains many genes similar to HSV-1 suggesting they are functional homologues. Thus, the general steps during productive infection are similar for VZV and HSV-1, and will not be discussed in detail. In contrast to HSV-1, VZV infectious virus produced during productive infection is tightly cell associated making it difficult to obtain high yields of virus.

VZV appears to be latent only in ganglia and viral genomes are primarily found in sensory neurons. Analysis of latent VZV is restricted to human ganglia obtained at autopsy. Based on *in situ* hybridization (ISH) studies combined with sequencing, four transcripts corresponding to VZV genes 21, 29, 62, and 63 have been identified in latently infected human ganglia (Gilden et al. 2007). A monospecific polyclonal antiserum directed against VZV ORF 63 protein detected this protein in the cytoplasm of neurons [reviewed in (Mitchell et al. 2003)]. These VZV proteins are primarily in the nucleus during productive infection (zoster), suggesting that the cytoplasmic location might maintain VZV in a latent state. In contrast to HSV-1, VZV does not appear to encode a LAT that is abundantly expressed during latency. Several independent studies have demonstrated that T cells, $CD8^+$ T lymphocytes in particular, are crucial for controlling HSV infection in sensory ganglia (Nash et al. 1987; Simmons et al. 1992). A persistent cell-mediated immune response occurs in TG during HSV-1 latency, and that $CD8^+$ as well as CD4+ T lymphocytes reside in TG and inhibit reactivation from latency long after acute infection is over (Nash et al. 1987; Simmons and Tscharke 1992; Simmons et al. 1992; Khanna et al. 2003; Liu et al. 1996, 2000a, b, 2001; Prbhakaran et al. 2005). In sharp contrast, persistent infiltration of lymphocytes in human or macaque TG latently infected with human VZV (Verjans et al. 2007) or simian VZV (Ouwendijik et al. 2013) does not occur. However, infiltration of lymphocytes does occur in TG when simian VZV reactivates from latency (Ouwendijik et al. 2013).

29.2.2.4 Neurological Disorders Associated with VZV

In general, neurological diseases occur as a result of reactivation from latency. The neurological complications after VZV reactivation are serious and can be life-threatening. VZV is the causal agent in 29 % of 3231 cases of encephalitis, meningitis, and myelitis, and the most common cause of encephalitis in patients over the age 65 (Rantalaiho et al. 2001). More than 500,000 Americans develop zoster (severe dermatomal distribution pain and rash) every year. Zoster is frequently followed by postherpetic neuralgia (pain that persists for months and often years after the rash disappears), myelitis, or unifocal or multifocal vasculopathy. Many cases of VZV vasculopathy, myelitis, and polyneuropathy occur in the absence of rash. Since VZV causes a wide spectrum of neurological disorders, testing for VZV DNA and antibody in cerebrospinal fluid (CSF) should be routinely performed. Proper diagnosis is critical because antiviral treatment can be curative, even after weeks to months of chronic VZV infection.

Reactivation of latent VZV in dorsal root ganglia results in a localized cutaneous eruption termed "herpes zoster" (or shingles). The annual incidence is about 1.5-3.0 cases per 1000. Zoster occurs during the lifetime of 10–20 % of all persons (Liesegang 1999). The epidemiology of herpes zoster differs from that of chickenpox. Decreasing virus-specific cell-mediated immune responses, which occur naturally as a result of aging or from immunosuppressive illness or medical treatments, increase the risk of shingles (Gnann and Whitley 2002). Most patients who develop herpes zoster have no history of exposure to other persons with VZV infection at the time of the appearance of lesions. Over 90 % of adults in the U.S. have serologic evidence of VZV infection and are at risk for herpes zoster. Patients with cancer, those receiving immunosuppressive agents and organ-transplant recipients are thus at an increased risk of shingles. Furthermore, individuals who are positive for human immunodeficiency virus also develop herpes zoster at a higher frequency than those who are negative (Liesegang 1999).

29.2.2.5 Potential Models to Study VZV Neuropathogenesis

Unlike HSV-1, VZV does not reactivate from ganglia after experimental infection of primates or rodents. However, after footpad inoculation of rats with VZV, the protein encoded by gene 63 can be detected in lumbar ganglia 1 month after infection (Debrus et al. 1995). Viral protein is also detected in neurons, both in the nuclei and cytoplasm of infected cells. An independent study using the same rat model detected VZV gene 63 DNA in 5–10 % of neurons and VZV RNA in neurons and non-neuronal cells (Kennedy et al. 1999). Simian varicella virus may also be a valuable model to study the pathogenesis of varicella virus-host interactions. Finally, VZV infection of humanized immuno-defficient mice (SCID-hu) has provided new information about viral genes that regulate viral growth and pathogenesis (Ku et al. 2005).

29.2.3 Human Cytomegalovirus (HCMV) Induced Encephalitis

29.2.3.1 Epidemiology of HCMV

HCMV is widely distributed among humans from developed and industrial nations as well as isolated aboriginal groups (Pass 1995). The prevalence of HCMV increases with age in every group that has been studied. In general, prevalence is greater and acquired earlier in life in developing countries, and in lower socioeconomic sections of developed countries (Pass 2001).

29.2.3.2 Clinical Features of HCMV

Although HCMV acute infection is usually asymptomatic in patients with intact immune systems, it is a common opportunistic pathogen in immunocompromised patients. In HIV-infected individuals, HCMV disease appears to be due to reactivation of the latent virus. The clinical manifestations of HCMV disease are generally seen when the $CD4^+$ T-lymphocyte count falls below 100 cells/ml. Retinitis is perhaps the most well known disease associated with this infection. Other features associated with infection include gastro-intestinal disease, pneumonitis and neurologic disease. HCMV is associated with various neurologic infections in persons infected with HIV, particularly inflammation of the ventricle accompanied by encephalitis (ventriculoencephalitis) and ascending polyradiculopathy (disease or injury involving multiple nerve roots). Ventriculoencephalitis usually occurs in advanced HIV infection of patients with a prior HCMV diagnosis. Polyradiculopathy is the most common CNS infection caused by HCMV and is characterized by urinary retention and progressive bilateral leg weakness. Clinical symptoms generally progress over several weeks to include loss of bowel and bladder control, and paralysis. A spastic myelopathy has been reported and sacral paresthesias may also occur. The CSF often shows a greater than normal number of cells, less than normal content of glucose, and elevated protein levels (Cheung and Teich 1999; Cheeseman et al. 2004).

29.2.3.3 Summary of Virus Lifecycle

HCMV is a β-herpesvirinae subfamily member that is an important causative agent of congenital disease, and a significant opportunistic infection (Knipe and Howley 2001). Like other herpesviruses, HCMV is a large DNA virus that is estimated to encode approximately 165 genes. In contrast to HSV-1, HCMV exhibits a restricted host range in cell culture. Primary differentiated fibroblasts show the greatest susceptibility to infection. As with other herpesvirus members, HCMV immediate early genes regulate viral transcription, and inhibit cellular responses to infection (apoptosis and interferon induction for example).

29.2.3.4 Pathogenesis and Persistence of HCMV

Unlike HSV-1 and VZV, HCMV does not establish latency in the nervous system. Myeloid-lineage hematopoietic cells (granulocytes, macrophages, and dendritic cells for example) are important targets for lifelong latency. It is now well established that one site of HCMV latency in vivo is cells of the myeloid lineage including CD14+ monocytes and their CD34+ progenitors, reviewed in (Poole et al. 2014). Low passage HCMV strains (Toledo and FIX for example) can efficiently establish latency in CD34+ cells whereas strains extensively passaged in cell culture (AD169 and Towne) do not because the low passage strains contain additional genes (UL133-UL138). The UL138 ORF is required for HCV to establish and maintain a latent infection in CD34+ hematopoietic progenitor cells infected in vitro (Goodrum et al. 2007).

The UL138 protein localizes to the Golgi apparatus and a mutant that expresses the UL138 transcripts, but not the protein, has an impaired loss of latency phenotype (Petrucelli et al. 2012), which raises the possibility that additional viral genes located between UL133-UL138 are important for latency.

29.2.3.5 HCMV Induced Encephalitis

Approximately, two out three newborn children that have symptomatic congenital CMV infection have CNS involvement (Bopanna et al. 1992). CNS pathology includes microcephaly, elevation of cerobrospinal fluid protein, and neurologic abnormalities (poor feeding, lethargy, or generalized hypotonia for example). Cranial computed tomography scans are abnormal in 75% of symptomatic newborns, with the most common abnormality being periventricular calcification (Bopanna et al. 1997). Fortunately, only 5–10% of newborns with congenital HCMV infection are symptomatic.

29.2.4 Human Herpesvirus 6 (HHV-6) Induced Encephalitis

Like HCMV, HHV-6 is a β-herpesvirinae subfamily member. HHV-6 was originally isolated from peripheral blood leukocytes of patients with lymphoproliferative disease (Salahuddin et al. 1986) and is now recognized as the causative agent of exanthem subitum, also referred to as roseola, (Yamanishi et al. 1988). Following acute infection, HHV-6 can persist in several different cell types, including peripheral lymphocytes. Since the receptor for HHV-6 (complement-regulatory trans membrane protein CD46), is widely expressed in humans, HHV-6 has the potential to infect many cell types (Santoro et al. 1999).

HHV-6 DNA and certain viral transcripts, but not viral antigens, have been detected in brains of healthy immunocompetent humans suggesting the virus is latent, reviewed in (Reynaud and Horvat 2013). Several studies have concluded that HHV-6 can cause encephalitis (Reynaud and Horvat 2013; Yoshikawa and Asano 2000; Nagasawa et al. 2007). The clinical symptoms associated with HHV-6 induced encephalitis appear to be distinct relative to other herpesviruses because there is a cluster of convulsions during the eruptive stage. The features of HHV-6 induced encephalitis are summarized below (Nagasawa et al. 2007). First, primary infection occurs in a normally developing infant followed by the initial convulsion with the onset of encephalopathy occurring on the second day of febrile illness. Following the first convulsion, consciousness is disturbed. Frequent convulsions occur within one day after fever is resolved, which is associated with the onset of exanthem subitum (eruptive stage). Conversely, "typical" encephalitis that features convulsions and severe disturbance of consciousness has been described following initial stages of disease: then a slow recovery ensues.

29.2.5 γ-Herpesvirus Induced Encephalitis

Although Epstein Barr Virus (EBV) can cause encephalitis (Fujimoto et al. 2003; Hussain and Hussain 2013; Bhatti et al. 1990), it is a relatively rare event when compared to HSV-1 or CMV. Since EBV acute infection is primarily initiated in pharyngeal tonsils (infectious mononucleosis) and then establishes a latent infection in B cells, reviewed by (Young and Rickinson 2004; Cohen 2000), it is not surprising that encephalitis occurs only rarely.

29.2.6 Therapeutic Agents Available to Treat Herpesvirus Infections and Encephalitis

29.2.6.1 Acyclovir

Acyclovir is an acyclic guanine nucleoside analog that lacks a 3′-hydroxyl on the side chain. Acyclovir was the first drug clearly demonstrated to be effective against herpes simplex virus infections (Wagstaff et al. 1994). Acyclovir selectively inhibits viral DNA synthesis because it is preferentially activated in virally infected cells. Cellular uptake and initial phosphorylation are facilitated by the herpes virus thymidine kinase. The affinity of acyclovir for HSV thymidine kinase is about 200-fold greater than for the mammalian enzyme. Cellular enzymes subsequently convert the monophosphate to acyclovir triphosphate. Acyclovir triphosphate is present in 40- to 100-fold higher concentrations in HSV-infected than in uninfected cells, and competes for endogenous deoxyguanosine triphosphate. The triphosphate competitively inhibits viral DNA polymerases to a much greater extent than cellular DNA polymerases. The triphosphate is also incorporated into viral DNA where it acts as a chain terminator as a result of the lack of the 3′-hydroxyl group. The terminated DNA template containing acyclovir binds the enzyme and leads to irreversible inactivation of the DNA polymerase (Wagstaff et al. 1994; Scholar 2000). The oral bioavailability of acyclovir is poor and ranges from 10–30%. The drug is poorly protein bound but is widely distributed throughout body fluids and tissues including the cerebrovascular fluid. It is primarily excreted unchanged in the urine (Wagstaff et al. 1994).

Acyclovir is useful for treating infections caused by HSV, herpes zoster and for VZV infections (Whitley and Roizman 2001). Acyclovir is the major therapy used for HSV encephalitis. It should be given intravenously at a dose of 10 mg/kg every 8 h for 14–21 days. It is usually well tolerated with few side effects. Although HCMV is relatively resistant to acyclovir, some cytomegalovirus infections have responded marginally to large doses of acyclovir and it seems to be effective for the prophylaxis of cytomegalovirus infections in immunocompromised patients. Epstein-Barr virus is not sensitive to acyclovir and clinical infections do not respond to the drug.

Oral acyclovir is recommended for the treatment of VZV infection (chickenpox) in patients over 13 years-of-age who are otherwise healthy, children over 12 months of age with a chronic cutaneous or pulmonary condition, or receiving long-term salicylate therapy, and in children receiving short or intermittent courses of aerosolized corticosteroids. Intravenous acyclovir should be used for treatment of varicella infection in immunocompromised children, including those receiving high doses of corticosteroids. In general, acyclovir is the most effective agent for the treatment of infections caused by VZV (Snoeck et al. 1999).

Parenteral acyclovir is the drug of choice for the treatment of initial and recurrent mucosal or cutaneous herpes simplex infections in immunocompromised patients and for the treatment of disseminated, neonatal, encephalitic, and severe first episodes of genital herpes simplex infections in immunocompetent patients (Whitley 1997). Intravenous acyclovir should also be used for severe diseases such as encephalitis (Brady and Bernstein 2004). Acyclovir is generally well tolerated whether administered topically, orally or by the intravenous route. Gastrointestinal disturbances, headache, and rash may occur. Renal dysfunction due to crystalline nephropathy is more likely with IV administration, rapid infusion, and in patients in the dehydrated state and with underlying renal disease and large doses. CNS effects are rare but include encephalopathy, tremors, hallucinations, seizures, and coma. Due to an elevated pH, intravenous administration may also cause phlebitis and inflammation at sites of extravasation (Wagstaff et al. 1994).

29.2.6.2 Valacyclovir

Valacyclovir is an ester prodrug of acyclovir. It provides significantly better oral bioavailability compared to acyclovir. This advantage results in substantially higher serum concentrations than is possible with oral acyclovir. In addition, fewer daily doses are required with valacyclovir (Curran and Noble 2001). Valacyclovir and famciclovir are alternative drugs used for the treatment of HSV encephalitis (Griffiths 1995; Stanberry et al. 2004; Stanberry et al. 2002).

After oral administration and absorption, valacyclovir is converted to acyclovir which is the active antiviral component of valacyclovir. The antiviral activity and mechanism of action of valacyclovir is identical to that of acyclovir (Perry and Faulds 1996). The oral bioavailability of valacyclovir is significantly greater than that of acyclovir. Oral administration of valacyclovir results in plasma acyclovir concentrations comparable to those observed with intravenous acyclovir.

Valacyclovir is effective for the treatment of herpes zoster (shingles), for the treatment of initial and recurrent episodes of genital herpes, and for suppression of recurrent genital herpes in immunocompetent and HIV-infected patients. It is also indicated for the reduction of transmission of genital herpes in immunocompetent individuals, and for the treatment of cold sores. Valacyclovir appears to be equally effective in treating herpes zoster and recurrent genital herpes in immunocompetent adults. Valacyclovir has shown efficacy in the prophylaxis of cytomegalovirus infections in transplant patients (Perry and Faulds 1996).

Like acyclovir, valacyclovir is a well-tolerated drug. The most common adverse effects of valacyclovir are headache and nausea. Other adverse effects associated with valacyclovir administration include vomiting, weakness, dizziness, and abdominal pain. Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome has also been reported in a few patients after high doses of valacyclovir as has confusion, hallucinations and nephrotoxicity (Perry and Faulds 1996; Curran and Noble 2001).

29.2.6.3 Famciclovir

Famciclovir is an oral prodrug of the antiviral agent penciclovir. Famciclovir lacks intrinsic viral activity and this drug owes its activity to formation of penciclovir. Penciclovir is an acyclic guanine nucleoside analog. Penciclovir and its prodrug famciclovir are chemically similar to acyclovir. Penciclovir differs structurally from acyclovir only by the presence of an additional hydroxyl group. Famciclovir is the diacetyl 6-deoxy analogue of penciclovir. The mechanism of antiviral activity of penciclovir is similar to acyclovir. Both drugs inhibit viral DNA synthesis (Scholar 2000). Penciclovir is rapidly and selectively phosphorylated in virus-infected cells by viral thymidine kinase to the monophosphate and this is followed by further phosphorylation to the triphosphate, which is the active form of the drug. Over 90 % of penciclovir triphosphate in virus cells is the (S)-enantiomer, a competitive inhibitor of DNA polymerases with respect to the natural substrate deoxyguanosine triphosphate (dGTP). Inhibition of the polymerase results in prevention of viral replication by inhibition of viral DNA synthesis. The R-enantiomer of penciclovir triphosphate has only minimal activity on viral DNA polymerases (Scholar 2000). In contrast to acyclovir triphosphate, which is an obligate DNA chain terminator, penciclovir triphosphate allows DNA chain extension owing to its free hydroxyl group; however, penciclovir appears at least as effective as acyclovir as an inhibitor of herpes virus DNA synthesis.

Famciclovir is rapidly converted to penciclovir in intestinal and liver tissue after oral administration. More than half of an oral dose of famciclovir is excreted in the urine as unchanged penciclovir. The plasma elimination half-life of penciclovir is about 2 h, similar to that of acyclovir; however, the intracellular half-life of penciclovir in herpes virus-infected cells is considerably longer than that of acyclovir.

Oral famciclovir is used for the treatment of immunocompetent patients with herpes zoster infections and for the treatment and suppression of recurrent genital HSV. It is also effective for the treatment of recurrent mucocutaneous her-

pes simplex in both immunocompetent and immunocompromised patients. Famciclovir is fairly well tolerated. Adverse effects include headache, dizziness, nausea, and diarrhea (Scholar 2000).

29.2.6.4 Ganciclovir

Ganciclovir is an acyclic guanine nucleotide analog with a structure similar to acyclovir but with an additional hydroxymethyl group on the acyclic side chain. It is inhibitory to all herpes viruses but is especially active against cytomegalovirus. Like acyclovir and penciclovir, ganciclovir inhibits viral DNA synthesis. Also like these other agents, the virus-induced enzyme to the monophosphate form first phosphorylates it intracellularly. Cellular enzymes catalyze further phosphorylation to the di and tri phosphates. Intracellular ganciclovir triphosphate concentrations are tenfold higher than those of acyclovir triphosphate and decrease much more slowly with an intracellular half-life of elimination greater than 24 h. These differences probably explain at least in part the greater activity of ganciclovir against HCMV and provide a rationale for single daily doses in suppressing HCMV infections. (Scholar 2000; Markham and Faulds 1994). Ganciclovir-triphosphate acts as an inhibitor and substrate for the cytomegalovirus DNA polymerase. Ganciclovir-triphosphate competitively inhibits the binding of deoxyguanosine triphosphate to DNA polymerase that results in the inhibition of DNA synthesis and termination of DNA elongation. Ganciclovir is incorporated into both viral and cellular DNA. It appears to limit viral DNA synthesis and packaging of viral DNA into infectious units.

The bioavailability of orally administered ganciclovir is quite low. In patients with normal renal function, the plasma half-life is about 2–4 h. Concentrations of ganciclovir in cerebrospinal fluid are lower than those in serum after intravenous administration (Markham and Faulds 1994). More than 90 % of the drug is eliminated unchanged in the urine. The plasma half-life increases as creatinine clearance declines and may reach 28–40 h in patients with severe renal insufficiency. Ganciclovir is an effective antiviral agent for the treatment of serious life threatening or sight-threatening HCMV infections in immunocompromised patients. Intravenous ganciclovir, foscarnet or the combination of both are recommended for the treatment of HCMV neurological syndromes (Markham and Faulds 1994).

The dose limiting and most common adverse effects with intravenous and oral ganciclovir is bone marrow suppression (anemia, leukopenia, neutropenia and thrombocytopenia). These effects are usually reversible upon withdrawal of the drug. CNS side effects are less common and range in severity from headache to behavioral changes to convulsions and coma. Fever, edema, phlebitis, disorientation, nausea, anorexia, rash, and myalgias have also been reported with ganciclovir therapy (Markham and Faulds 1994).

29.2.6.5 Foscarnet

Foscarnet is an inorganic pyrophosphate analog that has antiviral activity against all herpes viruses and the human immunodeficiency virus. Foscarnet is a pyrophosphate analogue that acts as a noncompetitive inhibitor of many viral RNA and DNA polymerases as well as HIV reverse transcriptase (Chrisp and Clissold 1991). It is approximately 100 fold more effective against the herpes virus DNA polymerase than the cellular DNA polymerase-α; however, some human cell growth suppression has been observed with high concentrations in vitro. Inhibition of DNA polymerase results in inhibition of pyrophosphate exchange which prevents elongation of the DNA chain (Scholar 2000). Similar to ganciclovir, foscarnet is a virostatic agent. Foscarnet is not a nucleoside and thus is not phosphorylated. It reversibly blocks the pyrophosphate-binding site of the viral DNA polymerase in a noncompetitive manner and inhibits cleavage of pyrophosphate from deoxynucleotide triphosphates.

The oral bioavailability of foscarnet is poor so intravenous therapy is needed to treat viral infections. It is fairly well distributed throughout the body with CSF levels averaging two-thirds of those in plasma. Foscarnet is taken up slowly by cells, and biotransformation of foscarnet does not occur. The drug is excreted mainly unchanged in the urine (Chrisp and Clissold 1991). Foscarnet is frequently used for treatment of HCMV retinitis and mucocutaneous acyclovir-resistant HSV infections. It may also be beneficial in other types of CMV or HSV infections (Wagstaff and Bryson 1994).

In contrast to ganciclovir, foscarnet is not associated with dose-limiting neutropenia, enabling it to be used in combination with zidovudine and other bone marrow suppressant drugs. Nephrotoxicity and hypocalcemia are the major dose-limiting toxicities. Renal toxicity can be minimized with adequate hydration. Changes in serum calcium and phosphate levels may be related to incorporation of the drug into bone. Other adverse effects of the drug include tremor, headache, fatigue, nausea, and vomiting. Some cases of penile and vaginal ulceration have also been reported.

29.2.6.6 Cidofovir

Cidofovir is an antiviral cytidine nucleotide analog with inhibitory activity against HCMV and other herpes viruses. Cidofovir is first converted to an active diphosphate form by cellular enzymes. Antiviral effects of cidofovir are due to inhibition of viral DNA polymerase by the diphosphate metabolite (Scholar 2000; Neyts and De Clercq 1994; Plosker and Noble 1999). The diphosphate probably interacts with DNA polymerase either as an alternate substrate (incorporation at the 3′-end or within interior of DNA chain) or as a competitive inhibitor (with respect to the normal substrate dCTP). Cidofovir inhibits HCMV DNA synthesis at intracellular concentrations 1000-fold lower than are

required to inhibit cellular DNA synthesis (Neyts and De Clercq 1994). For HSV-1 and HSV-2, corresponding concentrations are at least 50-fold lower.

Cidofovir has poor oral bioavailability (<5 %) and is therefore administered intravenously. It has a long intracellular half-life that allows for a prolonged interval between maintenance doses. Cidofovir is excreted extensively by the kidneys and is eliminated almost entirely as unchanged drug in the urine (Plosker and Noble 1999). Intravenous cidofovir is well tolerated. The major treatment limiting toxicity of this drug is irreversible nephrotoxicity (Plosker and Noble 1999). Intravenous pre-hydration with normal saline and administration of oral probenecid must be used with each cidofovir infusion to lessen the effects on the kidney. Serum creatinine and urine protein must be monitored with each infusion and adjusted accordingly. Other adverse effects associated with its use are neutropenia and peripheral neuropathy (Plosker and Noble 1999).

Cidofovir, ganciclovir, and foscarnet are effective at treating HCMV disease, and are approved for use in the U.S. (Cheeseman et al. 2004; Cheung and Teich 1999). Antiviral therapy for esophagitis, enterocolitis, encephalitis, peripheral neuropathy, polyradiculoneuropathy and pneumonitis is usually treated with intravenous ganciclovir or foscarnet regimens similar to those used for retinitis. Patients with CNS or neurologic disease often respond best to combination therapy (Arribas et al. 1996).

29.3 Arboviruses

Arboviruses are a group of RNA viruses transmitted by arthropod vectors. Clinical symptoms occur between 3–15 days after exposure and typically consist of fever, headache, and malaise, reviewed in (Kuno and Chang 2005). Less frequently, life-threatening encephalitis and hemorrhagic fever can occur. Arboviruses are maintained in nature by cycling between a vector, (mosquitoes, ticks, sandflies, as well as other arthropods) that consumes the blood of vertebrates. Vertebrates that have their blood consumed act as the hosts, with each vector usually preferring the blood of a specific species, making those species the host. Transmission between the vector and the host occurs when the vector feeds on the blood of the vertebrate, consequently the virus establishes infection in the salivary glands of the vector. High levels of infectious virus must be present in the blood of the host to allow transmission to the vector. If high levels of virus are not present in the host, viremia is not achieved and this infection is referred to as a "dead end host", which cannot be transmitted back to the vector. Below is a discussion of the major arboviruses that pose a health threat to humans.

29.3.1 West Nile Virus (WNV) Induced Encephalitis

29.3.1.1 Summary of Virus Lifecycle and Virus Transmission

West Nile virus (WNV) is a member of the Flaviviridae family (Lindenback and Rice 2001), and is a small positive strand RNA virus that is approximately 11,000 bases long. Genomic RNA serves as a messenger RNA that is translated into a single polyprotein. This polyprotein is then cleaved into at least 10 discrete proteins by cellular proteases and a virally encoded serine protease. Three structural proteins (C, prM, and E) are produced from the polyprotein (Fig. 29.1). Seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) are generated from the polyprotein. NS5 is the most conserved protein in the Flavirviridae family because this protein is the viral encoded RNA dependent RNA polymerase. The other non-structural proteins are not as well conserved suggesting they have virus-specific functions.

WNV has a broad range of antigenic variation and restriction-length polymorphisms indicating WNV has a highly variable genome. Strains from Africa, Europe, and the Middle East form a distinct group relative to strains isolated in India and the Far East (Price and O'Leary 1967). WNV is widely disseminated throughout Africa, Europe, the Middle East, and the Far East. During the summer of 1999, WNV was introduced to the east coast in the United States, and has since spread westward.

WNV can be readily grown in a variety of mammalian cell lines, and Drosophila cells (Lindenback and Rice 2001). In the wild, WNV is vectored by female mosquitoes of the genus *Culex*, and can infect a variety of small rodents and birds. In addition, WNV can infect soft and hard ticks under natural and experimental conditions. Almost all species of birds tested (wild species, chickens, and pigeons) develop viremia. During the recent US outbreak, a number of crows have been killed by

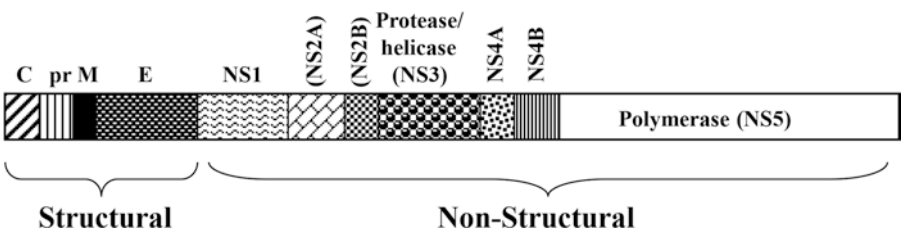

Fig. 29.1 Schematic of West Nile Virus genome. The various genes of the WNV genome are presented, and those comprising the non-structural proteins are denoted. For details, see text

the virus, which has been used to track virus spread (Anderson et al. 1999). Sporadic cases of naturally acquired infections can occur in horses, and these infections can lead to encephalitis. Bovine species do not develop viremia, but antibodies in cattle are prevalent. Finally, dogs are susceptible to infection, but low viremia levels preclude a significant role in virus transmission. Humans are a dead end host and human to human transmission is rare, but as described below infections can be serious.

29.3.1.2 Pathogenesis of encephalitis

The incubation period is 1–6 days, and the typical case is mild. Typical clinical features are fever, headache, backache, generalized myalgia, and anorexia. Rash occurs in about 1/2 of the cases, the rash is usually roseolar or macuolpapular, and usually involves the chest, back, and upper extremities. The disease usually runs its course in 3–6 days, and is usually milder in children. WNV can also cause severe, potentially fatal neurological disease, including encephalitis, meningitis, paralysis, and anterior myelitis. Although neurons are the primary target of WNV infection, a hallmark of WNV encephalitis is the accumulation of inflammatory infiltrates extending from the meninges in the brain parenchyma. These infiltrates are primarily comprised of lymphocytes and macrophages (Kelley et al. 2003). Most cases of WNV induced encephalitis generally occur in older individuals.

29.3.1.3 Animal Models for Studying WNV Induced Encephalitis

Mice have been used extensively to examine virus host interactions, and to examine virus induced encephalitis. The adaptive immune response plays a crucial role in controlling WNV infections in mice, including encephalitis (Diamond et al. 2003; Shresta and Diamond 2004; Wang et al. 2003). WNV infection leads to a toll-like receptor 3 dependent inflammatory response, which promotes brain penetration of the virus, neuronal injury, and enhanced encephalitis (Wang et al. 2004). Since toll-like receptor 3 recognizes double stranded RNA and promotes innate immune responses, this was somewhat surprising. The innate immune response also protects against WNV induced encephalitis because when mice lacking the alpha/beta interferon receptor are infected with WNV an increase in the frequency of encephalitis is seen in mice (Samuel and Diamond 2005). With the availability of a number of knockout mice, future studies should lead to identification of additional cellular factors that regulate WNV induced encephalitis.

29.3.2 Other Arboviruses Associated with Encephalitis

In addition to WNV, there are several additional encephalitic viruses that are transmitted via an insect vector, reviewed in (Stahl et al. 2011). With respect to North and South America, the notable arboviruses that cause encephalitis include Saint Louis encephalitis, Eastern encephalitic virus, Western equine encephalitic virus, La Crosse virus, and Colorado Tick Fever virus. In addition, there are several arboviruses that can cause encephalitis in other parts of the world, and these include Japanese encephalitis virus, Tick-borne encephalitis virus, and Toscana virus. Like WNV, these are RNA viruses.

29.3.3 Therapy

Currently there is no specific treatment for arboviruses. Treatment consists only of supportive and symptomatic care, including support of respiration, intravenous fluids and prevention of secondary infections. In addition, insect repellents and other antivectorial measures are used to reduce the incidence of human transmission.

29.4 Other Encephalitic Viruses

The final category of encephalitic viruses are non-herpesviruses that are not arbovirus members, reviewed in (Stahl et al. 2011). All viruses included in this category are transmitted via human to human and have no intermediate vector. The RNA viruses included in this category are Mumps virus, Measles, Rubella, Henipah, and Enteroviruses. The only other DNA virus known to cause encephalitis is the JC virus, which belongs to the Polymavirinae subfamily.

29.5 Review Questions

1. What are the common non-specific symptoms of a patient in the early stages of encephalitis?
2. If you are a physician and you diagnose a patient with encephalitis, which virus family would you fist expect and how would you treat these patients.
3. A patient who has been on vacation in a tropical setting exhibits signs of encephalitis, what family of viruses would you suspect to cause this disease? What is the logic for your choice?
4. What are the major differences between herpesviruses and arboviruses?
5. Can West Nile Virus be spread from human to human?
6. If you develop shingles and then develop headaches and other symptoms consistent with encephalitis, what virus might be the culprit?
7. There are three subfamily of herpesviruses? Which one would you suspect is the most common causative agent of encephalitis and why?

29.6 Answers

1. Patients in the early stages of encephalitis suffer from fever, headache, seizures, and photophobia. Less frequently, patients can also experience stiffness of the neck, stiffness of the limbs, slowness in movement, and clumsiness.
2. A member of the herpesviridae family would be expected. In particular, HSV-1, would be a reasonable guess because it causes encephalitis more frequently than other herpesviruses. Acyclovir or derivatives of acyclovir would be effective because this family of drugs inhibits the viral encoded thymidine kinase.
3. I would suspect arboviruses because they are frequently spread by insect bites, in particular mosquitoes.
4. Herpesviruses are large double stranded DNA viruses (>130,000 base pairs) that encode more than 80 viral proteins. Conversely, arboviruses are all RNA viruses that have a genome of approximately 10,000 bases that encode approximately 10 viral proteins. Transmission of arboviruses to humans is usually via an insect vector. In contrast, herpesviruses are spread via human to human spread; most common mechanism of spread is by aerosol and to a lesser extent by sexual transmission.
5. No. Human to human spread does not normally occur. Humans are considered to be a dead-end host. Birds commonly develop viremia and virus replication is high in birds.
6. Varicella Zoster Virus (VZV), the "Chicken Pox Virus". The rationale for this suspicion is many elderly suffer from VZV reactivation from latency, which frequently leads to chicken pox. When VZV reactivates from latency in the elderly, the virus may also enter the central nervous system where is can cause encephalitis.
7. ANSWER: Since α-herpesvirinae subfamily members establish a latent infection in sensory neurons, there ability to infect neurons is why they cause encephalitis more frequently. β- or γ-herpesvirinae subfamily members typically have a more restricted cell tropism and establish a latent infection in non-neural cells. Thus, they do not cause encephalitis as frequently as members of the α-herpesvirinae subfamily.

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