The Neurological Manifestations of Pediatric Infectious Diseases and Immunodeficiency Syndromes

Infectious Disease™

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We dedicate this work to those who have:

- *Enabled and encouraged us—our spouses, William Holmes (LLB) and Joanne Friedman (NRF), our children, our grandchildren (LLB), our parents and Johanna Grimes (LLB)*
- *Inspired us—our students, housestaff, and teachers*
- *Endured us—our colleagues*

Foreword

A major portion of all of acute child neurology involves the neurological complications of infectious diseases. However, none of the currently available excellent texts on infectious disease focus specifically on the neurological aspects. Drs. Neil R. Friedman and Leslie L. Barton have filled this important void with a superb, multi-authored text, addressing directly "the neurological manifestations of pediatric infectious diseases and immunodeficiency syndromes."

The book is organized logically according to the responsible microorganisms and addresses sequentially a broad spectrum of viruses, bacteria, fungi, rickettsiae, spirochetes, mycobacteriae, and parasites, as well as cat-scratch disease and human immunodeficiency virus (HIV) infection. The chapters are consistently similar in organization and begin with an introduction that provides a synopsis and perspective. The substance of the chapters follows in sections devoted to epidemiology, pathogenesis, clinical manifestations, diagnosis, treatment, and references. The discussions of epidemiology are particularly informative and current. The sections on pathogenesis include valuable neuropathology and critical distinctions among disorders caused by primary infection by the microorganism and those related to parainfectious and postinfectious immunological phenomena. The sections on clinical manifestations emphasize the neurological features and often are subdivided into specific neurological syndromes. Results of modern brain imaging are illustrated, and tables highlight neurological and other features. Sections on diagnosis are especially valuable and emphasize the value of polymerase chain reaction (PCR) and related means of identifying microbial nucleic acids and proteins. The discussions of treatment are especially current and valuable. The citations are up-to-date and reflect a broad spectrum of both the neurological and infectious disease literature.

This text is very well balanced. It is comprehensive yet readable. It emphasizes neurological aspects, yet includes detailed and current infectious disease aspects. The balance undoubtedly reflects particularly the expertise of the two editors, one a child neurologist (Dr. Neil R. Friedman), and the other, an infectious disease expert (Dr. Leslie L. Barton).

The editors are to be congratulated for the superb organization of the text and their important personal contributions, the assembling of an outstanding group of authors,

and the orchestration of a consistent and clear message throughout the text. It should prove useful to anyone involved in the evaluation and care of sick children.

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Preface

Infectious diseases and immunodeficiencies remain the leading causes of morbidity and mortality in the world's children today (World Health Organization [WHO], 2006). The WHO estimates that nearly one third of the global deaths in 2005 were attributable to communicable diseases, an acknowledged underestimate. Despite the optimism engendered by the development of antimicrobial therapy and vaccines, and improvements in sanitation—especially in developed countries—infections both prevail (e.g., malaria) and emerge (e.g., human immunodeficiency virus/acquired immunodeficiency syndrome). Infectious diseases respect neither geographic nor medical specialty boundaries.

Pediatricians and all who care for children are faced virtually on a daily basis with classic and unusual presentations of infectious diseases and immunodeficiencies in their patients. The neurological consequences of infectious diseases and immunodeficiency syndromes have, however, not been previously compiled in a readily accessible volume.

Our goal is to provide a succinct authoritative, up-to-date, evidence-based, practical, and accessible reference. This book is written for physicians-in-training, primary care physicians, and subspecialists. We aim to alert practitioners to the neurological manifestations of infectious disease entities and, conversely, to alert physicians who encounter a neurological process to the possibility of an underlying infectious disease or immunodeficiency syndrome.

All chapters provide a general description of the disease or disorder, its epidemiology, etiology, clinical synopsis, neurological manifestations, diagnosis, differential diagnosis, and therapy. We have endeavored to enhance the volume's usefulness by maintaining a structured format, at the same time offering refreshing and diverse expositions by an international group of authors. Although we attempted to minimize duplication, some repetition was unavoidable.

The editors are grateful to these expert contributors, to our teachers and to our mentors, and to the many individuals who helped bring this text to fruition.

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Chapter 1
Herpes Viruses

Sean P. Elliott, M.D.

Herpes Simplex Virus

Introduction

Herpes simplex virus (HSV) is a ubiquitous virus that infects most humans and is responsible for a broad spectrum of disease, ranging from asymptomatic infection to fatal, sporadic viral encephalitis. HSV occupies a prominent place in the differential diagnosis of infectious neurological disease and has led to large modifications in the diagnostic and interventional approach to acute encephalitis and neonatal infection.

Epidemiology

HSV is highly infectious, but requires close interpersonal contact for transmission. Such transmission can occur via saliva or direct apposition of infected with uninfected mucous membranes. HSV-1 typically is associated with gingivostomatitis, pharyngitis, and encephalitis in children and adults. HSV-2 primarily is associated with genital herpes. Both can cause neonatal disease, acquired either transplacentally or via exposure to cervical secretions. Age-linked seroprevalence data differ for HSV-1 and HSV-2, reflecting patterns expected for a sexually transmitted disease (HSV-2) compared with a mostly nonsexually transmitted disease (HSV-1). HSV-1 seroprevalence increases in a linear fashion with increasing age, reaching at least 40% by age 15 years and 60 to 90% in older adults; HSV-2 seroprevalence is very low in those younger than 15 years, but increases precipitously during the sexually active years and plateaus after age 40 years [1]. The seroprevalence of HSV-2 continues to increase in the United States, recently reaching 20.8% overall, with high-risk groups demonstrating 46 to 77% [1, 2]. Asymptomatic shedding of HSV is common: patients with known recurrent genital disease shed HSV up to 10% of the time that they are lesion free [3]. Not surprisingly, the incidence of neonatal HSV infection has shown a similar increase, rising from 2.6 per 100,000 live births to 11 to 28.2 per 100,000 live births [4, 5]. Preventive measures and planned cesarean delivery may eventually halt or reverse this trend [6].

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Pathogenesis

HSV is the fastest growing member of the *Herpesviridae* family of DNA viruses, existing in humans in two serotypes, HSV-1 and HSV-2, which share approximately 50% nucleotide homology. HSV is highly neurotropic and can establish latent infections with periodic reactivation. Initial infection and viral replication occur at the site of entry, typically skin or mucous membranes. Cellular response to injury precipitates local inflammation with formation of vesicles in the affected areas. After resolution of primary infection, HSV remains latent in sensory ganglia. The route of transmission to the brain in encephalitis is less well understood. Neonates with disseminated HSV disease likely experience viremia with secondary diffuse encephalitis resulting in generalized encephalomalacia [7, 8]. Neonates, children, and adults with primary encephalitis may experience retrograde axonal transport via the trigeminal ganglia or nerve after HSV reactivation or new infection, resulting in distinctive, localized inflammation in the mediotemporal and orbitofrontal lobes [9,10].

Clinical Manifestations

Perinatal Disease

Neonates are especially vulnerable to HSV infections, acquired most often via vertical transmission in the peripartum period and less frequently in utero or via postpartum exposure. Prevention of HSV transmission is difficult because 70 to 80% of infected infants are born to mothers with asymptomatic HSV infection [11]. Risk for neonatal infection is much higher in those babies born to mothers with primary infection (33%) than those born to mothers with reactivated disease (3%) [12]. Additional risk factors include maternal antibody status, duration of ruptured membranes, and placement of a scalp monitor [13]. Neonatal infection may be classified into four syndromes: intrauterine disease; skin, eye, and mouth (SEM) disease; disseminated disease; and encephalitis. Demographics and characteristics of infants with neonatal HSV disease are listed in Table 1.1, compiled from National Institute of Allergy and Infectious Diseases (NIAID) Collaborative Antiviral Study Group Data [14,15].

Intrauterine Disease

True congenital HSV infection acquired in utero is rare. Infants are born with congenital malformations and evidence of HSV infection detected at or shortly after delivery. One series of such infants found the clinical manifestations to include skin lesions, chorioretinitis, microcephaly, hydranencephaly, and microphthalmia, with all infants demonstrating at least two malformations in combination.

Table 1.1 Demographic and clinical characteristics of infants enrolled in a National Institute of Allergy and Infectious Diseases (NIAID) collaborative antiviral study [14,15]

	Disease classification		
	Disseminated	CNS	SEM
No. of infants	93 (32%)	95 (33%)	102 (35%)
Clinical findings			
Skin lesions	72 (77%)	60 (63%)	86 (84%)
Brain involvement	69 (74%)	95 (100%)	0 (0%)
Pneumonia	46 (49%)	4 (4%)	3 (3%)
Mortality at 1 yr[a]	56 (60%)	13 (14%)	0 (0%)
Neurological impairment of survivors (affected/total)			
Total	15/34 (44%)	45/81 (56%)	10/93 (11%)
Adenine arabinoside	13/26 (50%)	25/51 (49%)	3/34 (9%)
Acyclovir	1/6 (17%)	18/27 (67%)	4/51 (8%)
Placebo	1/2 (50%)	2/3 (67%)	3/8 (38%)

[a]Regardless of therapy.

All survivors developed significant neurological sequelae, including hearing and vision defects, mental retardation, severe developmental delay, and complex seizure disorders [16]. The triad of skin vesicles/scarring, eye damage, and microcephaly/hydranencephaly suggests the diagnosis. Central nervous system (CNS) damage is caused by intrauterine encephalitis. Other data indicates a higher risk of spontaneous abortion for women with genital HSV infections, suggesting the majority of fetuses infected in utero are not viable [17,18].

Skin, Eye, and Mouth Disease

SEM disease typically presents in the first or second week of life, with discrete, vesicular skin lesions present on any part of the body. Clusters of vesicles also occur, especially on traumatized skin, such as scalp monitor sites, or on the presenting part of the body. SEM disease is not associated initially with significant neurological disease. However, if left untreated, 35 to 40% of patients with SEM disease may develop neurological disease [13]. Recurrences occur in 90% of patients and may be associated with CNS involvement. Moreover, 20 to 30% of infants who experience more than three recurrences in the first 6 months of life develop evidence of neurological impairment [11,15], including cognitive defects, spastic quadriplegia, microcephaly, and blindness [13]. Risk for neurological sequelae seems to be even higher with HSV-2 infections than HSV-1 infections [11]. Although the safety of oral suppressive acyclovir therapy has been established [19], evaluation of its efficacy in preventing such recurrences and neurological sequelae is ongoing. Thus, infants with both primary and recurrent SEM disease deserve evaluation for CNS involvement and initial, aggressive treatment with antiviral agents.

Disseminated Disease

Infants with disseminated HSV disease develop symptoms in the first week of life, although diagnosis occurs more commonly in the second week of life. Disseminated HSV disease carries the worst prognosis. Any organ may be affected, but the lungs, liver, adrenal glands, and brain are the most common targets. Encephalitis occurs in 60 to 70% of infants, most likely as a result of hematogenous spread to the brain, causing multiple areas of cortical hemorrhagic necrosis [15]. Signs and symptoms of disseminated disease include irritability, lethargy, seizures, respiratory distress, jaundice, bleeding diathesis, and shock. Unfortunately, at least 20% of infants with disseminated disease will not demonstrate skin vesicles [13], thus complicating initial diagnosis. Without treatment, mortality exceeds 80%. Even with timely initiation of antiviral agents, mortality remains high (50–60%) [11].

Neonatal Encephalitis

Primary neonatal HSV encephalitis usually presents in the second to third week of life. Typical signs and symptoms include focal, multifocal, or generalized seizures; lethargy; irritability; poor feeding; temperature instability; apnea; bradycardia; and cranial nerve abnormalities [15]. Only 60% will develop skin lesions during their disease course [11]. Typical cerebrospinal fluid (CSF) findings include pleocytosis and mild reduction of glucose. Although initial CSF protein concentrations may be normal or only slightly elevated, most infants usually demonstrate progressive increases up to more than 1000 mg/dL. The hemorrhagic nature of HSV encephalitis may result in apparent bloody CSF, making differentiation from a traumatic lumbar puncture difficult. Electroencephalography (EEG) and neuroimaging demonstrate abnormalities in 85% and 74%, respectively, of patients with HSV CNS disease [14]. Untreated neonatal HSV encephalitis carries a 50% mortality. With prompt initiation of antiviral therapy, mortality drops to 15 to 18% [8,11]. Antiviral therapy has no significant impact on neurological sequelae in survivors: 50 to 66% will develop neurological impairment such as psychomotor retardation, microcephaly, hydranencephaly, spasticity, blindness, chorioretinitis, or learning disabilities [8,11,15]. Neuroimaging typically demonstrates progression of focal parenchymal lesions into multicystic cerebral degeneration [20].

Sporadic Encephalitis

HSV is the most common cause of sporadic, acquired, focal encephalitis in the United States, occurring in approximately 1 in 250,000 to 500,000 people annually [8]. A bimodal age distribution exists, with more than 80% of cases found in patients younger than 20 years or older than 50 years of age and, unlike most other causes of viral encephalitis, cases occur throughout the year [10]. HSV-1 is the cause of 93 to 96% of

cases, more often as a result of recurrent or reactivated (70%) disease than primary (30%) infection [21].

HSV encephalitis may have an acute or subacute onset. Most patients develop signs of localized lesions in the temporal lobes, often taking the form of personality changes, hallucinations, or bizarre behavior. Fever, headache, and alterations in consciousness also are prominent early symptoms, followed by seizures, hemiparesis, dysphasia, and superior quadrant visual field defects (Table 1.2). Without treatment, most patients progress from stupor to coma to death very rapidly [9].

The CSF frequently demonstrates pleocytosis ranging from 50 to 2000 white blood cells/mm^3, with a lymphoid predominance. Red blood cells may be seen in 75 to 85% of cases, reflecting the hemorrhagic, necrotic nature of HSV encephalitis. Five to 25% of patients have hypoglycorrhachia, and 80 to 88% have elevated protein levels, beginning at a median of 80 mg/dL and rising dramatically as the disease progresses. CSF findings in early disease may be subtle, with mild pleocytosis and neutrophil predominance, normal glucose, and minimally elevated protein levels [9,22]. EEG (Fig. 1.1) may show unilateral or bilateral periodic focal spikes against a background of slow (flattened) activity (periodic lateralized epileptiform discharges [PLEDS]), which typically has been associated with HSV encephalitis [22]. PLEDS is not, however, pathognomonic for this, and may be associated with other neurological conditions. Magnetic resonance imaging (MRI) scanning is more sensitive than computed tomographic (CT) scanning for early detection of HSV encephalitis [23]. Findings include hyperintensity on T2-weighted images of temporal areas and gadolinium enhancement (Fig. 1.2)

Without appropriate antiviral treatment, the mortality of HSV encephalitis exceeds 70% [8]. Use of acyclovir reduces the mortality rate to 19%, although this may be negatively influenced by increased patient age and lower initial level of consciousness [9]. A poor therapeutic outcome is uniform in those patients with an initial Glasgow Coma Score of 6 or less [8]. Even with treatment, patients who survive HSV encephalitis may have severe sequelae, including major motor and sensory deficits, aphasia, and an amnestic syndrome (Korsakoff's psychosis) [9].

Table 1.2 Historical and clinical findings in HSV encephalitis [8–10,22]

Historical findings		Clinical findings at presentation	
Alteration of consciousness	97%	Fever	92%
Fever	90%	Personality changes	85%
Headache	81%	Dysphasia	76%
Persistent seizures	67%	Autonomic dysfunction	60%
Personality change	71%	Ataxia	40%
Vomiting	46%	Seizures	38%
Hemiparesis	33%	Focal	28%
Memory loss	24%	Generalized	10%
		Cranial nerve defects	32%
		Visual field loss	14%
		Papilledema	14%

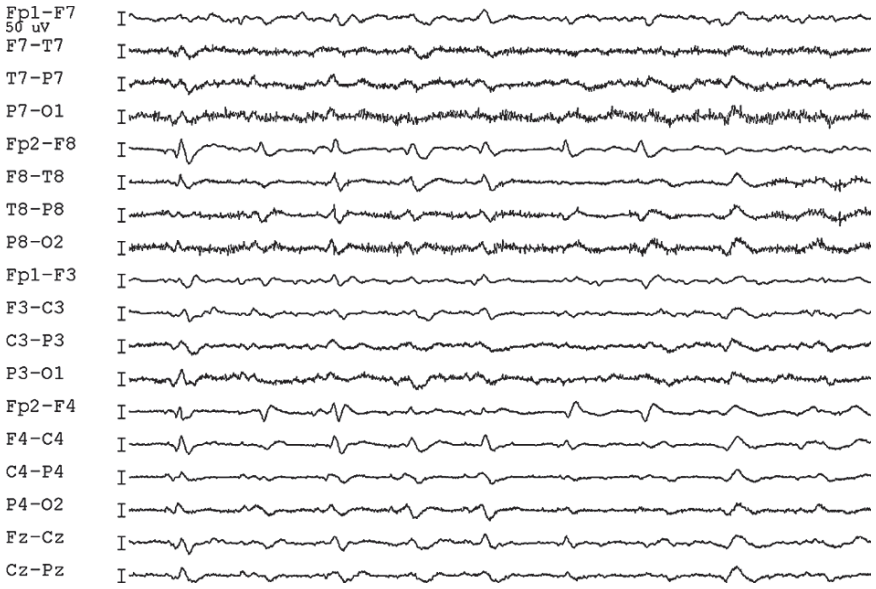

Fig. 1.1 Focal right PLEDS in a patient with HSV encephalitis (EEG courtesy of Deepak Lachhwani, M.D.)

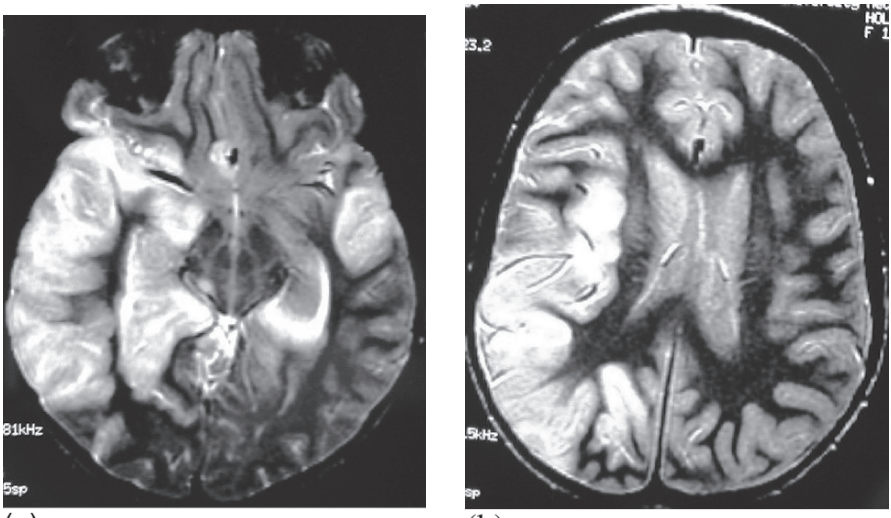

Fig. 1.2 Head MRI scan, T2-weighted axial images, of a 9-year-old girl with sporadic HSV encephalitis demonstrates temporal lobe inflammation (**a**) and parietooccipital lobe inflammation (**b**), both with mass effect.

Meningitis

HSV-induced aseptic meningitis syndrome is typically caused by HSV-2, usually as a complication of primary genital infection. Signs of meningitis appear shortly after genital lesions are noted, and include headache, photophobia, and nuchal rigidity. Seizures and focal CNS findings are generally absent. CSF findings demonstrate pleocytosis (300–2600 white blood cells/mm^3) with lymphoid predominance and occasionally hypoglycorrhachia [22]. Recovery is spontaneous and complete, requiring no specific antiviral therapy. However, this syndrome may recur with genital recurrences.

HSV is now thought to be the major agent responsible for benign recurrent lymphocytic meningitis (Mollaret's meningitis) [24]. This syndrome involves recurrent attacks of fever and meningismus with CSF demonstrating lymphocytic pleocytosis (48–1600 cells/mm^3), normal glucose, and elevated protein (41–240 mg/dL). HSV-2 DNA has been detected in CSF of patients with Mollaret's meningitis while the patients are symptomatic but not in asymptomatic patients or in healthy controls [10,24].

Other Neurological Disease

HSV is also associated with diseases of the peripheral nervous system, generally as a result of recurrence within the dermatome of primary infection. However, recurrent disease does not necessarily occur at precisely the same anatomic location [25]. Common sites of infection and the associated diseases are listed in Table 1.3. HSV-1 seems to be the most likely cause of peripheral facial nerve palsy (Bell's palsy), although multiple infectious agents and clinical syndromes are also possible. Patients with HSV encephalitis may also develop acute retinal necrosis syndrome [26–28], parainfectious encephalomyeloradiculitis, recurrent encephalitis, ascending myelitis, and postinfectious encephalopathy [29,30]. Although usually associated with encephalitis, acute HSV cerebellitis has been demonstrated in the absence of previous CNS infection [31].

Table 1.3 HSV infections of the peripheral nervous system [25]

Nerve	Disease manifestation
Vth cranial nerve	Gingivostomatitis
	Recurrent cold sores
	Corneal infections
	HSV gladiatorum[a]
VIIth cranial nerve	Facial paralysis
Cervical and thoracic sensory nerves	Herpetic whitlow
	Nipple infection
Lumbosacral sensory nerves	Genital herpes

[a] Can also affect cervical and thoracic sensory nerves.

Diagnosis

Culture remains the most sensitive method for diagnosing active infection of non-CNS sites, such as skin, eyes, and mucous membranes. Samples should be obtained by swabbing the base of denuded lesions with premoistened cotton swabs followed by direct inoculation into either viral transport or culture media. HSV cytopathic effect may be observed from between 24 hours and 5 days, depending on the viral load of the sample. More rapid diagnosis is available through direct detection methods, most commonly direct immunofluorescent staining. This method is more sensitive (80–90%) and specific than the Tzanck test [32]. Serologic evaluation is possible via enzyme-linked immunosorbent assays (ELISA) or latex agglutination procedures. However, these results are difficult to interpret because detectable IgM may occur in both reactivated disease and new disease, and infected infants may demonstrate diminished or absent production of IgM. Mothers of infected infants may be seronegative or seropositive. However, many assays do not distinguish between HSV-1 and HSV-2. Thus, new infection by one type may be obscured by serologic evidence of previous infection with the other type.

The gold standard for diagnosis of HSV-associated CNS disease has been isolation of HSV obtained at brain biopsy. However, polymerase chain reaction (PCR) testing now has replaced brain biopsy as the diagnostic test of choice for HSV encephalitis. HSV PCR of CSF carries a sensitivity and specificity of 98% and 96%, respectively [33], and now is widely available in commercial laboratories. False negative results may occur early in the course of CNS disease. However, detection of HSV in CSF by PCR remains possible for up to 10 days in the setting of concurrent antiviral therapy [34]. HSV PCR has, thus, become an extremely useful tool in the diagnosis of a variety of neurological disorders, including encephalitis, meningitis, Mollaret's meningitis, myelitis, and Bell's palsy [35].

Treatment

Acyclovir remains the drug of choice for most HSV infections. It is available for parenteral, oral, and topical delivery. Oral preparations of its prodrug improve the bioavailability of active drug. Use of acyclovir for non-CNS HSV disease or recurrence is of unclear benefit in most cases. Treatment decisions in such cases must, therefore, be individualized. Preliminary research has shown a clinical benefit from use of both corticosteroids and acyclovir together in patients with Bell's palsy, although this finding remains to be confirmed [10]. Data regarding dose and duration is lacking, although initiation early in the course of disease seems more beneficial than when a treatment delay occurs. Use of acyclovir has significant positive impact on HSV encephalitis mortality. The currently accepted treatment of non-neonatal HSV encephalitis is parenteral acyclovir 30 mg/kg/d, divided every 8 hours, for 21 days. Neonates with HSV disease localized to skin, eye, and mouth require

parenteral acyclovir 60 mg/kg/d, divided every 8 hours, for 14 days. However, neonates with evidence of disseminated disease or encephalitis may require 21 days of treatment. Higher doses (90 mg/kg/d) currently are being studied to assess the possibility of added benefit. Acyclovir is well tolerated. It rarely has been associated with renal dysfunction and neutropenia [36]. The possibility of a HSV vaccine remains enticing and is the subject of considerable research interest [37].

Cytomegalovirus

Introduction

Cytomegalovirus (CMV) is the most common cause of congenital infection in the United States, a leading infectious cause of brain damage and sensorineural hearing loss in children in developed countries [38], and an important opportunistic pathogen in patients with abnormal immune function. It has been called "a ubiquitous agent with protean clinical manifestations [39],"a testimony to the difficulty of recognizing and predicting its potential for neurological disease.

Epidemiology

CMV transmission occurs primarily through exposure to urine, respiratory secretions, and sexual contact, and, rarely, via blood and blood products. Vertical transmission from mother to fetus occurs transplacentally and via exposure to cervical secretions. Breast milk has been identified as a significant source of postnatal acquisition of symptomatic CMV disease in very low birth weight infants [40]. CMV causes congenital infection in 0.2 to 2.5% of all live births in the world [41]. In the United States, approximately 1% of newborns shed CMV in the urine at birth, leading to approximately 40,000 new cases of congenital CMV per year [42]. Most of these infections are asymptomatic; however 10% of congenitally infected infants will demonstrate clinically apparent disease [42].

Pathogenesis

CMV is the largest and slowest growing member of the *Herpesviridae* family of DNA viruses. Inoculation of CMV usually takes place via a mucosal surface in the upper respiratory or genital tract and is likely followed by viremia, accounting for dissemination to many different organs and viral shedding from saliva, urine, and genital secretions. Disease may be caused by a primary cytopathic effect, immunopathologic process, or both. The extent of brain injury induced by primary

infection is very variable and most often affects the periventricular subependymal matrix, especially in the lateral ventricles. Necrosis and accompanying calcification can be associated with these lesions [42].

Clinical Manifestations

Congenital CMV Infection

The spectrum of symptomatic congenital CMV infection is wide, and can include mild disease as well as intrauterine growth retardation, hepatitis, hepatosplenomegaly, pneumonitis, hyperbilirubinemia, thrombocytopenia, hemolytic anemia, petechiae, and purpura. Associated CNS and ocular abnormalities are noted in Table 1.4. Five to 17% of infants with asymptomatic congenital CMV at birth are also at risk for development of neurological sequelae, including microcephaly, developmental and intellectual impairment, mental retardation, and sensorineural deafness. This risk drops significantly if the child demonstrates normal development at 12 months of age [43]. However, congenitally acquired CMV remains a leading cause of sensorineural deafness and mental retardation in the United States [38,44,45]. In patients with both symptomatic and asymptomatic congenital CMV infection, evidence of viremia during infancy is associated with development of hearing loss [190,191].

Perinatal CMV Infection

CMV acquired in the perinatal period typically causes infection in infants from 1 to 4 months of age. Although most of these infections are asymptomatic, approximately one third of infants may demonstrate some signs and symptoms. These include

Table 1.4 CNS and ocular abnormalities associated with congenital CMV disease [41]

Anomaly of optic disc, optic atrophy[a]
Anterior chamber malformation
Cerebellar aplasia
Cerebral cyst formation
Chorioretinitis[a]
Encephalomalacia
Microcephaly[a]
Microgyria
Microphthalmia
Periventricular leukomalacia, calcifications[a]
Psychomotor retardation
Sensorineural hearing loss[a]
Spongiosis of brain
Strabismus
Ventriculomegaly with hydrocephalus

[a]Most commonly observed.

self-limited lymphadenopathy, hepatosplenomegaly, hepatitis, and pneumonitis. Perinatal CMV infection has not been shown to cause sensorineural hearing loss or neurodevelopmental disease [46].

Acquired CMV Infection

CMV acquired by both immunocompetent and immunosuppressed children and adolescents most often manifests as mononucleosis syndrome. Typical CMV-induced mononucleosis is characterized by fever, severe fatigue, and malaise, for approximately 3 to 4 weeks duration. Associated laboratory manifestations include mild elevation of liver enzymes and peripheral lymphocytosis with atypical lymphocytes seen on smear. In contrast to the more commonly recognized Epstein-Barr virus (EBV)-induced mononucleosis, CMV-induced mononucleosis rarely causes pharyngitis or splenomegaly. Neurological complications of CMV-induced mononucleosis are rare and include Guillain-Barré syndrome and meningoencephalitis [47].

Neurological Manifestations

CNS disease is a well recognized and described component of symptomatic congenital CMV disease. A review of 106 neonates with symptomatic congenital CMV infection identified 54 (53%) infants with microcephaly, 28 (27%) with lethargy/hypotonia, 20 (19%) with poor suck, and 7 (7%) with seizures. Seventy-two (68%) had one or more of these findings [48]. Direct viral infection of neural tissue probably plays a significant role in CNS disease from congenital CMV infection, although infectious vasculitis and thrombocytopenia-related intracranial hemorrhage may also contribute (Fig. 1.3) [49]. Findings on neuroimaging include intracranial calcifications, dilated lateral ventricles, enlarged subarachnoid space, oligo/pachygyria, abnormal myelination, and periventricular cysts (Fig. 1.4). Intracranial calcifications may be visualized in up to 40% of symptomatic infants [42]. The magnitude of the prenatal insult is suggested by the presence of microcephaly, cerebral calcification, and intrauterine growth retardation [50,51]. It may take years to realize the full neurological impact of congenital CMV infection. Ultimately, 50 to 90% of patients with symptomatic congenital CMV infection will develop CNS impairment, including cognitive defects or mental retardation, as will 7 to 25% of asymptomatic CMV infected patients [38]. Early findings demonstrated to be predictive of later CNS impairment include microcephaly, chorioretinitis, lethargy, poor feeding, or abnormalities on cranial CT scan [44,52,53]. Of these, microcephaly at birth seems to be the most specific predictor of poor cognitive outcome, with a highly significant positive correlation between head size at birth and the intelligence–developmental quotient. Conversely, symptomatic children with normal findings on cranial CT scan and a head circumference proportional to their weight seem to exhibit good cognitive outcome [53].

Congenitally CMV-infected infants with no initial signs of disease may develop signs or symptoms of neurological disease within the first 1 to 2 years of life, manifesting as mental retardation, motor disabilities (e.g., spastic diplegia or quadriplegia),

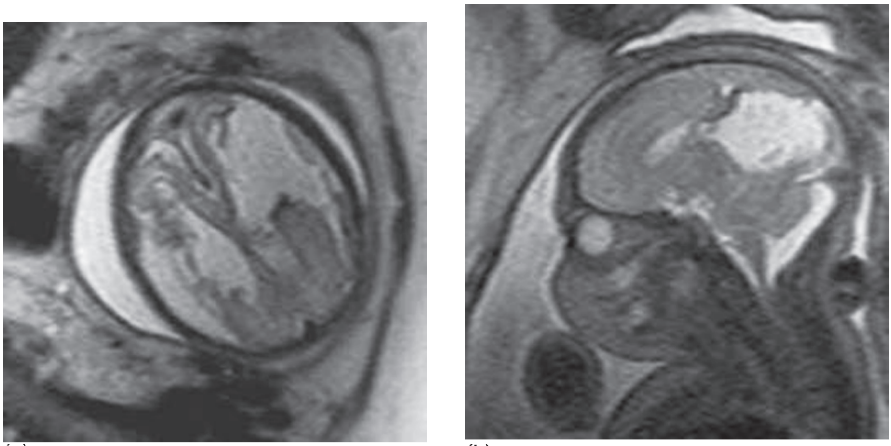

Fig. 1.3 Axial (**a**) and parasagittal (**b**) single-shot fast spin echo T2-weighted half-Fourier-acquisition single-shot turbo-spin-echo MRI scan of the brain of a third trimester fetus infected with CMV in the early second trimester shows brain destruction, colpocephaly, and periventricular magnetic susceptibility consistent with calcification (images courtesy of Janet Reid, M.D.; reproduced with permission from: Faerber E. TORCH infections. In: Reid JR, ed. Pediatric radiology curriculum [Internet]. Cleveland, OH: Cleveland Clinic Center for Online Medical Education and Training; 2005. Available from: https://www.cchs.net/pediatricradiology).

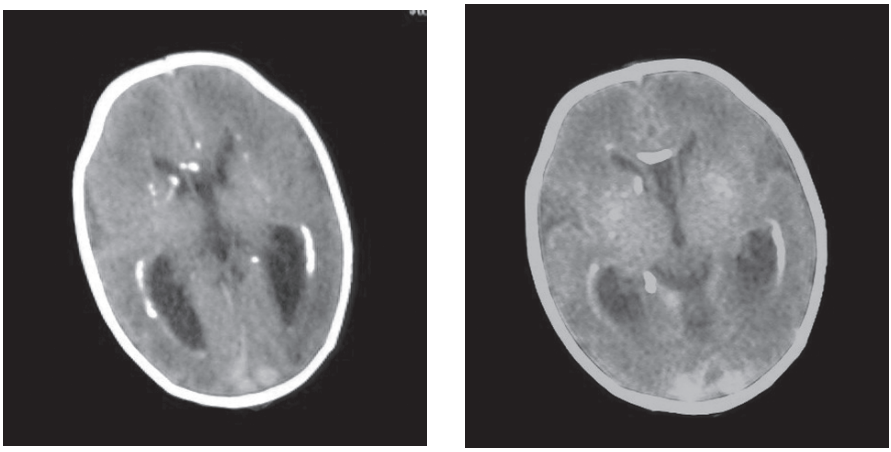

Fig. 1.4 Head CT scan, axial images, of two patients with congenital CMV demonstrates periventricular calcifications and dilated lateral ventricles.

sensorineural hearing impairment, or microcephaly. It is currently estimated that 2 to 7% of infants with initial asymptomatic congenital CMV infection will develop microcephaly with various degrees of mental retardation and neuromuscular defects by 2 years of age [50]. Long-term, prospective evaluation of the intellectual and neurological development of children with asymptomatic congenital CMV infections has

shown conflicting results. Although some studies suggest that asymptomatic CMV disease may be associated with a broad range of subtle neurodevelopmental sequelae [45], others find no significant differences in comparison with patient controls [46]. Thus, a need exists for identification and longitudinal follow-up of infants with asymptomatic congenital CMV, with careful assessments of psychomotor development and sensorineural hearing abilities, to identify those children deserving of corrective and supportive measures.

Primary meningoencephalitis may occur in patients with acquired CMV infection [49] or as a primary or recurrent infection in immunocompromised hosts. Symptoms include headache, photophobia, nuchal rigidity, memory deficits, and inability to concentrate; fever is not prominent [47]. CSF may demonstrate mild mononuclear pleocytosis and slightly elevated protein, but normal or slightly low glucose. Neuroimaging studies may demonstrate periventricular enhancement and ventricular enlargement but may also be normal [34]. The differential diagnosis of CMV meningoencephalitis in an immunocompetent host includes other viruses with neurotropism: HSV, EBV, varicella-zoster virus (VZV), enteroviruses, and arboviruses.

CMV encephalitis is increasingly recognized in patients with acquired immunodeficiency syndrome (AIDS) and may be seen in transplant recipients. Pathologic studies of patients with end-stage AIDS suggest that 20 to 30% patients have evidence of CMV infection of the brain, although not all will demonstrate clinical signs of this [34]. CMV disease will occur in 50 to 100% of solid organ transplant recipients if either donor or recipient is CMV seropositive [54]. However, primary CMV encephalitis in this population remains rare. Clinical manifestations of CMV encephalitis in an immunocompromised host include rapid deterioration of cognition, occasionally accompanied by cranial nerve palsies. CSF findings are similar to those found in immunocompetent patients with CMV encephalitis. CMV has also been associated with peripheral neuropathy in patients with AIDS [55], as well as an ascending paralysis similar to Guillain-Barré syndrome and polyradiculopathy [47]. However, direct causality is difficult to establish, because HIV may also produce similar neurological disease.

As with other neurotropic viruses, CMV is suspected to be associated with many other diseases of the CNS, either via a primary infection of neural tissue or via a postinfectious inflammatory cascade. An association of CMV with Rasmussen's syndrome, lissencephaly-pachygyria, infantile spasms, Guillain-Barré syndrome, and such neuropsychiatric disorders as schizophrenia has been reported [47,49,51,56]. However, difficulties in demonstrating CMV presence in affected tissues have precluded confirmation of a causal relationship for these diseases.

Chorioretinitis

Ocular involvement by CMV is primarily retinal and can involve all layers of the retina. Strabismus, optic atrophy, microphthalmos, cataracts, retinal necrosis and calcification, blindness, anterior chamber and optic disk malformations, and papillary membrane vestige have also been described [50]. Fifteen percent (range 5–30%) of

newborns with symptomatic congenital CMV will have CMV chorioretinitis [57,58], although this entity is rarely seen in asymptomatic congenitally infected newborns. Most retinal lesions in congenitally infected infants appear inactive at birth. Recent observations suggest the possibility of progression as well as late-onset new retinal lesions [47,58]. CMV retinitis is a far greater problem in severely immunocompromised patients. Fifteen percent to 30% of patients with AIDS will develop retinal lesions from CMV, usually in the more advanced stages, in which CD4 counts drop below 50 cells/μl in adults and 100 cells/μl in children [57,59]. Similarly, CMV retinitis may occur in solid organ and bone marrow transplant patients, especially those who experience primary infection with viremia or who receive T-lymphocyte suppressive therapy [54]. Because younger children may not complain of vision changes, ophthalmologic screening is essential in immunocompromised pediatric patients.

CMV produces characteristic white, perivascular lesions and hemorrhage (Fig. 1.5), descriptively called cottage cheese and ketchup, or brushfire retinitis [60]. Progressive retinitis can cause blurred vision, decreased visual acuity, visual field defects, strabismus, and blindness. Although the ophthalmologic appearance of CMV chorioretinitis is characteristic, laboratory diagnosis by PCR of vitreous fluid may be performed in unusual cases. Of note, detection of CMV DNA in an ocular sample does not exclude presence of another infectious agent, and dual infections have been reported [57].

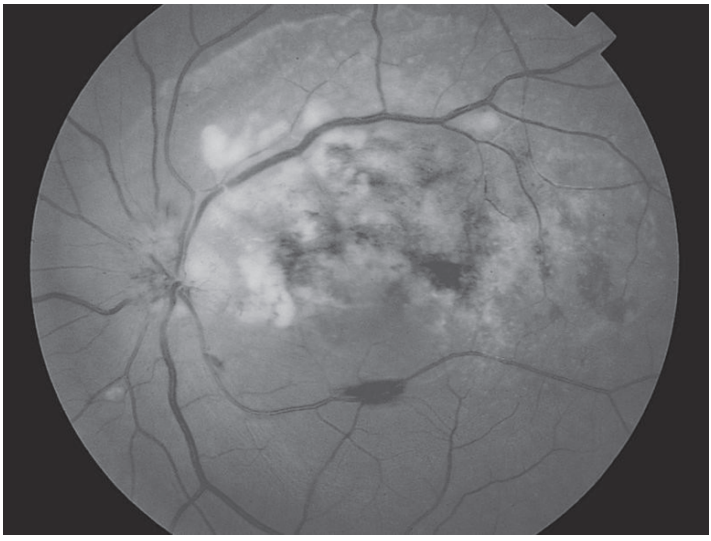

Fig. 1.5 CMV retinitis with characteristic white, perivascular lesions and hemorrhage.

Sensorineural Hearing Loss

Sensorineural hearing loss is present at birth in 25 to 50% of infants with symptomatic congenital CMV infection and in 15% of infants with otherwise asymptomatic CMV infection [47,61]. One follow-up study of children with asymptomatic congenital CMV infection demonstrated subsequent development of hearing loss in 18% of children [62]. With the large number of infants born with congenital CMV infection each year in the United States, congenitally acquired CMV thus represents the most common cause of nonhereditary sensorineural deafness and is estimated to account for at least one third of sensorineural hearing loss in young children [50].

Approximately two thirds of all congenitally CMV-infected infants experience postnatal deterioration of their hearing deficit [61–63]. Although presence of intrauterine growth retardation and petechiae are independently associated with presence of hearing loss at birth, neither seems predictive of hearing loss progression. Of interest, one study demonstrated a significant association between hearing loss at any time and depressed cognitive and motor function in children with confirmed congenitally acquired CMV infection [53]. Thus, children with congenital CMV infection, whether symptomatic or not, deserve careful, serial audiometric examinations and those children in whom deficits are discovered should undergo cognitive and neuromotor evaluation.

Diagnosis

CMV presence is best confirmed by viral cultures from urine or mucosal tissues, especially the oropharynx or nasopharynx. However, a positive culture from these sites does not necessarily confirm active disease or recent infection, because viral shedding may occur intermittently over a prolonged period after initial infection. Regardless, CMV isolated from the urine of an infant younger than 2 weeks of age strongly indicates congenital infection, with only a slight chance of postnatal acquisition. Detection of CMV IgM or CMV IgG in a previously seronegative patient may also suggest recent infection. However, false-positive and false-negative CMV IgM antibody results are common, making interpretation of these results problematic. PCR assays are commercially available to detect CMV in both blood and CSF samples; some laboratories will also perform this test on vitreous fluid to identify CMV chorioretinitis. Because CMV may not grow in culture from these sites, PCR is a useful, rapid, diagnostic tool in patients with suspected neurological or systemic disease. Rapid diagnosis is also available using DNA hybridization. The gold standard for diagnosis of CMV infection or reactivation in solid organs is histopathology. CMV may be identified by presence of typical inclusion bodies or by immunohistochemical analysis.