Pediatr Radiol (2007) 37:949–963
DOI 10.1007/s00247-007-0506-1

REVIEW

Neuroimaging of herpesvirus infections in children

Henry J. Baskin · Gary Hedlund

Received: 31 January 2007 / Revised: 20 March 2007 / Accepted: 10 April 2007 / Published online: 22 May 2007

Abstract Six members of the herpesvirus family cause well-described neurologic disease in children: herpes simplex virus-1 (HSV-1), herpes simplex virus-2 (HSV-2), varicella-zoster (VZV), Epstein-Barr (EBV), cytomegalovirus (CMV), and human herpes virus-6 (HHV-6). When herpesviruses infect the central nervous system (CNS), the clinical presentation is non-specific and often confounding. The clinical urgency is often underscored by progressive neurologic deficits, seizures, or even death, and prompt diagnosis and treatment rely heavily on neuroimaging. This review focuses on the spectrum of cerebral manifestations caused by these viruses, particularly on non-congenital presentations. Recent advances in our understanding of these viruses are discussed, including new polymerase chain reaction techniques that allow parallel detection, which has improved our recognition that the herpesviruses are neurotropic and involve the CNS more often than previously thought. Evolving knowledge has also better elucidated viral neuropathology, particularly the role of VZV vasculitis in the brain, HHV-6 in febrile seizures, and herpesvirus reactivation in immunosuppressed patients. The virology, clinical course, and CNS manifestations of each virus are reviewed, followed by descriptions of neuroimaging findings when these agents infect the brain. Characteristic but often subtle imaging findings are discussed, as well as technical pearls covering appropriate use of MRI and MRI adjuncts to help differentiate viral infection from mimics.

Keywords Herpesvirus · MRI · Children · Infants

H. J. Baskin (✉)
Department of Radiology,
Cincinnati Children's Medical Center,
3333 Burnet Ave.,
Cincinnati, OH 45229-3039, USA
e-mail: baskinhj@gmail.com

G. Hedlund
Department of Medical Imaging,
Primary Children's Medical Center,
Salt Lake City, UT, USA

Introduction

All of the members of the herpesvirus family are large, enveloped, double-stranded DNA viruses. The name "herpes" itself is derived from the Greek word *herpein* [1], which means "to creep," an appellation that reflects the important theme and unique ability of these viruses to cause a permanent, lifelong infection in their host. After primary infection, the herpesviruses persist in various cells of the body and maintain the ability to reactivate during periods of relative immunosuppression. Of the eight members of the herpesvirus family, six are well-known etiologic agents of central nervous system (CNS) disease: herpes simplex virus-1 (HSV-1), herpes simplex virus-2 (HSV-2), varicella-zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human herpes virus-6 (HHV-6). These viruses are ubiquitous and in most cases infect a large percentage of the population with only mild, self-limiting symptoms. Besides a tendency to remain latent, neurotropism is another characteristic shared by the herpesviruses [2, 3]. After initial infection, these viruses remain latent in the nerves, later seeding the CNS by diffusing across endothelial cells of cerebral vessels or by traveling retrograde along the nerves of the meninges [4–6]. These different mechanisms of entry are important to understand, because they influence the patterns of abnormalities seen with neuroimaging.

CNS involvement by the herpesviruses can occur in several settings. Congenital transmission is fairly common

in the case of CMV but also occurs with some frequency in HSV-1 and HSV-2. Vertical, non-congenital transmission is important in the epidemiology of HSV-2, and to a lesser degree HSV-1. HHV-6 have been increasingly recognized as agents of CNS disease in infants, particularly as a major cause of febrile seizures. Occasionally, unvaccinated but immunocompetent children with chickenpox will have CNS complications, and VZV is certainly important in children with suppressed immune systems. Finally, although EBV seropositivity is almost universal and only rarely causes CNS disease, EBV encephalitis often presents with acute status epilepticus [7] and is the most common agent to mimic herpes simplex virus encephalitis (HSE) [8].

New polymerase chain reaction (PCR) techniques have dramatically improved the sensitivity of detecting the herpesviruses [9] by allowing parallel PCR detection of all six aforementioned herpesviruses with a single sample of CSF [9–11]. The increased ability to diagnose herpesvirus infection by PCR does not mitigate the importance of neuroimaging. Indeed, MRI findings often provide the impetus to perform PCR. Several patients have been reported to have MRI findings highly suggestive of HSE but negative PCR. Presumptive treatment was begun based on MRI findings and later PCR test confirmed HSV infection [12]. In addition, the early use of MRI and MRI adjuncts such as diffusion-weighted imaging (DWI) and magnetic resonance spectroscopy (MRS) can help identify or exclude an alternative diagnosis in a patient with suspected viral encephalitis [13].

Herpes simplex viruses, types 1 and 2

Virology, clinical course, and CNS manifestations

There are two serotypes of HSV: HSV-1 and HSV-2. For practical purposes, HSV-1 typically involves the skin and mucosa of the face while HSV-2 is associated with genital infection. Because neonates usually acquire the infection during birth, neonatal herpes, which can cause CNS complications, is usually secondary to HSV-2. In contradistinction, the most common etiology of HSE in non-neonatal children is reactivation of HSV-1 [14]. Both serotypes are capable of causing congenital infection [5, 15].

Congenital HSV

True congenital HSV infection, i.e. transplacental transmission of the virus by the mother to the fetus, accounts for only 5–10% of "neonatal herpes." Congenital infection is usually caused by HSV-2 [16, 17] and is apparent within the first days of life. In these cases, the virus has crossed the placenta to infect the newborn and can be found in amniotic fluid and placental tissue [18, 19]. Affected neonates present with a combination of skin lesions, chorioretinitis, microcephaly, and/or hydranencephaly [5, 15]. This congenital presentation differs from neonatal herpes, and because it is outside the scope of this review, will not be discussed in further detail.

Neonatal HSV

The incidence of neonatal herpes is difficult to track because it is not a reportable disease, and HSV-1 and HSV-2 seroprevalence varies regionally. Most sources quote an incidence of one per 3,000 to 20,000 live births [20]. In contradistinction to congenital infection, which presents within the first few days of life, neonatal herpes results from contact with infected lesions or secretions during or shortly after birth [5, 15, 16, 21], and presentation is delayed for 2–4 weeks [5]. Children can contract the virus from an asymptomatic mother or even from close contact with caregivers during the perinatal period [15]. Neonatal HSV infection is divided into three categories: skin-eye-mouth (SEM) disease, CNS disease, and disseminated infection [15, 22], although there is clinical overlap, particularly of the latter two manifestations. Animal models have shown that cutaneous contraction of the virus results in SEM or mild disseminated disease, both with a relatively benign course. Individuals infected through the mucous membranes, respiratory tract, or eyes develop disseminated and/or CNS disease and have increased morbidity and mortality [23, 24]. Approximately 30% of all infected neonates develop CNS manifestations, presenting with seizures, irritability, lethargy, and/or fever [5, 15, 22]. Approximately two-thirds of neonatal herpes encephalitis is caused by infection with HSV-2 [15] and the prognosis is worse for these patients. In a study comparing the long-term outcome of treated neonatal herpes encephalitis, infants infected with HSV-2 had higher morbidity. Whereas children with HSV-1 CNS disease (n=9) were normal at follow-up, those with HSV-2 infection (n=15) had increased rates of microcephaly, seizures, cerebral palsy, and mental retardation [25]. It is recommended that neonates with herpes encephalitis be treated at higher doses than adults and children with HSE [26].

Non-neonatal herpes simplex encephalitis

Non-neonatal HSV is yet another entity, with unique clinical and imaging features compared to neonatal HSV infection [27]. To differentiate these two patient groups, throughout this article CNS manifestations in non-neonatal herpes will be referred to as HSE. HSE is the most common cause of non-epidemic focal encephalitis in children older than 6 months [14, 28, 29], and 25–30% of cases occur in

children [30]. HSE is usually caused by HSV-1 and is the manifestation of reactivated disease. HSV-1 is a ubiquitous virus that rarely causes neurologic complications. Children usually become infected with the virus early in life from direct contact with the secretions or lesions of infected individuals (who may or may not be symptomatic). The primary infection is more often asymptomatic, and likewise, the virus is typically shed from an asymptomatic individual. Gingivostomatitis is the second most common presentation of the primary viremia and is self-limiting. After primary infection, the virus persists in a latent form within the trigeminal sensory ganglion [6]. By unclear mechanisms, the virus occasionally reactivates and can travel retrograde along branches of the trigeminal nerve, along the ventral leptomeninges, and infect the brain, particularly the frontal and temporal lobes [5, 6]. This mechanism of entry, perhaps in concert with cellular tropism [2], accounts for the typical involvement of the limbic system in HSE discussed below. Patients with reactivation of HSV-1 typically present with antecedent fever and headache. Those with encephalitis have a combination of seizures, personality changes, acute mental status changes, and focal neurologic deficits [30], whereas those with meningitis typically lack focal neurologic abnormalities [29]. Early detection and diagnosis of HSV-1 encephalitis is crucial, as prompt administration of acyclovir can dramatically reduce morbidity and mortality [30]. Excellent recent reviews of pediatric [31] HSE [14] are available.

Neuroimaging findings

Neonatal herpes

In contrast to HSE seen in older children and adults, neonatal herpes rarely is hemorrhagic [5, 27] and the medial temporal and inferior frontal lobes are typically spared [4, 5, 32, 33]. CT of neonatal herpes encephalopathy shows patchy low density throughout the periventricular white matter [4, 32, 34] with corresponding T1-W hypointensity and T2-W hyperintensity on MRI. Proton density scans can best show the signal changes in neonates because increased T2-W signal can be hard to visualize on a background of immature unmyelinated white matter, which itself has high T2-W signal. Early changes of neonatal herpes might also be better seen on DWI as areas of restricted diffusion in the periventricular white matter [5, 35, 36] (Fig. 1). MRS can help narrow the differential by revealing decreased *N*-acetyl aspartate (NAA), elevated excitatory neurotransmitters, and possibly elevated lactate [5]. Post-contrast imaging is usually negative but occasionally demonstrates mild meningeal enhancement [5, 34]. As the disease progresses, some neonates have increased density of the cortex, which on MR is seen as increased T1-W and decreased T2-W signal. In the correct setting, this is a fairly specific pattern [5, 32] and is iatrogenic, the sequela of retained iodinated contrast agent rather than hemorrhage or calcification [37, 38]. Several months later, there is true gyriform calcification of the cortex, seen in concert with cortical thinning, white matter atrophy, and multicystic encephalomalacia [5, 39, 40].

Herpes simplex encephalitis and meningitis

Although patients with HSE occasionally have normal MRI scans, the majority have imaging findings in the inferomedial temporal lobes [13]. Indeed, because PCR is not 100% sensitive [28], MRI can sometimes identify patients with HSE in whom the PCR is initially negative. Weil et al. [12] documented three patients in whom initial PCR was negative, but because of high clinical suspicion and compelling MRI findings, the patients were presumptively

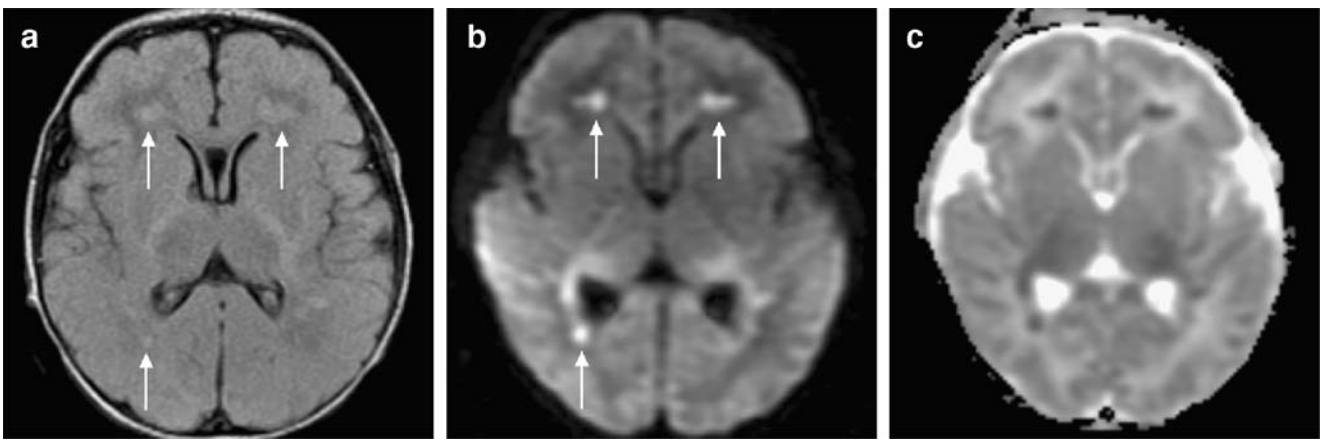

Fig. 1 Images of a 12-day-old neonate with disseminated HSV confirmed by PCR who presented with prolonged apneic episodes and "jitteriness." His delivery was uncomplicated, he was previously healthy, and his mother had no history of herpes. **a** Axial FLAIR image shows scattered hyperintense lesions in the bilateral periventricular white matter (*arrows*). **b** DWI at the same level shows that these lesions have restricted diffusion (*arrows*). **c** Dark signal on the corresponding apparent diffusion coefficient map indicates that this is true diffusion restriction rather than "T2 shine-through"

treated for HSE. All three patients had MRI abnormalities in the temporal lobes and later had positive PCR results. The spectrum of imaging abnormalities in HSE reflects the edema, hemorrhage, and necrosis seen pathologically. Similarly, the disease distribution in the inferior frontal and inferomedial temporal lobes and insular cortex [13] lends credence to the proposed route of entry into the brain along small branches of the trigeminal nerve.

CT scans can be normal or show non-specific areas of hypodensity in the inferior frontal and inferomedial temporal lobes [4]. Findings can be bilateral or unilateral but are usually asymmetric. MRI better demonstrates abnormalities in the aforementioned areas with characteristic signal changes also involving the limbic system and insular cortex. The cingulate gyrus, basal ganglia, and cortex of the parietal and occipital lobes are less frequently involved [13, 41]. T2-W images show swelling and increased signal intensity in the brain parenchyma. The corresponding areas have decreased T1-W signal and variable enhancement [4] (Fig. 2). Petechial hemorrhage is typical in HSE and can manifest on imaging studies as T1-W shortening or blooms of hypointensity on gradient recalled echo (GRE) scans [42]. Increased T1-W signal can be seen in a linear, gyriform configuration in the acute stage. This T1-W shortening represents cortical hemorrhage rather than laminar necrosis and is found to have resolved on follow-up imaging [43, 44]. The cytotoxic damage of HSE is well imaged with DWI. Areas of diffusion restriction have been shown to be one of the earliest signs of HSE [45, 46].

Leonard et al. [27] have described another pattern of non-neonatal HSE that occurs in infants. Their patients with documented HSV-1 lacked the typical findings of periventricular white matter abnormalities seen in neonatal herpes. On the other hand, imaging showed minimal hemorrhage and no involvement of the medial temporal or inferior frontal lobes, findings that are characteristic of HSE in older children. Instead, these infants had signal abnormalities that mirrored the anterior, middle, or posterior cerebral artery vascular territories. There was slight hypointensity and cortical thickening on T1-W imaging and corresponding increased T2-W signal in the hemispheric cortex and underlying white matter (Fig. 3). After contrast agent administration, diffuse enhancement was shown in the cortex but not in the overlying meninges. Absence of meningeal enhancement is peculiar if the virus' only mode of CNS entry is spread along the meningeal nerves. These observations have led some authors to hypothesize that HSV has a different route of entry to the CNS in younger children than in older children, spreading hematogenously across an immature blood–brain barrier rather than along nerve branches [4, 27].

HSV differential diagnosis and summary

HSV-1 and HSV-2 infections represent the archetype for herpesvirus CNS disease. The protean nature of the virus family is reflected in the spectrum of clinical presentations and imaging findings seen with CNS HSV infection. The differing mechanisms of CNS entry lead to the varied presentations and to the different neuroimaging appearances. The differential diagnosis of any given case will vary depending on the type of herpes encephalitis. In the older child with HSE, there is a pattern of non-enhancing cortical

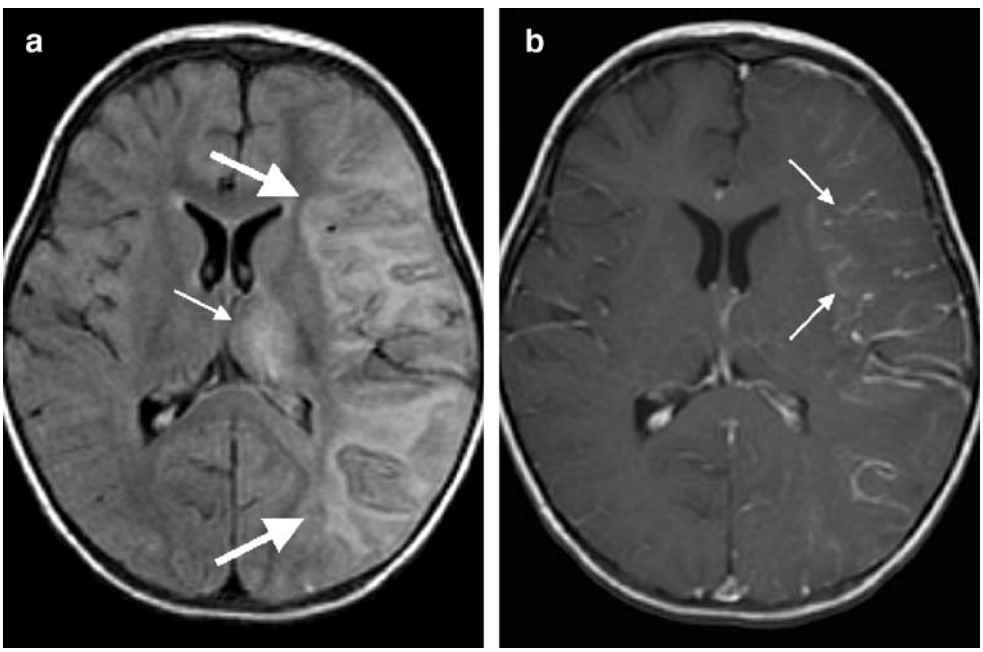

Fig. 2 HSV-1 encephalitis in a patient with fever and seizures of new onset. **a** Axial FLAIR image shows abnormal signal in a typical limbic distribution of HSE (*large arrows*). Abnormal signal in the left thalamus is also seen (*small arrow*). The signal abnormalities were best seen on FLAIR because the CSF signal is suppressed. **b** On the T1-W image after contrast agent administration, there is little enhancement in the parenchyma compared to that in the meninges and engorged veins (*arrows*). Note the edema and mid-line shift toward the right seen on both images

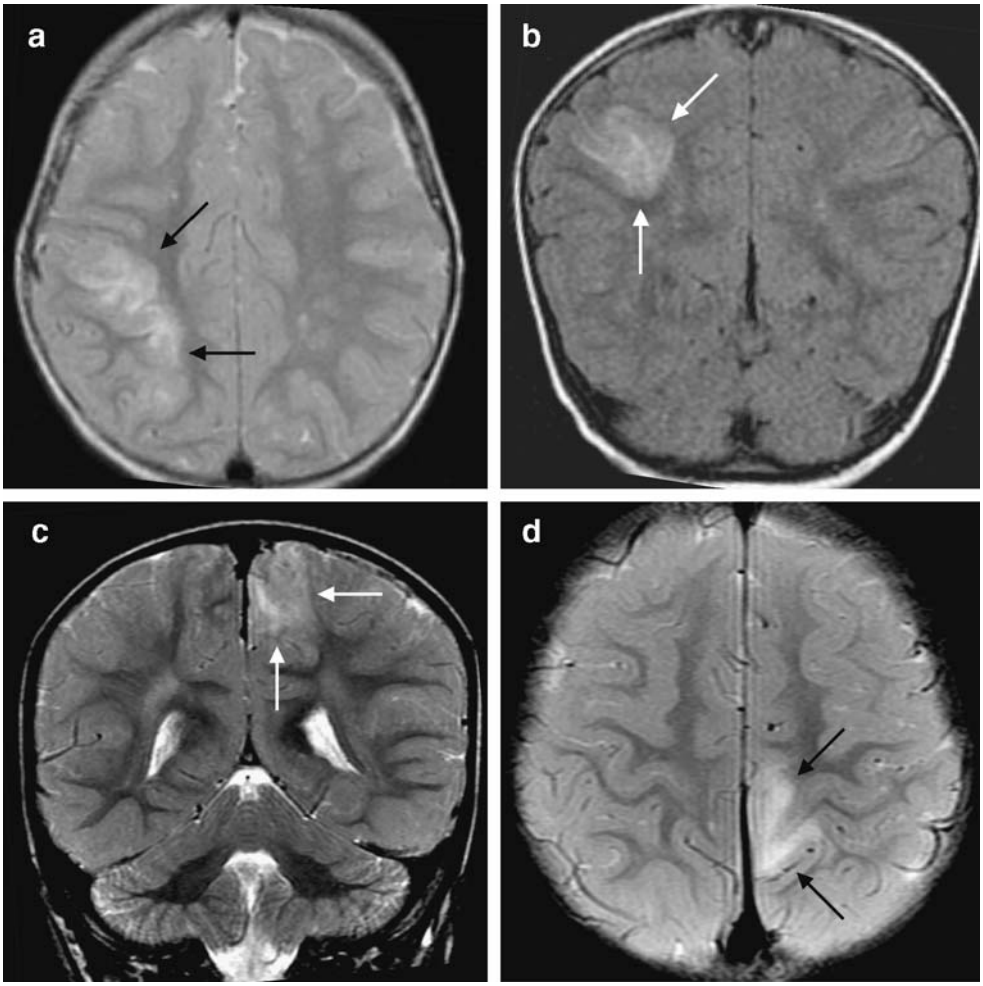

Fig. 3 Images of a 17-month-old with HSE who presented with fever and seizure. Axial T2-W (**a**) and coronal FLAIR (**b**) images show cortical thickening in the right high fronto-parietal lobes with increased signal in the cortex and underlying white matter. The distribution is not typical of HSE as seen in older children but rather involves the cortex and subcortical white matter in the territory of the posterior middle cerebral artery. **c**, **d** The vascular territory pattern of HSE peculiar to infants and young children is further emphasized in a second infant with HSE who had signal abnormalities (*arrows*) in the posterior portion of the left anterior cerebral artery distribution seen on coronal (**c**) and axial (**d**) T2-W images

and subcortical signal abnormalities. The differential considerations in this setting would include other viral encephalitides, acute demyelinating encephalomyelitis (ADEM) and, especially in a seizing child, tubers of tuberous sclerosis. Diffusion abnormalities seen in HSV infection can lessen the suspicion for ADEM, while a lack of other stigmata of tuberous sclerosis would exclude that entity. Older children with HSE have signal abnormalities in the medial temporal and inferior frontal lobes, insula, and cingulate gyrus that distinguish HSV among other causes of encephalitis. Further specificity derives from the fact that HSV infection often causes hemorrhage, which is seen as increased signal on T1-W images or decreased signal on GRE sequences because of deoxyhemoglobin. DWI is also an excellent adjunct when there is suspicion of HSE because this aggressive cytotoxic encephalitis can cause brain necrosis, which, when imaged early, manifests as diffusion restriction [45, 46]. Of course, with diffusion abnormalities, stroke (both venous and arterial) and mitochondrial cytopathy enters into the differential diagnosis. In the case of HSV, the hypothesized mechanism of spread along the meningeal nerves in an older child is helpful. One would not expect ischemia to center along the insular cortex but rather to have a more classic vascular territory pattern. Magnetic resonance arteriography (MRA) and venography would be of benefit when trying to differentiate HSE from stroke. When the MRI findings raise the suspicion of HSV infection, it is important to impress upon referring clinicians the likelihood of HSE, as some authors advocate starting acyclovir even in cases of a negative initial PCR when the imaging findings are compelling [12].

Varicella-zoster virus

Virology, clinical course, and CNS manifestations

The natural history of VZV infection has been well described [47, 48]. VZV enters the body through the respiratory tract or conjunctiva. The primary viremia occurs within 4–6 days and is followed about 10 days later by a mild, self-limiting viral exanthema. Like other herpes viruses, VZV remains latent within the trigeminal ganglion [49]. CNS complications are the most common cause of VZV-associated hospitalization in otherwise healthy chil-

dren [50] and occur with an incidence of 1% [51]. Although the incidence of chickenpox has decreased in the 10 years since use of the VZV vaccine became widespread [52], the increasing use of PCR has increased awareness of VZV as an important etiologic agent of acute CNS symptoms [53, 54]. CNS complications of VZV infection include acute cerebellar ataxia, encephalitis, and vasculitis [3, 50, 55–58]. As elucidated below, these complications are each sequelae of vascular involvement by the virus rather than the result of completely separate disease pathways.

Cerebellitis

Cerebellar ataxia is a clinical syndrome of headache, vomiting, irritability, and gait abnormalities that is usually self-limiting. Acute cerebellar ataxia occurs in the days or weeks following primary VZV infection and was previously considered an immune-mediated process. It is now known that acute cerebellar ataxia results from varicella's cerebellar neurotropism and corresponds to VZV cerebellitis pathologically and radiographically [3, 31, 57, 59].

Multifocal leukoencephalopathy

The term VZV encephalitis is really a misnomer. VZV does not cause a primary encephalitis [56] but rather directly infects cerebral vessels, resulting in a small-vessel arteriopathy, which is more properly referred to as VZV multifocal vasculopathy or leukoencephalopathy [3, 53, 56, 60]. We prefer the latter term because it better reflects the imaging findings that help the radiologist form a useful differential diagnosis. VZV multifocal leukoencephalopathy is the most common CNS complication of chickenpox. In a study of 38 patients (mean age 8.6 years) with VZV infection and acute neurologic symptoms, it was the most common presentation, occurring in 79% of patients [58]. Clinically, the presentation of leukoencephalopathy varies. Signs and symptoms are non-specific and resemble those seen in other viral encephalitides. Children can present with headache, confusion, and/or fever [3, 60], or present with more profound CNS complications such as mental status changes, seizure, stroke, or focal deficits [56]. Focal neurologic deficits are caused by ischemia and are usually subacute symptoms of hemiplegia, aphasia, and/or visual deficits. Patients are commonly immunocompromised from transplantation or HIV infection [60].

Vasculitis

Throughout the literature, large-vessel VZV vasculopathy is referred to as herpes zoster ophthalmicus, granulomatous angiitis, VZV vasculitis, and VZV-associated stroke. Pathologically, the spectrum ranges from necrotizing arteritis with aneurysms to vascular occlusion with or without inflammatory changes [3]. Globally, we refer to this spectrum as VZV vasculitis. Varicella is a well-documented risk factor for ischemic stroke in children and is responsible for approximately one-third of childhood strokes. Children with stroke from VZV vasculitis tend to be healthier than children with stroke from other causes [55], and, in contrast to children with multifocal leukoencephalopathy, they tend to be immunocompetent. The vasculitis presents weeks to months after the rash has resolved and presents as an acute focal deficit [60, 61]. VZV-associated stroke often causes acute hemiparesis in the setting of basal ganglia infarction, a fairly characteristic presentation in pediatric stroke [55, 61–63].

Neuroimaging findings

Cerebellitis

The imaging literature of VZV cerebellitis is sparse because cerebellar ataxia was previously considered an immune-mediated process and the diagnosis was therefore based on laboratory and clinical findings. Although little emphasis has been placed on VZV cerebellitis, multiple investigators have recently described characteristic neuroimaging findings of cerebellitis in children with acute cerebellar ataxia and serologically confirmed acute VZV infection [31, 59]. Mass effect is seen on CT scans, and MRI reveals diffuse or focal areas of decreased T1-W and increased T2-W signal in the cerebellum and/or cerebellar peduncles [63, 64] (Fig. 4).

Multifocal leukoencephalopathy

VZV multifocal leukoencephalopathy has two imaging patterns: a non-specific pattern similar to other encephalitides and the second with a clear arterial distribution. Although these patterns can be superimposed, the latter betrays true nature of VZV infection as a primary vasculopathy and is therefore discussed separately below. The non-specific pattern typical of other encephalitides is seen when VZV involves the smaller peripheral vessels of the brain. Neuroimaging demonstrates diffuse, multifocal cortical and subcortical abnormalities that are non-enhancing and low density on CT scans. MRI reveals edema in the cerebral cortex and underlying white matter with low T1-W and high T2-W signal changes [3, 4, 53, 56, 60, 65] (Fig. 5).

Vasculitis

When varicella involves more central vessels, neuroimaging more clearly shows an arterial distribution with different patterns based on the size of the affected vessels. Because VZV has a predilection for small vessels of the basal ganglia, isolated ischemia is characteristically seen

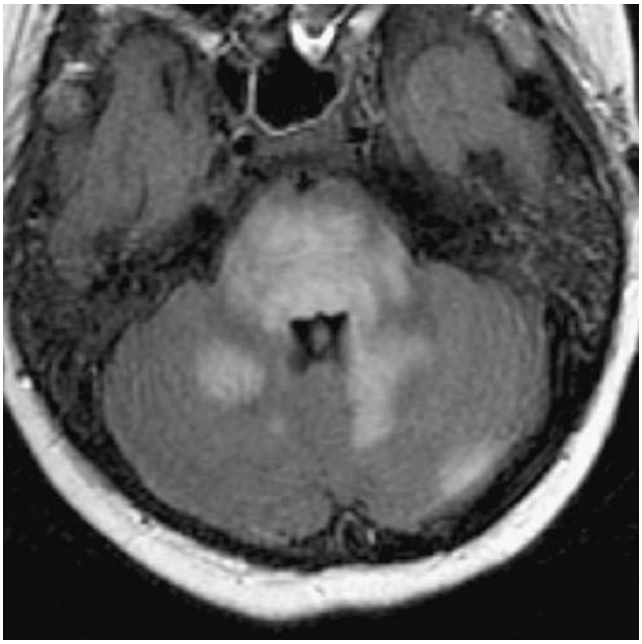

Fig. 4 Axial FLAIR image through the posterior fossa in a patient with recent chickenpox shows non-specific findings of VZV cerebellitis and rhombencephalitis, including a mild mass effect and increased FLAIR signal in the pons, cerebellar peduncles and cerebellum

with VZV vasculitis [55, 63]. Basal ganglia ischemia can be unilateral or bilateral and manifests as hypodense, non-enhancing lesions on CT that have low T1-W and high T2-W MR signal [53, 61, 65, 66]. VZV can also infect large cerebral vessels, causing hemispheric strokes [53, 56, 61], and DWI will show diffusion restriction immediately after symptoms appear. Another important MRI adjunct is MRA [61]. MRA and CT angiography are highly sensitive for flow abnormalities and less invasive than conventional angiography. In VZV vasculitis, arterial imaging demonstrates irregularity, segmental narrowing, beading, or stenosis involving the anterior and middle cerebral arteries and their branches [4, 56, 60, 61, 63]. The carotid and posterior circulation are less commonly involved [61].

VZV summary

Whenever a child with recent chickenpox or a VZV-exposed non-immunized or immunosuppressed child presents with acute neurologic symptoms, the diagnosis of VZV infection should be considered. Likewise, a history of chickenpox should be sought and VZV vasculitis considered when an

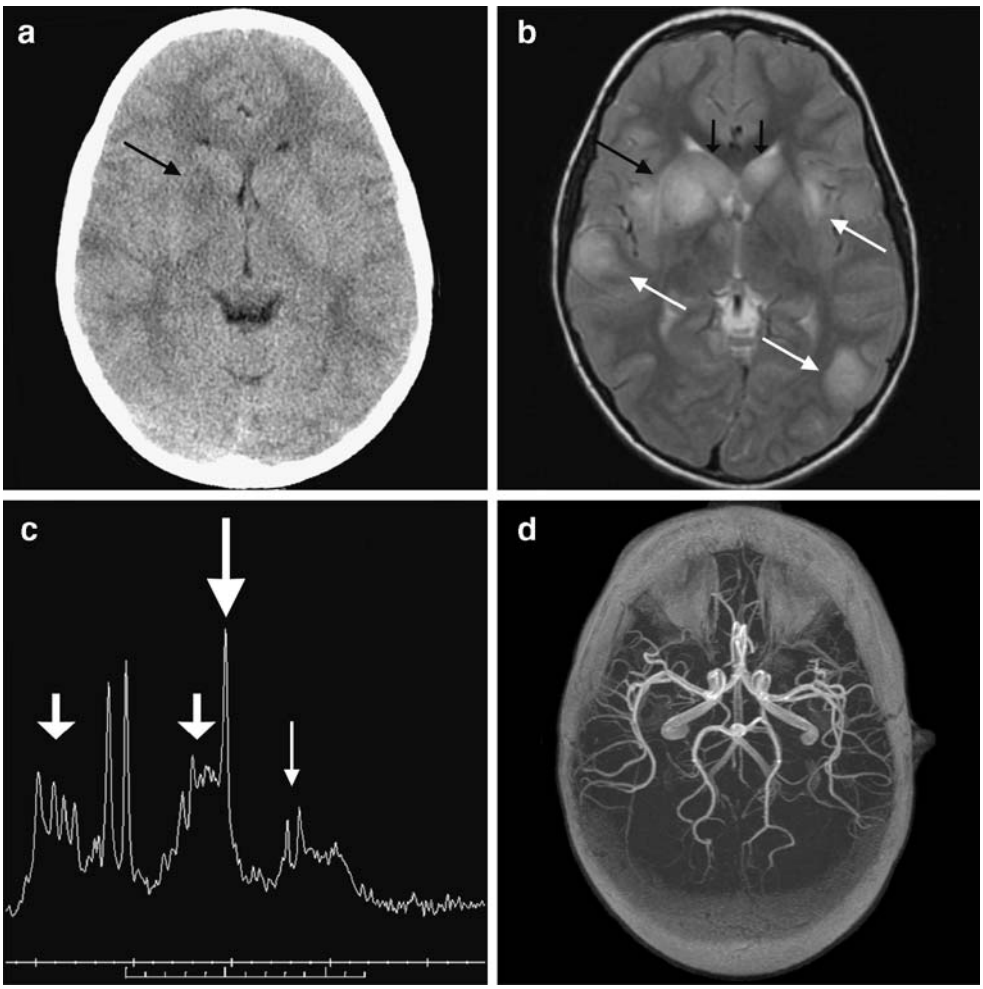

Fig. 5 VZV leukoencephalopathy in a child with chickenpox and mental status changes. **a** A non-enhanced CT image shows a subtle area of low attenuation in the right anterior globus pallidus, putamen, and anterior limb of the internal capsule (*arrow*). **b** T2-W image shows edema and increased signal in the region of the CT abnormalities (*large black arrow*), as well as the bilateral caudate heads (*small black arrows*) and scattered throughout the cerebral cortex and subcortical white matter (*white arrows*). These areas were low signal on T1-W images and did not enhance (*not shown*). **c** Short echo proton MRS (TE 35 ms) over the right basal ganglia demonstrates decreased NAA (*large arrow*), elevated excitatory neurotransmitters (*short arrows*), and a prominent lactate peak (*thin arrow*). **d** A 3-D time-of-flight MR angiogram shows no abnormalities in the large cerebral vessels because VZV leukoencephalopathy is caused by small-vessel involvement rather than large-vessel abnormalities

otherwise healthy child presents with stroke and MRI abnormalities in the basal ganglia and/or hemispheric white matter [55, 62, 63]. In these days of widespread immunization, the pediatrician might not consider VZV infection in the differential of acute neurologic deficits.

There are numerous examples of pre-eruptive chickenpox causing neurologic complications [31, 67]. In one study [54, 58], 44% of patients with primary VZV infection, documented by PCR or elevated IgM, had no rash in the 4 weeks surrounding acute neurologic changes. The differential of childhood stroke includes metabolic and mitochondrial disorders, progressive multifocal leukoencephalopathy (PML), trauma (arterial dissection), and hemolytic uremic syndrome (HUS). Imaging can be very helpful in narrowing these considerations. In the setting of diffuse white matter changes, spectroscopy will show elevated lactate and decreased NAA. Diffuse white matter signal abnormalities in children with HIV infection can represent either PML or VZV infection. The white matter abnormalities of these two entities differ in that those in VZV vasculitis are usually smaller and less confluent than seen in PML [60], and in PML the high signal white matter has a strikingly sharp interface with the subcortical U-fibers. Trauma is also a major cause of pediatric stroke. MRA is particularly helpful in this setting because it can help differentiate the arteriopathic changes of VZV vasculitis described above from the tapering associated with dissection. (Fat-suppressed T1-W axial source images also nicely show the crescentic bright T1-W signal of a dissection hematoma.)

We have shown that the range of CNS imaging manifestations in VZV infection extends from mild cerebellitis to multifocal parenchymal edema to overt stroke. These different patterns should be familiar to the radiologist reading pediatric neuroimaging studies. It is also helpful to understand that these protean manifestations all result from VZV vasculitis and that patients have different clinical presentations depending on their pattern of vascular involvement. Imaging can be the first clue to a diagnosis of VZV infection and help lead toward PCR confirmation. This is of particular importance because most experts recommend treating severe VZV vasculopathy with a combination of prednisone (60–80 mg/day for 3–5 days) and intravenous acyclovir (500 mg/m^2 body surface area for a total of 7 days [60]).

Epstein-Barr virus

Virology, clinical course, and CNS manifestations

Like the other herpesviruses, EBV is a ubiquitous pathogen found in almost all people by the end of their second decade. The virus infects the nasopharyngeal epithelium and circulating peripheral B lymphocytes. The virus remains dormant within circulating B-cells but occasionally activates in the presence of mucosal epithelium, then sheds silently into infectious saliva. Primary EBV infection is typically asymptomatic in younger children but causes the syndrome of high fever, tonsillopharyngitis, hepatosplenomegaly, and lymphadenopathy characteristic of infectious mononucleosis in adolescents [68]. About 20% of patients with primary EBV infection have various complications, and neurologic involvement occurs in about 5% [7, 69]. Cerebral involvement of EBV infection can range from encephalitis and meningoencephalitis to optic neuritis [70, 71]. Current evidence supports an immunologic mechanism rather than direct viral invasion as the cause of EBV-related CNS disease [68, 72].

EBV encephalitis/meningoencephalitis

EBV encephalitis is more common than often appreciated and in the NIAD Collaborative Antiviral Study Group series was the most common agent to mimic HSE [8]. One unusual feature of children with EBV encephalitis is that other than headache and fever, typical symptoms of infectious mononucleosis are conspicuously absent [68, 70, 71]. Common symptoms include altered consciousness, visual hallucinations, psychosis, and/or fever [70, 71]. Seizures are present in almost half of patients with EBV encephalitis [68]. Most children have a benign clinical course without neurologic sequelae, but about 10% have residual persistent deficits, and several deaths have been reported [53, 68, 70, 71]. Some have advocated treatment with acyclovir and steroids, and although there is little to support this approach, this may augment supportive care in some patients [68, 69, 73].

EBV optic neuritis

Optic neuritis is an unusual complication of acute EBV infection and can occur outside of, or after the onset of, infectious mononucleosis [74–76]. Like EBV encephalitis, it is thought that the process is immune-mediated. Involvement can be unilateral or bilateral and is usually retrobulbar but can extend to the optic chiasm [74]. Antiviral or steroid treatment has been given, but complete recovery can occur without treatment [75].

Neuroimaging findings

EBV encephalitis and meningoencephalitis

Neuroimaging will show non-specific areas of decreased attenuation on CT in a minority of children with EBV encephalitis [70]. The sensitivity of MRI is better than that

of CT and will be positive in up to 80% of patients [68] with multiple foci of T2-W or FLAIR hyperintensity in the hemispheric cortex, basal ganglia, brainstem, and/or splenium [68, 70, 71, 75, 77–79] (Fig. 6). EBV has a characteristic tropism for the deep nuclei and therefore a common and characteristic pattern is that of increased T2-W signal in the bilateral thalami and basal ganglia [75, 79–81] (Fig. 6). MRS is a useful MRI adjunct that might show decreased NAA and increased levels of myoinositol and amino acid moieties [82].

EBV optic neuritis

EBV associated optic neuritis has non-specific neuroimaging findings of optic nerve edema. The inflammation and edema are manifest on MRI as increased T2-W signal and enhancement on T1-W images after contrast agent administration (Fig. 7). Because the process is immune-mediated, it can be bilateral and involve the optic chiasm [74].

EBV summary

CNS involvement as a result of EBV infection is associated with diverse neurologic manifestations including meningitis, meningoencephalitis, cerebellitis, cranial neuritis (optic nerves and optic chiasm), and occasionally brain stem encephalitis and myelitis. Reported cerebral sites of involvement include the striatal body (putamen and caudate nucleus), thalami, subcortical cerebral white matter, insular cortex, cerebellar gray matter and white matter, optic nerves and chiasm, and rarely the brain stem. Fortunately, most cases are associated with an excellent clinical outcome.

MRI findings of EBV are typically those of T1-W hypointensity, T2-W hyperintensity, lack of diffusion restriction, and an intact blood–brain barrier. Liberal use of MRS, particularly in the investigation of basal ganglia involvement, can sometimes help distinguish between infection, ischemia, and other toxic/metabolic derangements in many cases.

Cytomegalovirus

Virology, clinical course, and CNS manifestations

Like HSV infection, CMV infection can be congenital or present later in life, either as primary or recurrent infection. Although outside the scope of this review, a brief discussion of congenital CMV infection is appropriate. Congenital CMV infection is the most common congenital viral infection worldwide and occurs in about 1 per 100 births [83]. Vertical transmission across the placenta results in fetal infection, and the earlier the transmission occurs during gestation, the poorer the outcome [84]. The vast majority of infected neonates are asymptomatic, but about 10% present have low birth weight, hepatitis, pneumonitis, and/or neurologic and hematologic abnormalities [83, 84]. Congenitally infected infants can later have failure to thrive and progressive hearing deficits. Neuroimaging features of congenital CMV infection include periventricular calcifications, ventriculomegaly, delayed myelination, hippocampal dysplasia, periventricular occipital cysts, lissencephaly, and cortical migration abnormalities [5, 83, 85, 86]. Neuroimaging abnormalities are an excellent predictor of poor neurologic outcome [86, 87].

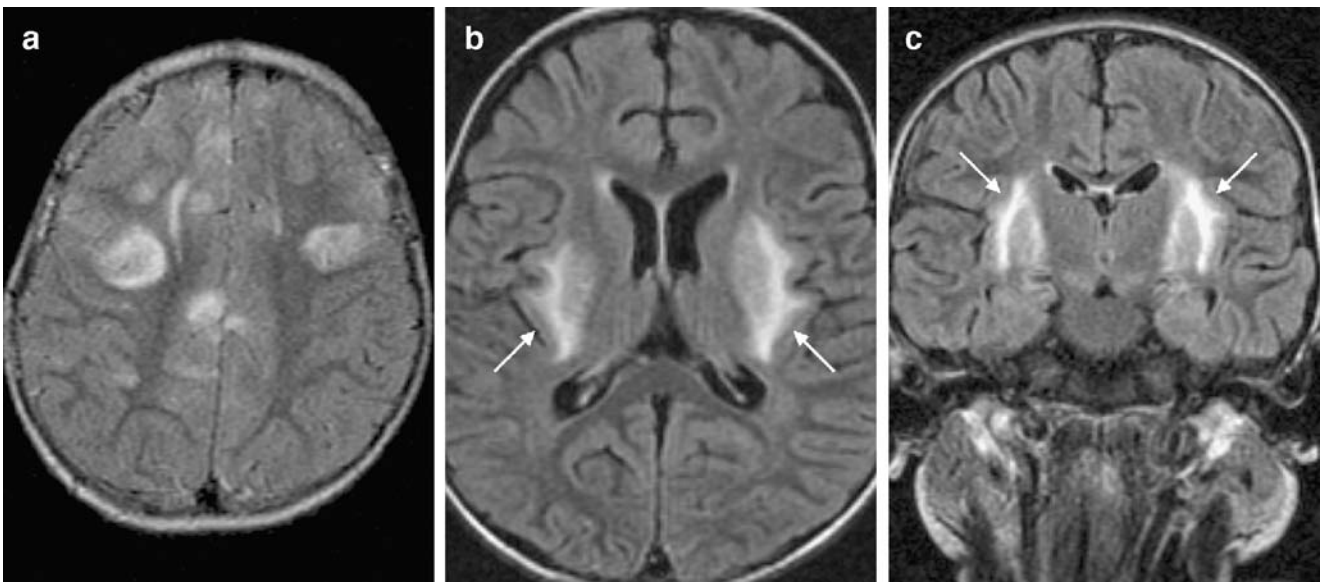

Fig. 6 EBV encephalitis. **a** Axial FLAIR image demonstrates abnormal T2-W signal in the bilateral frontal cortex and subcortical white matter. This is a typical pattern for viral encephalitis. The multiple vascular territories involved make ischemia unlikely. Additionally, a child presenting with multifocal strokes of this magnitude would have a profound clinical presentation with fixed neurologic deficits. **b**, **c** Axial (**b**) and coronal (**c**) FLAIR images demonstrate increased signal in the bilateral basal ganglia reflecting the unique tropism of EBV for this area

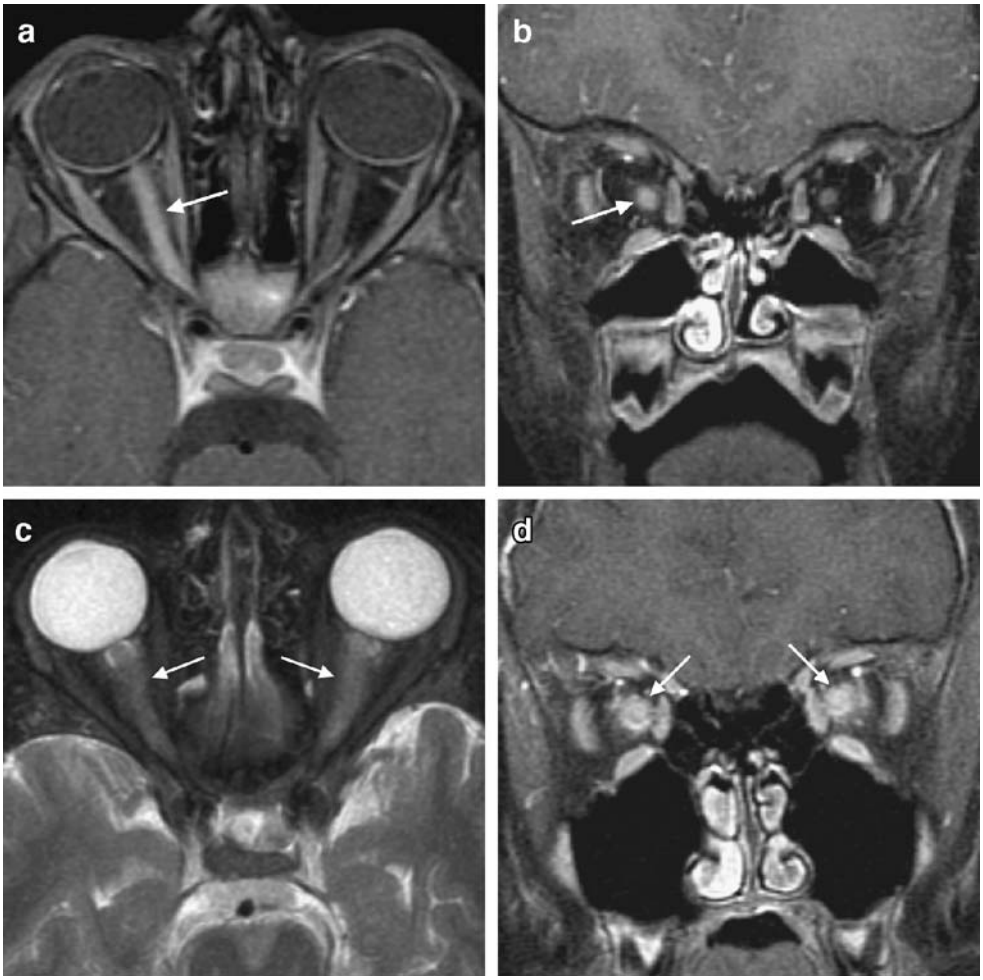

Fig. 7 Optic neuritis in a child with elevated EBV IgM titers. Axial (**a**) and coronal (**b**) enhanced T1-W images with fat saturation. Note the enlarged, enhancing right optic nerve (*arrows*). **c**, **d** Axial T2-W (**c**) and coronal enhanced T1-W (**d**) images in another child with EBV and acute painful ophthalmoplegia show bilaterally enlarged and edematous optic nerves (*arrows*) with marked enhancement

Outside the context of congenital disease, pediatric CMV infection occurs most commonly in immunosuppressed patients such as those with HIV infection or after solid organ or bone marrow transplantation. Immunocompetent children are rarely affected [88]. If a patient has a normal immune system, meningoencephalitis is usually the only CNS manifestation of CMV and is typically self-limiting [89, 90]. In the immunocompromised, CNS CMV infection can manifest as meningoencephalitis, ventriculoencephalitis, and/or cerebral mass lesions. Diffuse encephalitis is the most common of these and presents with fever, headache, and non-specific non-focal neurologic signs such as confusion and memory loss. Immunosuppressed patients are more likely to have focal neurologic signs [88, 91, 92]. Ventriculoencephalitis is particularly associated with a positive HIV status [88, 91] and typically has a rapid onset with quick neurologic decline, usually to coma and death [88]. Accompanying cranial neuropathies are often seen in these patients and are a clue to the diagnosis [93]. The rarest form of acute cerebral CMV infection is that of mass lesions, a very rare presentation only reported in AIDS patients [94–96].

Neuroimaging findings

The MRI findings of CMV meningoencephalitis are non-specific and similar to those of other viral encephalitides. Most investigators describe cortical and/or subcortical areas of decreased T1-W and increased T2-W signal, usually in the frontal and parietal lobes [5]. Pathologically, CMV infection often involves the ependyma and subependyma [97]. Imaging typically shows meningeal enhancement after administration of gadolinium contrast agent (Fig. 8). In patients with ventriculoencephalitis, there is also periventricular enhancement [88, 91, 98, 99]. In 1990, Balakrishnan et al. [97] documented decreased T1-W signal in these patients and explained that increased T2-W signal was obscured by adjacent CSF signal. Presumably, with increased use of FLAIR imaging today, the ventriculitis and periventricular necrosis would be better visualized as increased ependymal FLAIR signal against dark CSF that has been suppressed. In cases of ventriculitis, some authors have also reported ventriculomegaly [99]. The cerebral masses caused by CMV in AIDS patients manifest as solitary enhancing or ring-enhancing parenchymal lesions [94, 95, 100].

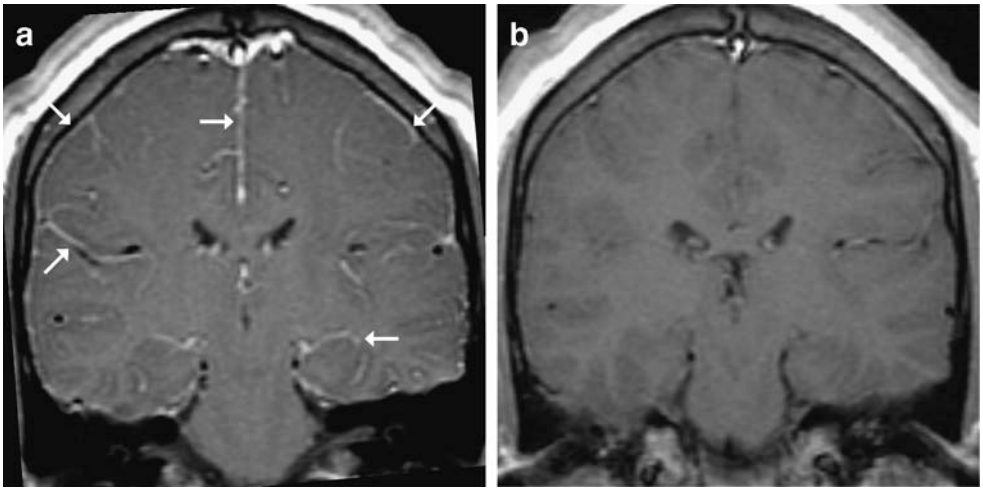

Fig. 8 Acute CMV meningitis. This immunocompetent child had headache, dizziness, mental status changes and elevated CMV IgM titers. His CSF was PCR-negative for EBV and HSV. **a** A T1-W image after administration of contrast agent shows diffuse leptomeningeal enhancement (*arrows*) and no other abnormalities. **b** A T1-W image after administration of contrast agent obtained coincidentally 1 week prior to admission for trauma and possible vertebral dissection was normal and showed no leptomeningeal enhancement

CMV summary

CMV infection should be considered in the immunosuppressed child with encephalopathy and non-focal neurologic signs. The ultimate diagnosis relies on PCR to demonstrate CMV DNA in the CSF, but imaging has been shown to be useful in the diagnosis of CMV infection [11]. When the radiologist sees encephalitis or ventriculoencephalitis in an immunosuppressed child with non-specific neurologic signs, the possibility of CMV should be raised and CSF tested. Prompt treatment of CMV with intravenous antiviral agents such as ganciclovir or foscarnet has been shown to improve outcome [101]. Because CMV infections are largely seen in HIV-positive patients who may have concomitant HIV encephalitis, differentiation of these two entities can be difficult. Two things may help: the clinical deterioration of patients with CMV encephalitis is more rapid than of those with HIV encephalitis alone, and MRI can demonstrate ependymal enhancement of the ventricles and/or parenchymal masses associated with CMV [92]. In patients with HIV infection and possible lymphoma, CMV ventriculoencephalitis needs to be differentiated from lymphoma. Imaging can be helpful in that the periventricular enhancement of infection is usually more thin than the mass-like enhancement seen in lymphoma [102].

Human herpes virus-6

Virology, clinical course, and CNS manifestations

HHV-6 was discovered in 1986 and has two variants, HHV-6A and HHV-6B [103]. The latter is associated with childhood disease and infects almost all children worldwide. Antibodies to this ubiquitous virus are found in 95% of the population; most children are infected with the B variant before the age of 2 years [103]. Primary infection causes a febrile exanthem known as roseola infantum (sixth disease) [104], but some patients remain asymptomatic [105]. The virus enters the body through the salivary glands, where it replicates and sheds further particles via infectious saliva. The virus remains latent throughout the body, including the salivary glands, white blood cells, and the brain [103, 106–108]. It is well-accepted that the virus is quite neurotropic [103, 109, 110] and HHV-6 can result in prolonged, recurrent seizures in a minority of children. Acute HHV-6B infection is associated with seizures in 13% of children [107] and causes almost 30% of first-time febrile seizures in infants. Although the causality of this relationship is somewhat controversial [111], HHV-6 infection should be considered in children younger than 2 years with first-time febrile seizures [107, 112]. Primary HHV-6 infection has also been implicated in encephalitis [113, 114], but more commonly, HHV-6 encephalitis is encountered in immunosuppressed patients as reactivation. Reactivation of HHV-6 is seen in 50% of bone marrow transplant patients [106], usually 2–4 weeks after transplantation [115, 116], but only affects the CNS in a minority of patients. Patients with reactivation HHV-6 encephalitis present with mental status changes, fever, seizures, and headache [115]. Care should be taken that true HHV-6 reactivation is documented in such patients so as to exclude incidental latent infection coincident with encephalitis of another etiology. PCR detection of HHV-6 DNA in the CSF of immunocompromised patients with CNS symptoms has been shown to have a high specificity [117]. Mortality of HHV-6 encephalitis is more than 50%, but can be reduced dramatically by prompt treatment with ganciclovir or foscarnet [115].

Neuroimaging findings

CT findings in patients with HHV-6 encephalitis are usually negative [115, 118]. MRI is also occasionally negative but characteristically reveals non-enhancing areas of abnormal signal in the medial temporal lobes and limbic system,

reflecting edema [115, 118, 119]. In particular, bilateral or unilateral increased T2/FLAIR signal is found in the hippocampi, amygdala and/or parahippocampal gyrus, usually without diffusion restriction [118, 120–122]. In patients without initial MR abnormalities, delayed imaging usually demonstrates signal abnormalities as described above [118]. Months after the encephalitis, patients have resolution of signal abnormalities but persistent volume loss in the medial temporal lobes [118, 121, 122]. A more unusual but catastrophic CNS complication of HHV-6 is basal ganglia involvement with acute necrotizing encephalopathy. This has been reported in multiple infants or very young children with primary HHV-6 infection. These children had basal ganglia lesions that were low density on CT and high T2-W signal on MR. Findings are usually bilateral and symmetric and involve the striatum [123], thalami [124], cerebellum, and/or brainstem [125] (Fig. 9).

HHV-6 summary

HHV-6 infection is clinically under-appreciated. Fortunately, it almost always has a benign course and, other than associated febrile seizures, CNS complications are rare in immunocompetent children. On the other hand, HHV-6 can reactivate in immunosuppressed children and present with encephalopathy. When these patients have medial temporal signal changes without enhancement or diffusion restriction (which are typically seen in HSE), HHV-6 should be considered.

Summary

Clinicians have long appreciated the diversity of neurologic disease caused by the human herpesviruses. It is widely recognized that the herpesviruses cause various acute, subacute, and chronic disorders of the central and peripheral nervous systems. However, rapid clinical recognition of herpesvirus infection remains elusive. This is particularly evident with the recognition of neonatal HSE, where clinical trials demonstrate that the diagnosis can be delayed more than 5 days from the onset of clinical symptoms in more than 40% of patients [126]. This delay often leads to significant morbidity and increased mortality.

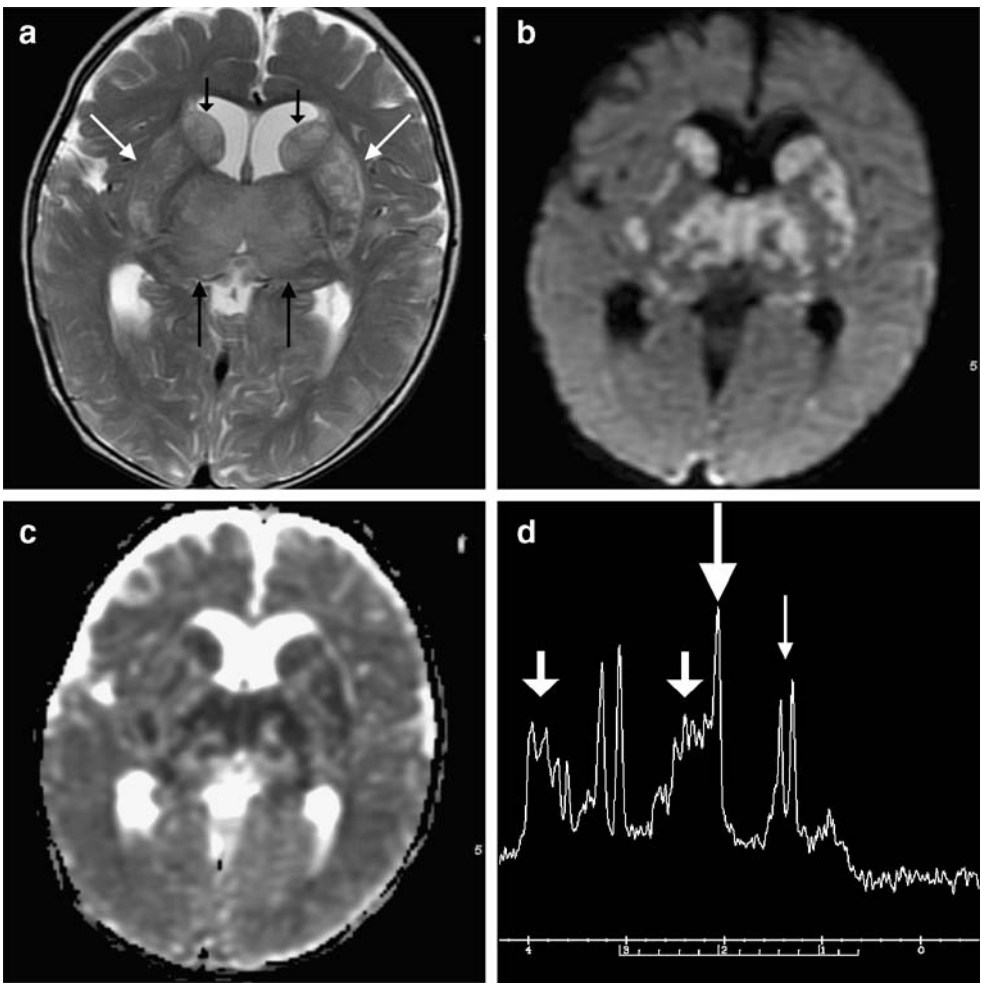

Fig. 9 Acute necrotizing encephalopathy in a previously healthy 8-month-old boy who presented with rapidly developing fussiness followed by fever and seizures. PCR showed HHV-6-positive CSF but HHV-6-negative plasma. An initial CT (not shown) was normal except for subtle heterogeneous low density in the basal ganglia. **a** Axial T2-W image demonstrates patchy increased signal in the bilateral basal ganglia, mainly in the putamena (*white arrows*), thalami (*large black arrows*), and caudate heads (*small black arrows*). **b**, **c** These areas had true diffusion restriction on DWI (**b**) and ADC (**c**), and no enhancement on enhanced T1-W images or hemorrhage by GRE imaging (not shown). **d** Single voxel proton spectroscopy over the left basal ganglia shows decreased NAA (*large arrow*), elevated excitatory neurotransmitters (*short arrows*), and a lactate peak (*thin arrow*). The patient died 2 weeks after admission

The union of detailed health history, physical examination, early CNS MRI, and established virologic and molecular PCR techniques leads to more timely diagnoses and prompt implementation of therapy. Current clinical MRI of the CNS at 1.5 and 3.0 T using eight-channel head coil technology provides the foundation of detailed anatomic information in the setting of suspected CNS viral infection. Adjunctive MRI techniques such as DWI and MRS contribute valuable information regarding cell viability and the biochemical milieu of the region sampled. The synthesis of anatomic and physiologic information often aids the radiologist in distinguishing infection from infectious mimics such as ischemic, toxic, or metabolic insults.

Although overlap in the clinical expression of the herpesviruses is a fact well known to clinical practitioners, there are distinct neuroimaging findings that provide helpful diagnostic clues among this virus family. This review attempts to highlight the clinical features and characteristic imaging findings of the expanding spectrum of human herpesvirus infections of the CNS in neonates, infants, and children.

References

1. Editors of the American Heritage Dictionaries (2000) The American Heritage dictionary of the English language, Houghton Mifflin, Boston
2. Damasio AR, Van Hoesen GW (1985) The limbic system and the localisation of herpes simplex encephalitis. J Neurol Neurosurg Psychiatry 48:297–301
3. Kleinschmidt-DeMasters BK, Gilden DH (2001) Varicella-Zoster virus infections of the nervous system: clinical and pathologic correlates. Arch Pathol Lab Med 125:770–780
4. Tien RD, Felsberg GJ, Osumi AK (1993) Herpesvirus infections of the CNS: MR findings. AJR 161:167–176
5. Barkovich AJ (2005) Pediatric neuroimaging. Lippincott Williams & Wilkins, Philadelphia, pp 801–868
6. Barnett EM, Jacobsen G, Evans G et al (1994) Herpes simplex encephalitis in the temporal cortex and limbic system after trigeminal nerve inoculation. J Infect Dis 169:782–786
7. Connelly KP, DeWitt LD (1994) Neurologic complications of infectious mononucleosis. Pediatr Neurol 10:181–184
8. Whitley RJ, Cobbs CG, Alford CA Jr et al (1989) Diseases that mimic herpes simplex encephalitis. Diagnosis, presentation, and outcome. NIAD Collaborative Antiviral Study Group. JAMA 262:234–239
9. Minjolle S, Michelet C, Jusselin I et al (1999) Amplification of the six major human herpesviruses from cerebrospinal fluid by a single PCR. J Clin Microbiol 37:950–953
10. Yamamoto T, Nakamura Y (2000) A single tube PCR assay for simultaneous amplification of HSV-1/-2, VZV, CMV, HHV-6A/-6B, and EBV DNAs in cerebrospinal fluid from patients with virus-related neurological diseases. J Neurovirol 6:410–417
11. Stocher M, Leb V, Bozic M et al (2003) Parallel detection of five human herpes virus DNAs by a set of real-time polymerase chain reactions in a single run. J Clin Virol 26:85–93
12. Weil AA, Glaser CA, Amad Z et al (2002) Patients with suspected herpes simplex encephalitis: rethinking an initial negative polymerase chain reaction result. Clin Infect Dis 34:1154–1157
13. Domingues RB, Fink MC, Tsanaclis AM et al (1998) Diagnosis of herpes simplex encephalitis by magnetic resonance imaging and polymerase chain reaction assay of cerebrospinal fluid. J Neurol Sci 157:148–153
14. Tyler KL (2004) Herpes simplex virus infections of the central nervous system: encephalitis and meningitis, including Mollaret's. Herpes 11(Suppl 2):57A–64A
15. Brown Z (2004) Preventing herpes simplex virus transmission to the neonate. Herpes 11(Suppl 3):175A–186A
16. Baldwin S, Whitley RJ (1989) Intrauterine herpes simplex virus infection. Teratology 39:1–10
17. Hutto C, Arvin A, Jacobs R et al (1987) Intrauterine herpes simplex virus infections. J Pediatr 110:97–101
18. Chatterjee A, Chartrand SA, Harrison CJ et al (2001) Severe intrauterine herpes simplex disease with placentitis in a newborn of a mother with recurrent genital infection at delivery. J Perinatol 21:559–564
19. Hoppen T, Eis-Hubinger AM, Schild RL et al (2001) Intrauterine herpes simplex virus infection. Klin Padiatr 213:63–68
20. Pickering LK (ed) (2006) Red Book: Report of the Committee on Infectious Diseases. American Academy of Pediatrics, Elk Grove Village, IL, pp 361–371
21. Fagnant RJ, Monif GR (1989) How rare is congenital herpes simplex? A literature review. J Reprod Med 34:417–422
22. Enright AM, Prober CG (2002) Neonatal herpes infection: diagnosis, treatment and prevention. Semin Neonatol 7:283–291
23. Bravo FJ, Myers MG, Stanberry LR (1994) Neonatal herpes simplex virus infection: pathogenesis and treatment in the guinea pig. J Infect Dis 169:947–955
24. Mani CS, Bravo FJ, Stanberry LR et al (1996) Effect of age and route of inoculation on outcome of neonatal herpes simplex virus infection in guinea pigs. J Med Virol 48:247–252
25. Corey L, Whitley RJ, Stone EF et al (1988) Difference between herpes simplex virus type 1 and type 2 neonatal encephalitis in neurological outcome. Lancet 1:1–4
26. Kimberlin D (2004) Herpes simplex virus, meningitis and encephalitis in neonates. Herpes 11(Suppl 2):65A–76A
27. Leonard JR, Moran CJ, Cross DT III et al (2000) MR imaging of herpes simplex type 1 encephalitis in infants and young children: a separate pattern of findings. AJR 174:1651–1655
28. Whitley RJ (1997) Herpes simplex viruses. Infections of the central nervous system. Lippincott-Raven, Philadelphia, pp 73–89
29. Whitley RJ, Gnann JW (2002) Viral encephalitis: familiar infections and emerging pathogens. Lancet 359:507–513
30. Kohl S (1988) Herpes simplex virus encephalitis in children. Pediatr Clin North Am 35:465–483
31. Wagner HJ, Seidel A, Grande-Nagel I et al (1998) Pre-eruptive varicella encephalitis: case report and review of the literature. Eur J Pediatr 157:814–815
32. Herman TE, Cleveland RH, Kushner DC et al (1985) CT of neonatal herpes encephalitis. AJNR 6:773–775
33. Toth C, Harder S, Yager J (2003) Neonatal herpes encephalitis: a case series and review of clinical presentation. Can J Neurol Sci 30:36–40
34. Noorbehesht B, Enzmann DR, Sullender W et al (1987) Neonatal herpes simplex encephalitis: correlation of clinical and CT findings. Radiology 162:813–819
35. Dhawan A, Kecskes Z, Jyoti R et al (2006) Early diffusion-weighted magnetic resonance imaging findings in neonatal herpes encephalitis. J Paediatr Child Health 42:824–826
36. Kubota T, Ito M, Maruyama K et al (2006) Serial diffusion-weighted imaging of neonatal herpes encephalitis: a case report. Brain Dev 29:171–173

37. Enzmann D, Chang Y, Augustyn G (1990) MR findings in neonatal herpes simplex encephalitis type II. J Comput Assist Tomogr 14:453–457
38. Junck L, Enzmann DR, DeArmond SJ et al (1981) Prolonged brain retention of contrast agent in neonatal herpes simplex encephalitis. Radiology 140:123–126
39. Sugimoto T, Woo M, Okazaki H et al (1985) Computed tomography in young children with herpes simplex virus encephalitis. Pediatr Radiol 15:372–376
40. Taccone A, Gambaro G, Ghiorzi M et al (1988) Computed tomography (CT) in children with herpes simplex encephalitis. Pediatr Radiol 19:9–12
41. Wasay M, Mekan SF, Khelaeni B et al (2005) Extra temporal involvement in herpes simplex encephalitis. Eur J Neurol 12:475–479
42. Fazekas F, Kleinert R, Roob G et al (1999) Histopathologic analysis of foci of signal loss on gradient-echo T2-weighted MR images in patients with spontaneous intracerebral hemorrhage: evidence of microangiopathy-related microbleeds. AJNR 20:637–642
43. Hedlund GL, Boyer RS (1999) Neuroimaging of postnatal pediatric central nervous system infections. Semin Pediatr Neurol 6:299–317
44. Tokumaru AM, Horiuchi K, Kaji T et al (2003) MRI findings of recurrent herpes simplex encephalitis in an infant. Pediatr Radiol 33:725–728
45. Heiner L, Demaerel P (2003) Diffusion-weighted MR imaging findings in a patient with herpes simplex encephalitis. Eur J Radiol 45:195–198
46. Kuker W, Nagele T, Schmidt F et al (2004) Diffusion-weighted MRI in herpes simplex encephalitis: a report of three cases. Neuroradiology 46:122–125
47. Arvin AM (1996) Varicella-zoster virus. Clin Microbiol Rev 9:361–381
48. Atkinson W, Hamborsky J, McIntyre L et al (2006) Epidemiology and prevention of vaccine-preventable diseases. Public Health Foundation, Washington, DC
49. Kennedy PG, Grinfeld E, Gow JW (1998) Latent varicella-zoster virus is located predominantly in neurons in human trigeminal ganglia. Proc Natl Acad Sci U S A 95:4658–4662
50. Ziebold C, von Kries R, Lang R et al (2001) Severe complications of varicella in previously healthy children in Germany: a 1-year survey. Pediatrics 108:E79
51. Barnes DW, Whitley RJ (1986) CNS diseases associated with varicella zoster virus and herpes simplex virus infection. Pathogenesis and current therapy. Neurol Clin 4:265–283
52. Decline in annual incidence of varicella – selected states, 1990 through 2001. MMWR Morb Mortal Wkly Rep (2003) 52:884–885
53. Hausler M, Schaade L, Kemeny S et al (2002) Encephalitis related to primary varicella-zoster virus infection in immunocompetent children. J Neurol Sci 195:111–116
54. Koskiniemi M, Rantalaiho T, Piiparinen H et al (2001) Infections of the central nervous system of suspected viral origin: a collaborative study from Finland. J Neurovirol 7:400–408
55. Askalan R, Laughlin S, Mayank S et al (2001) Chickenpox and stroke in childhood: a study of frequency and causation. Stroke 32:1257–1262
56. Gilden DH (2002) Varicella zoster virus vasculopathy and disseminated encephalomyelitis. J Neurol Sci 195:99–101
57. Gilden DH, Kleinschmidt-DeMasters BK, LaGuardia JJ et al (2000) Neurologic complications of the reactivation of varicella-zoster virus. N Engl J Med 342:635–645
58. Koskiniemi M, Piiparinen H, Rantalaiho T et al (2002) Acute central nervous system complications in varicella zoster virus infections. J Clin Virol 25:293–301
59. Hurst DL, Mehta S (1988) Acute cerebellar swelling in varicella encephalitis. Pediatr Neurol 4:122–123
60. Gilden D (2004) Varicella zoster virus and central nervous system syndromes. Herpes 11(Suppl 2):89A–94A
61. Kramer LA, Villar-Cordova C, Wheless JW et al (1999) Magnetic resonance angiography of primary varicella vasculitis: report of two cases. J Magn Reson Imaging 9:491–496
62. Losurdo G, Giacchino R, Castagnola E et al (2006) Cerebrovascular disease and varicella in children. Brain Dev 28:366–370
63. Silverstein FS, Brunberg JA (1995) Postvaricella basal ganglia infarction in children. AJNR 16:449–452
64. Montenegro MA, Santos SL, Li LM et al (2002) Neuroimaging of acute cerebellitis. J Neuroimaging 12:72–74
65. Darling CF, Larsen MB, Byrd SE et al (1995) MR and CT imaging patterns in post-varicella encephalitis. Pediatr Radiol 25:241–244
66. Chan MSM, Wong YC, Lee AC et al (2001) Postvaricella basal ganglia infarction – early and late computed tomography and magnetic resonance imaging findings. J Hong Kong Coll Radiol 4:153–156
67. Dangond F, Engle E, Yessayan L et al (1993) Pre-eruptive varicella cerebellitis confirmed by PCR. Pediatr Neurol 9:491–493
68. Doja A, Bitnun A, Ford Jones EL et al (2006) Pediatric Epstein-Barr virus-associated encephalitis: 10-year review. J Child Neurol 21:384–391
69. Junker AK (2005) Epstein-Barr virus. Pediatr Rev 26:79–85
70. Domachowske JB, Cunningham CK, Cummings DL et al (1996) Acute manifestations and neurologic sequelae of Epstein-Barr virus encephalitis in children. Pediatr Infect Dis J 15:871–875
71. Shian WJ, Chi CS (1996) Epstein-Barr virus encephalitis and encephalomyelitis: MR findings. Pediatr Radiol 26:690–693
72. Jenson HB (2000) Acute complications of Epstein-Barr virus infectious mononucleosis. Curr Opin Pediatr 12:263–268
73. Fujimoto H, Asaoka K, Imaizumi T et al (2003) Epstein-Barr virus infections of the central nervous system. Intern Med 42:33–40
74. Beiran I, Krasnitz I, Zimhoni-Eibsitz M et al (2000) Paediatric chiasmal neuritis – typical of post-Epstein-Barr virus infection? Acta Ophthalmol Scand 78:226–227
75. Phowthongkum P, Phantumchinda K, Jutivorakool K et al (2007) Basal ganglia and brainstem encephalitis, optic neuritis, and radiculomyelitis in Epstein-Barr virus infection. J Infect 54: e141–e144
76. Purvin V, Herr GJ, De Myer W (1988) Chiasmal neuritis as a complication of Epstein-Barr virus infection. Arch Neurol 45:458–460
77. Angelini L, Bugiani M, Zibordi F et al (2000) Brainstem encephalitis resulting from Epstein-Barr virus mimicking an infiltrating tumor in a child. Pediatr Neurol 22:130–132
78. Hagemann G, Mentzel HJ, Weisser H et al (2006) Multiple reversible MR signal changes caused by Epstein-Barr virus encephalitis. AJNR 27:1447–1449
79. Ono J, Shimizu K, Harada K et al (1998) Characteristic MR features of encephalitis caused by Epstein-Barr virus: a case report. Pediatr Radiol 28:569–570
80. Hausler M, Ramaekers VT, Doenges M et al (2002) Neurological complications of acute and persistent Epstein-Barr virus infection in paediatric patients. J Med Virol 68:253–263
81. Johkura K, Momoo T, Kuroiwa Y (2003) Thalamic involvement of Epstein-Barr virus encephalitis demonstrated by MRI. J Neurol 250:357–358
82. Cecil KM, Jones BV, Williams S et al (2000) CT, MRI and MRS of Epstein-Barr virus infection: case report. Neuroradiology 42:619–622
83. Neto EC, Rubin R, Schulte J et al (2004) Newborn screening for congenital infectious diseases. Emerg Infect Dis 10:1068–1073

84. Trincado DE, Rawlinson WD (2001) Congenital and perinatal infections with cytomegalovirus. J Paediatr Child Health 37:187–192
85. Boesch C, Issakainen J, Kewitz G et al (1989) Magnetic resonance imaging of the brain in congenital cytomegalovirus infection. Pediatr Radiol 19:91–93
86. de Vries LS, Gunardi H, Barth PG et al (2004) The spectrum of cranial ultrasound and magnetic resonance imaging abnormalities in congenital cytomegalovirus infection. Neuropediatrics 35:113–119
87. Malinger G, Lev D, Zahalka N et al (2003) Fetal cytomegalovirus infection of the brain: the spectrum of sonographic findings. AJNR 24:28–32
88. Arribas JR, Storch GA, Clifford DB et al (1996) Cytomegalovirus encephalitis. Ann Intern Med 125:577–587
89. Chaudhuri A, Kennedy PG (2002) Diagnosis and treatment of viral encephalitis. Postgrad Med J 78:575–583
90. Studahl M, Ricksten A, Sandberg T et al (1994) Cytomegalovirus infection of the CNS in non-compromised patients. Acta Neurol Scand 89:451–457
91. Burke DG, Leonard DG, Imperiale TF et al (1999) The utility of clinical and radiographic features in the diagnosis of cytomegalovirus central nervous system disease in AIDS patients. Mol Diagn 4:37–43
92. Maschke M, Kastrup O, Diener HC (2002) CNS manifestations of cytomegalovirus infections: diagnosis and treatment. CNS Drugs 16:303–315
93. Kalaylian RC, Cohen ML, Bonomo RA et al (1993) Cytomegalovirus ventriculoencephalitis in AIDS. A syndrome with distinct clinical and pathologic features. Medicine (Baltimore) 72:67–77
94. Bassil HF, William DC (1997) Cytomegalovirus encephalitis in an HIV positive patient presenting with a cerebral mass lesion. AIDS Patient Care STDS 11:319–321
95. Dyer JR, French MA, Mallal SA (1995) Cerebral mass lesions due to cytomegalovirus in patients with AIDS: report of two cases. J Infect 30:147–151
96. Moulignier A, Mikol J, Gonzalez-Canali G et al (1996) AIDS-associated cytomegalovirus infection mimicking central nervous system tumors: a diagnostic challenge. Clin Infect Dis 22:626–631
97. Balakrishnan J, Becker PS, Kumar AJ et al (1990) Acquired immunodeficiency syndrome: correlation of radiologic and pathologic findings in the brain. Radiographics 10:201–215
98. Salazar A, Podzamczer D, Rene R et al (1995) Cytomegalovirus ventriculoencephalitis in AIDS patients. Scand J Infect Dis 27:165–169
99. Seo SK, Regan A, Cihlar T et al (2001) Cytomegalovirus ventriculoencephalitis in a bone marrow transplant recipient receiving antiviral maintenance: clinical and molecular evidence of drug resistance. Clin Infect Dis 33:e105–e108
100. Huang PP, McMeeking AA, Stempien MJ et al (1997) Cytomegalovirus disease presenting as a focal brain mass: report of two cases. Neurosurgery 40:1074–1078
101. Avila-Aguero ML, Paris MM, Alfaro W et al (2003) Ganciclovir therapy in cytomegalovirus (CMV) infection in immunocompetent pediatric patients. Int J Infect Dis 7:278–281
102. Smirniotopoulos JG (2000) Cytomegalovirus. Disease topic 998, MedPix. http://rad.usuhs.edu/medpix/master.php3?mode=single&recnum=998&details=-1#top
103. Campadelli-Fiume G, Mirandola P, Menotti L (1999) Human herpesvirus 6: an emerging pathogen. Emerg Infect Dis 5:353–366
104. Asano Y, Yoshikawa T, Suga S et al (1994) Clinical features of infants with primary human herpesvirus 6 infection (exanthem subitum, roseola infantum). Pediatrics 93:104–108
105. Yamanishi K, Okuno T, Shiraki K et al (1988) Identification of human herpesvirus-6 as a causal agent for exanthem subitum. Lancet 1:1065–1067
106. De Bolle L, Naesens L, De Clercq E (2005) Update on human herpesvirus 6 biology, clinical features, and therapy. Clin Microbiol Rev 18:217–245
107. Hall CB, Long CE, Schnabel KC et al (1994) Human herpesvirus-6 infection in children. A prospective study of complications and reactivation. N Engl J Med 331:432–438
108. Luppi M, Barozzi P, Maiorana A et al (1994) Human herpesvirus 6 infection in normal human brain tissue. J Infect Dis 169:943–944
109. Braun DK, Dominguez G, Pellett PE (1997) Human herpesvirus 6. Clin Microbiol Rev 10:521–567
110. Caserta MT, Hall CB, Schnabel K et al (1994) Neuroinvasion and persistence of human herpesvirus 6 in children. J Infect Dis 170:1586–1589
111. Yamashita N, Morishima T (2005) HHV-6 and seizures. Herpes 12:46–49
112. Barone SR, Kaplan MH, Krilov LR (1995) Human herpesvirus-6 infection in children with first febrile seizures. J Pediatr 127:95–97
113. Asano Y, Yoshikawa T, Kajita Y et al (1992) Fatal encephalitis/encephalopathy in primary human herpesvirus-6 infection. Arch Dis Child 67:1484–1485
114. Ishiguro N, Yamada S, Takahashi T et al (1990) Meningoencephalitis associated with HHV-6 related exanthem subitum. Acta Paediatr Scand 79:987–989
115. Singh N, Paterson DL (2000) Encephalitis caused by human herpesvirus-6 in transplant recipients: relevance of a novel neurotropic virus. Transplantation 69:2474–2479
116. Yoshikawa T, Asano Y, Ihira M et al (2002) Human herpesvirus 6 viremia in bone marrow transplant recipients: clinical features and risk factors. J Infect Dis 185:847–853
117. Wang FZ, Linde A, Hagglund H et al (1999) Human herpesvirus 6 DNA in cerebrospinal fluid specimens from allogeneic bone marrow transplant patients: does it have clinical significance? Clin Infect Dis 28:562–568
118. Gorniak RJ, Young GS, Wiese DE et al (2006) MR imaging of human herpesvirus-6-associated encephalitis in 4 patients with anterograde amnesia after allogeneic hematopoietic stem-cell transplantation. AJNR 27:887–891
119. Drobyski WR, Knox KK, Majewski D et al (1994) Brief report: fatal encephalitis due to variant B human herpesvirus-6 infection in a bone marrow-transplant recipient. N Engl J Med 330:1356–1360
120. MacLean HJ, Douen AG (2002) Severe amnesia associated with human herpesvirus 6 encephalitis after bone marrow transplantation. Transplantation 73:1086–1089
121. Noguchi T, Mihara F, Yoshiura T et al (2006) MR imaging of human herpesvirus-6 encephalopathy after hematopoietic stem cell transplantation in adults. AJNR 27:2191–2195
122. Wainwright MS, Martin PL, Morse RP et al (2001) Human herpesvirus 6 limbic encephalitis after stem cell transplantation. Ann Neurol 50:612–619
123. Murakami A, Morimoto M, Adachi S et al (2005) Infantile bilateral striatal necrosis associated with human herpes virus-6 (HHV-6) infection. Brain Dev 27:527–530
124. Oki J, Yoshida H, Tokumitsu A et al (1995) Serial neuroimages of acute necrotizing encephalopathy associated with human herpesvirus 6 infection. Brain Dev 17:356–359
125. Ohsaka M, Houkin K, Takigami M et al (2006) Acute necrotizing encephalopathy associated with human herpesvirus-6 infection. Pediatr Neurol 34:160–163
126. Bell WE, Henderson FW (2005) Infections of the central nervous system. In: David RB (ed) Child and adolescent neurology. Blackwell Publishing, Richmond, VA, p 257