Herpes Simplex Virus Infections of the Central Nervous System

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Abstract Herpes simplex virus infections of the central nervous system are associated with significant morbidity in spite of efficacious antiviral therapy. Herpes simplex virus, type 1 (HSV-1), causes focal neurologic findings that are characteristic of temporal lobe localization. Herpes simplex encephalitis occurs in a biphasic age distribution with one-third of the cases less than 20 and the majority of remaining cases over 50. The diagnostic test of choice is the detection of HSV DNA by PCR in the cerebrospinal fluid. Acyclovir is the treatment of choice and is administered for 14–21 days intravenously at a dose of 10 mg/kg every 8 h. Neonatal HSV infections are more frequently caused by HSV-2 than HSV-1, although the number of cases of the latter is increasing. Infection is most frequently acquired intrapartum by contact with infected maternal genital secretions. Approximately 50 % of all newborns with neonatal infection will have central nervous system involvement. Importantly, HSV-2 infections of the central nervous system in neonates have a poorer outcome than those attributable to HSV-1. Therapy of neonatal infection is achieved with high-dose acyclovir that is administered at 20 mg/kg/every 8 h for 14–21 days. Six months of oral acyclovir post-intravenous treatment has resulted in an improved neurologic outcome for children with central nervous system infection. Likely, in the future, combination antiviral approaches will be employed for both adult and pediatric disease in order to improve neurologic outcome.

Keywords Herpesvirus • Herpes simplex encephalitis • Acyclovir • Polymerase chain reaction • Latency • Neonatal herpes virus infection

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1 Introduction

Eight herpesviruses routinely cause human disease. There are three subfamilies: alpha (herpes simplex virus 1 (HSV-1), HSV-2, and varicella-zoster virus (VZV)), beta (cytomegalovirus (CMV), human herpesvirus-6 (HHV-6), and HHV-7), and gamma (Epstein–Barr virus (EBV) and Kaposi sarcoma herpesvirus (i.e., HHV-8)). Members of the alpha herpesvirus subfamily are characterized by a very short reproductive cycle, prompt destruction of the host cell, and ability to establish latency, usually in sensory ganglia. Its two leading members—HSV-1 and HSV-2 as causes of CNS disease—are the subject of this chapter.

2 History

Infections caused by HSV have been recognized since the time of ancient Greece. Greek physicians used the word *herpes* to mean "creeping" or "crawling" in reference to skin lesions. Likely, this word was used to describe various skin conditions ranging from cancer to shingles and probably even fever blisters. The Roman scholar Herodotus associated mouth ulcers and lip vesicles with fever [1]. He called this event *herpes febrilis*. Genital herpetic infections were described first by Astruc, a physician to the French royalty [2].

The transmissibility of these viruses was established unequivocally by passage of virus from human lip and genital lesions to either the cornea or the scarified skin of the rabbit [3]. Goodpasture [4] further demonstrated that material derived from the lesions of herpes labialis consistently produced encephalitis when inoculated onto the scarified cornea of rabbits.

Since the first suggestions of herpes simplex encephalitis (HSE) by the Mathewson Commission in 1926 [5] and subsequent description of the histopathologic changes [6], HSV is reported as the most common cause of sporadic fatal encephalitis in the United States [7]. Intranuclear inclusion bodies consistent with HSV infection were first demonstrated in the brain of a neonate with encephalitis [6] in 1941, as is described later in this chapter. Virus was subsequently isolated from this brain tissue [6]. The first adult case of HSE providing similar proof of viral disease (i.e., intranuclear inclusions in brain tissue and virus isolation) was described in 1944 [8]. The most striking pathologic findings in this patient's brain were apparent in the left temporal lobe, where perivascular cuffs of lymphocytes and numerous small hemorrhages were identified. This temporal lobe localization is characteristic of adult HSE, and it differs from the patchy diffuse encephalitis of neonates with HSV brain infection.

In the mid-1960s, Nahmias and Dowdle [9] demonstrated two antigenic types of HSV. Viral typing allowed the demonstration that HSV-1 was virtually uniformly responsible for herpes encephalitis in older children and adults. In contrast, infection of the newborn brain is attributable to HSV-1 or HSV-2 but more frequently the latter.

3 Pathology and Pathogenesis

Recent detailed reviews highlight the importance of these organisms as models of viral replication and as pathogens for human infection [10–13].

3.1 Pathology of CNS Disease

HSE results in acute inflammation, congestion, and/or hemorrhage, most prominently in the temporal lobes and usually asymmetrically in adults [14] and more diffusely in the newborn. Adjacent limbic areas show involvement as well. The meninges overlying the temporal lobes may appear clouded or congested. After approximately 2 weeks, these changes proceed to frank necrosis and liquefaction.

Microscopically, involvement extends beyond areas that appear grossly abnormal. At the earliest stage, the histologic changes are not dramatic and may be nonspecific. Congestion of capillaries and other small vessels in the cortex and subcortical white matter is evident; other changes include the development of petechiae. Vascular changes that have been reported in the area of infection include areas of hemorrhagic necrosis and perivascular cuffing. The perivascular cuffing becomes prominent in the second and third weeks of infection. Glial nodules are common after the second week [15, 16]. The microscopic appearance becomes dominated by evidence of necrosis and inflammation; the latter is characterized by a diffuse perivascular subarachnoid mononuclear cell infiltrate, gliosis, and satellitosis neuronophagia [14, 17]. In such cases, widespread areas of hemorrhagic necrosis, mirroring the area of infection, become most prominent. Oligodendrocytic involvement and gliosis (as well as astrocytosis) are common, but these changes develop very late in the disease. Although found in only approximately 50 % of patients, the presence of intranuclear inclusions supports the diagnosis of viral infection, and these inclusions are most often visible in the first week of infection. Intranuclear inclusions (Cowdry type A inclusions) are characterized by an eosinophilic homogeneous appearance and are often surrounded by a clear, unstained zone beyond which lies a rim of marginated chromatin.

3.2 General Observations on the Pathogenesis of Human Disease

The pathogenesis of human disease depends on intimate, personal contact of a susceptible individual (namely, one who is seronegative) with someone excreting HSV. Virus must come in contact with mucosal surfaces or abraded skin for infection to occur. With viral replication at the site of infection, the capsid is transported by neurons to the dorsal root ganglia, where after another round of viral replication, latency is established. Transport of the virion is by retrograde axonal flow [18]. In some instances, replication can lead to severe CNS infection; however, more often a host–virus interaction results in latency. After latency is established, reactivation

can occur, with virus shedding at mucocutaneous sites appearing as skin vesicles or mucosal ulcers or being completely asymptomatic. Occasionally, primary infection can become systemic, affecting other organ systems besides the CNS and the peripheral nervous system. Such circumstances include disseminated neonatal HSV infection with multiorgan involvement, multiorgan disease of pregnancy, and infrequently dissemination in patients undergoing immunosuppressive therapy. Multiorgan disease is likely the consequence of viremia in a host not capable of limiting replication to mucosal surfaces.

3.3 Pathogenesis of Latency

All of the herpesviruses have the ability to become latent, persist in an apparent inactive state for varying durations, and be reactivated by a provocative stimulus, as yet unidentified [11, 19–24]. As a biologic phenomenon, latency has been recognized since the beginning of the twentieth century [19, 21–23, 25–31]. In 1905, Cushing [32] noted that patients treated for trigeminal neuralgia (by sectioning a branch of the trigeminal nerve) developed HSV lesions along the innervated areas of the sectioned branch, as suggested previously by Goodpasture [33]. Several investigators have demonstrated that microvascular surgery of the trigeminal nerve tract for tic douloureux resulted in recurrent herpetic lesions in more than 90 % of seropositive individuals [34–37]. Axonal injury and attempts at excision of lesions have been associated with recurrences [38, 39]. Reactivation of latent virus appears to depend on an intact anterior nerve route and peripheral nerve pathways [40].

Recurrences occur despite both cell-mediated and humoral immune responses and can be either symptomatic or asymptomatic. Recurrences are spontaneous, but there have been associations with physical or emotional stress, fever, exposure to ultraviolet light, tissue damage, and immune suppression [23, 30, 41, 42]. Viral DNA can be detected in neuronal tissue in the absence of cutaneous lesions [22, 27, 43–48]. Latent virus has been retrieved from the trigeminal, sacral, and vagal ganglia of humans [19, 25, 26, 44, 48].

3.4 Pathogenesis of Encephalitis

The pathogenesis of HSE in older children (older than 3 months) and adults is only partly understood. Both primary and recurrent HSV infections can cause disease of the CNS. From studies performed by the National Institute of Allergy and Infectious Diseases (NIAID) Collaborative Antiviral Study Group (CASG), approximately one-third of the cases of HSE are the consequence of primary infection. For the most part, the patients with primary infection are younger than 18 years. The remaining two-thirds of cases occur in the presence of preexisting antibodies, but

only approximately 10 % of patients have a history of recurrent herpes labialis. Patients with preexisting antibodies are considered to have HSE as a consequence of reactivation of HSV [49]. When the DNA from the peripheral nervous system (labial) and CNS isolates are compared by restriction endonuclease analysis, the isolates are usually identical; however, this is not always the case. The virus isolated from the peripheral site can be different from that retrieved from the CNS [50]. Thus, the issues of reactivation of virus directly within the CNS, the potential for enhanced neurotropism of certain viruses, and the selective reactivation and access of one virus by the trigeminal route or other routes to the CNS remain for further elucidation.

The route of access of virus to the CNS in primary infection is a subject of debate, especially in humans. Studies performed more than five decades ago defined pathways for HSV access to the brain in animals, including both the olfactory and trigeminal nerves among others [51]. However, which of these nerve tracts uniformly leads to HSV infection in the CNS of humans is not clear. The anatomic distribution of nerves from the olfactory tract into the limbic system, along with the recovery of virus from the temporal lobe (the site of apparent onset of HSE in the human brain), suggests that viral access to the CNS via this route is a tenable hypothesis. Reports in the literature have found electron microscopic evidence that suggests this has been the case in some individuals with HSE [52–55]. Animal model data support the contention that the olfactory tract provides one neurologic avenue for viral access to the CNS and causes localization of the infection in brain regions analogous to medial temporal structures in humans [56, 57]. Definitive proof of such progression in humans is lacking.

Reactivation of HSV, leading to focal HSE, is a similarly confusing problem from the standpoint of pathogenesis. Evidence of latent virus within infected brain tissue exists [58]; however, virus reactivation at that site remains purely hypothetical. Reactivation of virus peripherally (namely, in the olfactory bulb or the trigeminal ganglion) with subsequent neuronal transmission to the CNS has been suggested [51, 57, 59, 60]. Nevertheless, a relevant observation is that with recurrent herpes labialis, whereby reactivation of virus from the trigeminal ganglia occurs, HSE is a very uncommon event. Furthermore, HSE does not occur more frequently in immunocompromised patients. In addition, individuals who are seropositive for HSV and have brain tissue examined for the detection of HSV DNA by PCR will have detectable DNA in multiple areas of the brain and not just localized to the temporal lobe [25].

Host immunity plays an important, but undefined, role in the pathogenesis of HSE. Possibly, the CNS is particularly prone to HSV infection because intraneuronal spread may shelter virus from host defense mechanisms. HSE is no more common in the immunosuppressed host than in the normal host; however, when it does occur, the presentation is atypical, with a subacute but progressively deteriorating course [61].

More recently, a host genetic deficiency has been found to play a role in recurrent HSE but certainly does not exist in all patients [62].

4 Epidemiology

4.1 Herpes Simplex Virus, Type 1

The epidemiology of HSV infections is multifaceted. Because the focus of this book is CNS inflammation and infection, only a brief review of non-CNS HSV infections follows. The reader is referred to more complete reviews [13, 63–65]. HSV infections are distributed worldwide and have been reported in both developed and developing countries, including remote Brazilian tribes [66]. Animal vectors for human HSV infections have not been described; therefore, humans remain the sole reservoir for transmission of these viruses to other humans during close personal contact. There is no seasonal variation in the incidence of infection. Because infection is rarely fatal, and because these viruses become latent, more than two-thirds of the world's population can have recurrent HSV infections and can transmit HSV during episodes of reactivation. HSV disease ranges from totally asymptomatic in most patients to sporadic, severe, and life-threatening disease in a few infants, children, and adults. With clinical illness, oropharyngeal disease, namely gingivostomatitis, usually is the manifestation. The identification of primary gingivostomatitis that was proven to be caused by HSV infection [67, 68] led to the definition of the natural history of infection, including the appearance of neutralizing antibodies [69], absence of virus shedding in children younger than 6 months [70], and a higher rate of occurrence among individuals of lower socioeconomic status. Contemporary surveys document the viral shedding data, ranging from 2 to 5 % [71–78].

Antibody surveys have helped clarify the epidemiology of HSV infection. Geographic location, socioeconomic status, and age all influence the acquisition of HSV infection [67, 79–82]. In developing countries, seroconversion occurs early in life. In Brazilian Indians, HSV antibodies are detectable in more than 95 % of children by the age of 15 years [83]. Similarly, serologic studies performed in New Orleans demonstrated acquisition of antibodies in more than 90 % of children by the age of 15 years [84]. In developing countries, such as Uruguay, or in lower socioeconomic populations in the central United States, the appearance of antibodies occurred at similar but lower frequencies [84–87]. By 5 years of age, approximately one-third of patients had seroconverted; this frequency increased to 70 to 80 % by early adolescence.

Middle-class individuals of industrialized societies acquired infection later in life. Seroconversion occurred during the first 5 years of life in 20 % of children; there was no significant increase until the second and third decades of life, at which time the prevalence of antibodies increased to 40 and 60 %, respectively [88, 89]. One study of university students demonstrated that seroconversion of susceptible individuals occurred at an annual frequency of approximately 5 to 10 % [90–92]. In summary, primary infection occurs very early in children of underdeveloped countries and in those of lower socioeconomic classes; however, in developed countries and more affluent classes, primary infection is delayed until adolescence or, perhaps, even adulthood. The frequency of direct person-to-person contact is the major mediator of acquisition of infection.

4.2 Herpes Simplex Virus, Type 2

Because HSV-2 infections are usually acquired through sexual contact, antibodies to this virus are rarely found before the age at onset of sexual activity. Although most genital HSV infections are caused by HSV-2, an ever-increasing proportion is attributable to HSV-1, now as high as 50 % of all new primary infections [93–97]. Approximately 1.5 million new cases of HSV-2 occur annually in the United States [98]. Genital HSV infections are not reportable in the United States [99]. Current estimates of infected individuals with genital herpes in the United States range from 40 to 60 million [99–101].

Women have the highest rates of infection, particularly prostitutes and others with multiple sex partners, including those with HIV infection. The incidence of genital HSV infections in both indigent women and those of middle and upper socioeconomic classes is significantly lower than the incidence found among women attending sexually transmitted disease clinics [102]. As with HSV-1 infections of the mouth, HSV-2 can be excreted in the absence of symptoms at the time of primary, initial, or recurrent infection [103, 104]. The actual frequency of asymptomatic excretion of HSV-2 in women by culture is approximately 3 to 5 % of all days, and by polymerase chain reaction (PCR) 15 to 20 %. Furthermore, some individuals can start and stop shedding multiple times during the same day [105]. Its occurrence creates a silent reservoir for transmission of infection [105, 106]. The appearance of HSV-2 antibodies reflects the time of exposure or more simply the acquisition of infection and is positively correlated with the onset of sexual activity [86, 87, 107]. However, crowded living conditions may indirectly contribute to antibody prevalence [108, 109]. If HSV-2 type-specific antibodies are sought in healthy women, there is a wide discrepancy in prevalence, ranging from averages of 10 % in England and Italy to 25 % in the United States and 77 % in Uganda [110, 111]. Up to 50 to 60 % of lower socioeconomic populations in the United States and elsewhere develop antibodies to HSV-2 by adulthood [11]. The reader is referred to a review for worldwide seroprevalence of HSV-2 [112]. Seroprevalence is a function of age, number of sexual partners, race, and marital status [113–115].

4.3 Latent Genital Herpes Simplex Virus Infections

Latent genital infection with subsequent reactivation is the largest reservoir for transmission of HSV-2. As with HSV-1 infection, recurrent HSV-2 infection can be either symptomatic or asymptomatic; however, recurrence is usually associated with a shorter duration of viral shedding and fewer lesions [93]. Several studies have implicated a frequency of recurrence as high as 60 % [107, 116]. The type of genital infection, HSV-1 versus HSV-2, is predictive of the frequency of recurrence [116–118], with HSV-1 infection recurring less frequently than HSV-2 [119, 120].

5 Herpes Simplex Encephalitis

5.1 Background

HSV infections of the CNS are among the most severe of all viral infections of the human brain. Currently, HSE is estimated to occur in approximately 1 per 250,000–500,000 individuals per year. At the University of Alabama at Birmingham, the diagnosis of HSE was proven by brain biopsy in an average of ten patients per year, for an incidence of approximately 1 in 300,000 individuals, an incidence similar to those in Sweden and England [121, 122]. With the advent of PCR for diagnostic purposes, HSE accounts for 10 to 20 % of viral infections of the CNS [123].

The economic cost of HSE is considerable, as estimated in 1983 for hospitalization alone of adults to be more than $25 million [124, 125]. The total medical cost is considerably higher because of the long-term care and support services required for many of the survivors.

HSE occurs throughout the year and in patients of all ages, with approximately one-third of cases occurring in patients younger than 20 years but older than 6 months and approximately one-half in patients older than 50 years [126]. Whites account for 95 % of patients with biopsy-proven disease. Both sexes are affected equally.

The severity of disease is best determined by the outcome of patients who have received either no therapy or an ineffective antiviral medication, such as idoxuridine or cytosine arabinoside. In such situations, mortality is in excess of 70 %; only approximately 2.5 % of all patients with confirmed disease (9.1 % of survivors) returned to normal function after recovery from their illness [127–131]. Because brain biopsy with isolation of HSV from brain tissue was the method of diagnosis in these early studies, a far broader spectrum of HSV infections of the CNS actually was thought to exist. However, with the more recent use of PCR for diagnosis of HSE, virtually all patients have a focal neurologic disease, suggesting a limited spectrum of disease [132].

5.2 Diagnosis

Several aspects relating to the diagnosis of HSE merit discussion: (a) the clinical presentation in regard to the sensitivity and specificity of various clinical characteristics, (b) the historical use of brain biopsy to establish the diagnosis, (c) conditions that mimic HSE, and (d) noninvasive means of diagnosis. Data from the NIAID CASG compare presentation and outcome for brain biopsy-positive and brain biopsy-negative patients [126].

Most patients with biopsy-proven HSE presented with a focal encephalopathic process, including (a) altered mentation and decreasing levels of consciousness with focal neurologic findings, (b) CSF pleocytosis and proteinosis, (c) the absence of bacterial and fungal pathogens in the CSF, and (d) focal electroencephalographic

(EEG), computed tomographic (CT), and/or magnetic resonance image (MRI) findings [126]. The frequency of headache and CSF pleocytosis is higher in patients with proven HSE than in patients with diseases that mimic HSE. Nearly uniformly, patients with HSE present with fever and personality change. Seizures, whether focal or generalized, occur in only approximately two-thirds of all patients with proven disease. Thus, the clinical findings of HSE are nonspecific and do not allow for empirical diagnosis of disease predicated solely on clinical presentation. Although clinical evidence of a localized temporal lobe lesion is often thought to indicate HSE, various other diseases can mimic this condition.

Examination of the CSF is indicated in patients with fever and altered mentation, provided it is not contraindicated because of increased intracranial pressure. In patients with HSE, CSF findings are nondiagnostic, being similar in patients with confirmed disease or diseases that mimic HSE. Both the CSF white blood cell (WBC) count (lymphocyte predominance) and the CSF protein level are elevated. The average CSF WBC count is 100 cells/μL; the protein averages approximately 100 mg/dL. Sequential evaluation of CSF specimens from patients with HSE indicates increasing cell counts and levels of protein. The presence of CSF red blood cells is not diagnostic for HSE and indeed is absent in 30 % of cases. Approximately 5 to 10 % of patients have a normal CSF formula on first evaluation.

Noninvasive neurodiagnostic studies support a presumptive diagnosis of HSE. These studies have included EEG, CT, and MRI. Focal changes of the EEG are characterized by spike and slow-wave activity and periodic lateralized epileptiform discharges, which arise from the temporal lobe [133–136]. Early in the disease, the abnormal electric activity usually involves one temporal lobe and then spreads to the contralateral temporal lobe as the disease evolves, usually over 7–10 days. The sensitivity of the EEG is approximately 84 %, but the specificity is only 32.5 %. CT scans initially show low-density areas with mass effect localized to the temporal lobe, which can progress to radiolucent and/or hemorrhagic lesions [137, 138]. Bitemporal disease is common in the absence of therapy, particularly late in the disease course. When these neurodiagnostic tests are used in combination, the sensitivity is enhanced; however, the specificity remains inadequate. None of these neurodiagnostic tests is uniformly satisfactory for diagnosing HSE. MRI detects evidence of HSE earlier than CT scan [139].

PCR detection of HSV DNA in the CSF has become the diagnostic procedure of choice. Brain biopsy is of value in confusing clinical presentations not been substantiated by follow-up studies of patients in the NIAID CASG.

5.3 Serologic Evaluation

Several strategies using antibody production as a means of diagnosing HSE have been utilized [71]. Because most encephalitic patients are HSV seropositive at presentation, seroconversion per se is usually not helpful because fever alone can reactivate labial herpes, resulting in antibody elevations. A fourfold rise in serum antibody was neither sensitive nor specific enough to be useful. A fourfold or greater

rise in CSF antibody occurred significantly more often within a month after onset of disease in patients with biopsy-proven HSE: 85 % versus 29 %. By 10 days after clinical presentation, however, only 50 % of brain biopsy-positive patients had a fourfold rise in CSF antibody. This test is useful only for retrospective diagnosis. The use of a ratio of serum to CSF antibody of 20 or less did not improve sensitivity during the first 10 days of disease.

5.4 PCR Detection of Viral DNA

PCR detection of HSV DNA in the CSF is the diagnostic method of choice [140–147]. Data from the NIAID CASG defined the sensitivity and specificity as 94 and 98 %, respectively. These CSF specimens were obtained from patients with biopsy-proven or biopsy-negative disease. Notably, the specificity would have been higher except that some tissue specimens were fixed in formalin, which killed infectious virus. HSV DNA persisted in 80 % of tested CSF specimens for 1 week or more.

5.5 Diseases That Mimic Herpes Simplex Encephalitis

In a compilation of the NIAID CASG data, 193 (45 %) of 432 patients undergoing brain biopsy for a focal encephalopathic process had HSE [148]. The remaining patients were evaluated for diseases that mimic HSE [148]. Thirty-eight had disease amenable to other forms of therapy, including brain abscess, tuberculosis, cryptococcal infection, and brain tumor. An additional 19 patients had diseases that were indirectly treatable, and another 38 patients had an alternative diagnosis established for which there was no current therapy, usually other viral infections. Thus, those diseases that mimic HSV infection of the CNS and that require immediate medical intervention should be considered if the PCR is negative for HSV DNA.

5.6 Therapy

The first antiviral drug reported as efficacious therapy of HSE was idoxuridine; however, it was soon proven both ineffective and toxic [127]. Subsequent therapeutic trials defined vidarabine as a useful medication for the management of biopsy-proven HSE [130, 131]; however, it has been replaced by acyclovir in the physician's armamentarium. During these studies, the variables of age, disease duration, and level of consciousness at the onset of therapy were proven major determinants of clinical outcome. Patients younger than 30 years and with a more normal level of consciousness (lethargic as opposed to comatose) were more likely to return to normal function than older patients, especially those who were semicomatose or

comatose. From these data, older patients (older than 30 years), whether comatose or semicomatose, had mortality rates that approached 70 %, a figure very similar to that encountered in the placebo recipients of the previously cited studies. If therapy is to be effective, it must be instituted before the onset of hemorrhagic necrosis of a dominant temporal lobe and significant deterioration of consciousness.

Acyclovir is superior to vidarabine for the treatment of HSE [149]. The NIAID CASG study defined a mortality of 55 % at 6 and 18 months after the initiation of treatment for vidarabine recipients versus 19 and 28 %, respectively, for the acyclovir group. Late deaths were not a consequence of either persistent or reactivated HSV infection but occurred in patients who were severely impaired as a consequence of their disease. Acyclovir decreases mortality to 19 % 6 months after therapy. Importantly, 38 % of patients, irrespective of age, return to normal function.

Previous studies indicated that age and level of consciousness influenced long-term outcome. A more objective reflection of level of consciousness is the Glasgow Coma Scale (GCS). Scores that approached normal predicted enhanced survival. When GCS score and age were assessed simultaneously, a GCS score of 6 or less predicted a poor therapeutic outcome, irrespective of the agent administered or of the age of the patient [149].

Regarding morbidity for acyclovir recipients, 38 % of patients returned to normal or with minor impairment, 9 % of patients had moderate sequelae, and 53 % of patients were left with severe impairment or died. Relapse of HSE has been reported, though not well documented, in a few patients following the administration of vidarabine [150–152] and acyclovir [152, 153]. Many patients were not afebrile at the conclusion of treatment, suggesting that a longer duration of therapy to a minimum of 14–21 days may be desirable.

Of acyclovir recipients, 10 % experienced an increased BUN level, and 6 % developed a creatinine level in excess of 2 mg/dL. No clinical evidence of toxicity was detected. The current therapy of choice for the management of HSE is acyclovir. This drug is administered at a dosage of 10 mg/kg every 8 h (30 mg/kg per day) for 14–21 days.

6 Neonatal Herpes Simplex Virus Infections

6.1 History

In 1941, Smith, Lennette, and Reames [6] reported the first case of HSV infection of the CNS, as noted earlier. This case occurred in a newborn with neonatal HSE. In 1952, Zuelzer, Wolf, and Stulbery [154] reviewed eight cases of disseminated HSV infection in neonates with involvement of most organs, including the brain in many instances. This report was followed shortly by others indicating the association between HSV infection of the newborn and necrotizing encephalitis, including the isolation of HSV in cell cultures from brain tissue.

6.2 Pathology and Pathogenesis

6.2.1 Pathology

Although the pathology of HSE is discussed earlier in this chapter, a few characteristics appear more commonly in the newborn. Gross examination of the brain often reveals encephalomalacia and hydranencephaly, which are the consequence of extensive hemorrhagic necrosis. Porencephaly, hydranencephaly, and multicystic lesions are often sequelae in neonates who survive for several weeks or months following neonatal HSV infection of the brain. The microscopic appearance of the brain is characterized by a mononuclear inflammation, necrosis, and hemorrhage.

6.2.2 Pathogenesis

In utero disease is likely a consequence of transplacental infection and usually involves skin, brain, eye, liver, and adrenals. More commonly, the fetus comes in contact with infected maternal genital secretions at the time of delivery. Viral replication in the newborn either remains limited to the portal of entry—namely, the skin, eye, or mouth—or progresses to involve various other organs, including the brain (resulting in encephalitis), causing life-threatening disease. Host mechanisms responsible for control of viral replication at the site of entry are unknown. For babies with encephalitis, intraneuronal transmission of virus provides a privileged site that may be impervious to circulating humoral and cell-mediated defense mechanisms. Thus, transplacental maternal antibodies may be of less value in the prevention of encephalitic forms of neonatal HSV infections. Disseminated infection is a consequence of viremia or secondary to extensive cell-to-cell spread, as occurs with pneumonitis after aspiration of infected secretions.

Neonatal HSE illustrates the two major pathogenic routes for virus access to the brain, namely, hematogenous and intraneuronal. For example, hematogenous spread of virus usually occurs with disseminated disease, and diffuse involvement of the brain ensues in 60 to 80 % of patients. In contrast, neuronal transmission probably results in the focal CNS disease encountered in babies with encephalitis only when no distal organ involvement is documented [155].

6.3 Times of Transmission of Infection

Neonatal HSV infection is acquired at one of three times: in utero, intrapartum, or postnatally. Regardless of the time or route of acquisition, the newborn is at risk of CNS disease. Certainly, the mother is the most common source of infection for the first two of these routes of transmission of infection to the newborn.

6.3.1 Intrauterine Infection

In utero acquisition of HSV infection is becoming increasingly documented [156–159]. Manifestations of disease acquired in utero include chorioretinitis, cutaneous aplasia, hydranencephaly, and encephalomalacia [160]. Risk factors associated with intrauterine transmission of infection are unknown; however, both primary and recurrent maternal infection can result in infection of the fetus in utero. In utero infection is the consequence of either transplacental or ascending infection.

6.3.2 Intrapartum Infection

The most common time of transmission of infection from mother to the fetus is intrapartum. Transmission occurs when the infant comes in contact with infected maternal genital secretions at delivery, accounting for 80 % of cases [161].

Prospective assessment of HSV excretion in the genital tract at delivery indicates that shedding can occur in 0.5–1.3 % of women [162]. Factors that influence intrapartum acquisition of infection by the fetus include: (a) type of maternal infection (primary vs. recurrent) [93, 163], (b) maternal antibody status [164–166], (c) duration of ruptured membranes [164], and (d) placement of a fetal scalp monitor in a woman excreting HSV [167, 168].

Primary infection is associated with (a) larger quantities of HSV replicating in the genital tract ($>10^6$ viral particles/0.2 mL of tissue culture inoculum) and (b) a period of viral excretion that on average persists for 3 weeks. In contrast, in women with recurrent genital infection, HSV is shed for an average of only 2–5 days and at lower concentrations (approximately 10^3/0.2 mL of tissue culture inoculum). Because of the larger quantity of virus and the longer period of viral excretion, primary maternal infection is associated with a higher rate of transmission to the fetus—estimated between 30 and 50 % [93, 163, 169]. Reflecting the type of maternal infection, the delivery of transplacental maternal antibody to the fetus influences both the severity of disease in the newborn and the likelihood of fetal infection [164–166, 170]. Lastly, placement of a fetal scalp monitor in women excreting virus has been shown to lead to fetal infection. Monitor placement should be discouraged in women with a history of genital herpes or visualized lesions.

The duration of ruptured membranes is reported to be an important indicator of risk for acquisition of neonatal infection. Recent data suggest that cesarean section decreases the incidence of infection in women with lesions present at delivery [169].

6.3.3 Postnatal Infection

The third route of transmission is postnatal acquisition [171–178]. Documented sources include the mother (including the breast as a source of virus [171–173]), the father (labial lesions) [174, 175], nosocomial transmission (nursery personnel or other babies) [176–178], and as a consequence of the Jewish tradition of circumcision, known as mitzba ba pa (sp, CDC).

6.4 Incidence and Presentation of Neonatal Infection

The incidence of neonatal HSV infection is about 1 in 3,000 (0.03 %) deliveries [155]. Overall, two-thirds of children with neonatal HSV infection develop disease of the CNS, and the disease may remain localized to the brain or become disseminated to involve various other organs. If untreated, newborns with disseminated disease have a mortality of 80 %, and newborns with disease limited to the CNS have a mortality of approximately 50 %.

Classification of newborns with HSV infection is mandatory for prognostic and therapeutic considerations [164, 179]. Babies with congenital infection, by definition, must be identified within 48 h of birth. Those babies who are infected (either during delivery or postnatally) are divided into three categories: (a) those with disease localized to the skin, eye, or mouth; (b) those having encephalitis with or without skin, eye, and/or mouth involvement; and (c) those having disseminated disease involving multiple organs, such as CNS, lung, liver, adrenals, skin, eye, and/or mouth. This chapter focuses on CNS disease and considers prospectively acquired data obtained through the NIAID CASG. All babies, irrespective of disease classification, should be considered at risk for CNS complications of infection. The presentation and outcome of infection (particularly prognosis after therapy) according to category vary significantly with regard to both mortality and morbidity.

6.5 Intrauterine Infection

Intrauterine infection is usually apparent at birth and is characterized by a triad of findings: (a) skin vesicles and/or scarring (cuteus aplasia), (b) eye disease (chorioretinitis, optic atrophy), and (c) brain disease (microcephaly, encephalomalacia, or hydranencephaly). Retinitis alone can be a presenting sign and should alert the pediatrician to the possibility of intrauterine HSV infection, although HSV infection is a less common cause of chorioretinitis relative to other congenital infections. The frequency of occurrence of intrauterine HSV infection has been estimated to range between 1 in 100,000 (0.001 %) and 1 in 200,000 (0.0005 %) deliveries [156].

6.6 Disseminated Infection

Disseminated HSV infection has the worst prognosis with regard to mortality. Children with disseminated infection usually present to tertiary medical centers for therapy between 9 and 11 days of life; however, signs of infection are, on average, usually present 4–5 days earlier.

The principal organs involved following disseminated infection are the liver, brain, and adrenals; however, infection can involve various other organs, including the larynx, trachea, lungs, esophagus, stomach, lower gastrointestinal tract, spleen, kidneys, pancreas, and heart. Constitutional signs and symptoms include irritability,

seizures, respiratory distress, jaundice, bleeding diatheses, and shock, in addition to a characteristic vesicular exanthem that is often considered pathognomonic for neonatal HSV infection.

The vesicular rash, as described later in this chapter, is particularly important in the diagnosis of HSV infection. Notably, about 20 % of children with disseminated neonatal HSV infection will not develop skin vesicles during the course of their illness [161, 164, 180]. In the absence of skin vesicles, the diagnosis becomes exceedingly difficult because the clinical signs are often vague and nonspecific, mimicking those of neonatal sepsis. Mortality in the absence of therapy exceeds 80 %; if therapy is instituted before CNS disease ensues, outcome is usually good. The most common cause of death in babies with disseminated disease is either HSV pneumonitis or disseminated intravascular coagulopathy.

Evaluation of the extent of disease is imperative, as with all cases of neonatal HSV infection. The clinical laboratory should be used to define hepatic enzyme elevation (serum alanine aminotransferase and AST), direct hyperbilirubinemia, neutropenia, thrombocytopenia, and bleeding diatheses. Unless contraindicated, examination of the CSF is imperative. In addition, chest roentgenograms, abdominal X-rays, EEG, and CT or MRI of the head can be judiciously and serially employed to determine the extent of disease. The radiographic picture of HSV lung disease is characterized by a diffuse interstitial pattern that progresses to a hemorrhagic pneumonitis. Pneumatosis intestinalis can be detected when gastrointestinal disease is present. Encephalitis is a common component of disseminated infection, occurring in about 75 % of these newborns. Serial evaluation of the CSF and noninvasive neurodiagnostic tests, as defined later in this chapter, will help assess the extent of brain disease.

6.7 Encephalitis

Infection of the CNS alone or in combination with disseminated disease presents with findings indicative of encephalitis. Overall, nearly 90 % of babies with brain infection caused by HSV have evidence of an acute neurologic syndrome. Brain infection can occur in one of two fashions: either as a component of multiorgan disseminated infection or as encephalitis only, with or without skin, eye, and mouth involvement. Nearly one-third of all babies with neonatal HSV infection have only the encephalitic component of disease.

Clinical manifestations of these two types of encephalitis include seizures (both focal and generalized), lethargy, irritability, tremors, poor feeding, temperature instability, bulging fontanel, and pyramidal tract signs. Whereas babies with disseminated infection often have skin vesicles in association with brain infection, the same is not true for babies with encephalitis alone. In this latter group, only approximately 60 % have skin vesicles at any time during the disease course [161, 164, 180–182]. Cultures of CSF yield virus in 25–40 % of all patients. Anticipated findings on CSF examination include pleocytosis and proteinosis (as high as 500–1,000 mg/dL). Although a few babies with CNS infection, demonstrated by brain biopsy, have been reported to have no abnormalities of their CSF, certainly this is very uncommon.

Serial CSF examinations provide a useful diagnostic approach because the infected newborn with brain disease demonstrates progressive increases in its protein content. The importance of CSF examinations in all infants is underscored by the finding that even subtle changes have been associated with significant developmental abnormalities [183]. An EEG, CT, or MRI can be very useful in defining the presence of CNS abnormalities. Death occurs in 50 % of babies with localized CNS disease who are not treated, and it is usually related to involvement of the brainstem. In the absence of antiviral therapy, with rare exceptions, survivors are left with neurologic impairment, and the long-term prognosis after either disseminated infection or encephalitis alone is particularly poor. Up to 50 % of surviving children have some degree of psychomotor retardation, often in association with microcephaly, hydranencephaly, porencephalic cysts, spasticity, blindness, chorioretinitis, or learning disabilities. Whether visceral or CNS damage can be progressive after initial clearance of the viral infection is unclear, but it is a possibility suggested by long-term assessment of children with skin, eye, or mouth disease [161, 164, 184] and more recently by a study of a group of babies with more severe disease [185].

Several points warrant reiteration. Clinical manifestations of disease in children with encephalitis alone are virtually identical to those findings that occur with brain infection in disseminated cases, in spite of the presumed differences in pathogenesis. For babies with encephalitis only, approximately 60 % develop evidence of a vesicular rash characteristic of HSV infection. Thus, a newborn with pleocytosis and proteinosis of the CSF but without a rash can easily be misdiagnosed as having bacterial or other viral infection unless HSV infection is carefully considered. In such circumstances, a history of genital lesions in the mother or her sexual partner may be very important in the incrimination of HSV as a cause of illness.

6.8 Skin, Eye, and/or Mouth Infection

Infection localized to the skin, eye, and/or mouth is associated with virtually no mortality. When infection is localized to the skin, the presence of discrete vesicles remains the hallmark of disease. Clusters of vesicles often appear initially upon the presenting part of the body that was in direct contact with the virus during birth. With time, the rash can progress to involve other areas of the body as well. Vesicles occur in 80 % of children with skin, eye, or mouth infection. Children with disease localized to the skin, eye, or mouth generally present at about 10 to 11 days of life. Those babies with skin lesions invariably suffer from recurrences whether therapy is administered or not. Although death is not associated with disease localized to the skin, eye, and/or mouth, approximately 30 % of these children eventually develop evidence of neurologic impairment in the absence of antiviral therapy, which can result in significant neurologic morbidity [160, 161, 184].

Infections involving the eye may manifest as keratoconjunctivitis or later chorioretinitis. The eye can be the only site of HSV involvement in the newborn [160]. Findings include keratoconjunctivitis, microphthalmia, or retinal dysplasia. In the presence of persistent disease and no therapy, chorioretinitis can result. Chorioretinitis

can be caused by either HSV-1 or HSV-2 [186–188]. Keratoconjunctivitis, even in the presence of therapy, can progress to chorioretinitis, cataracts, and retinal detachment. Cataracts have been detected on long-term follow-up of proven perinatally acquired HSV infections [189].

Long-term neurologic impairment has been encountered in children whose disease appeared localized to the skin, eye, and/or mouth. The significant findings include spastic quadriplegia, microcephaly, and blindness. Despite normal clinical and CSF examinations at the time these children completed antiviral therapy, neurologic impairment became apparent between 6 months and 1 year of life. In retrospect, when CSF from these babies was subjected to PCR analysis, evidence of HSV DNA was detected in virtually all of these children, indicating an asymptomatic infection of the CNS [190].

6.9 Diagnosis

The appropriate use of laboratory tools is essential if a diagnosis of HSV infection is to be achieved [191]. Virus isolation remains one of two definitive diagnostic methods. If skin lesions are present, a scraping of skin vesicles should be made and transferred (in appropriate virus transport media) to a diagnostic virology laboratory. Typing of an HSV isolate must be done for prognostic purposes.

Cytologic examination of cells from the maternal cervix or from the infant's skin, mouth, conjunctivae, or corneal lesions has a sensitivity of only approximately 60–70 % and, therefore, should not be the sole diagnostic determinant for infection in the newborn [11, 192]. Cellular material obtained by scraping the periphery of the base of lesions should be smeared on a glass slide and promptly fixed in cold ethanol. The slide can be stained according to the methods of Papanicolaou, Giemsa, or Wright before examination by a trained cytologist. Deployment of Giemsa or, alternatively, Tzanck smears likely will not demonstrate the presence of intranuclear inclusions. Intranuclear inclusions and multinucleated giant cells are indicative, but not diagnostic, of HSV infection. The use of HSV monoclonal antibodies for rapid diagnosis has gained widespread acceptance. These fluorescence studies should be performed by laboratories experienced in the procedure.

Serologic diagnosis of HSV infection is not of great clinical value. Therapeutic decisions cannot await the results of serologic studies. The inability to differentiate transplacentally acquired maternal immunoglobulin G from endogenously produced antibodies makes the assessment of the neonate's antibody status both difficult and of little value during acute infection. Commercially available serologic tests are now capable of distinguishing HSV-1 from HSV-2 antibodies. These assays are based on differences in glycoprotein gG1 and gG2 [193]. These are the only antibody assays that should be used. Serial antibody assessments may be useful if a mother without a history of HSV infection has a primary infection late in gestation and, therefore, transfers little or no antibody to the fetus.

The use of CT and MRI scans to define CNS disease is essential, even in the child who appears normal.

6.10 PCR Detection of Viral DNA

The other definitive diagnostic method is PCR detection of viral DNA, as discussed earlier in this chapter [140, 194, 195].

6.11 Treatment

6.11.1 Background

Of all the perinatally acquired infections, the one most likely to be amenable to successful therapy is that caused by HSV. Of children presenting with disease localized to the skin, eye, and/or mouth, approximately 70 % will progress to involve the CNS or result in disseminated infection [181]. When such events occur, the likelihood of an adequate outcome, even with efficacious drugs, is not optimal because many of these children will either die or be left with significant neurologic impairment. The following paragraphs summarize our knowledge of therapy [184, 196–199].

First, the overall mortality rate for babies with encephalitis or disseminated infection 1 year after treatment with high doses of acyclovir (20 mg/kg every 8 h for 21 days) is lower than that of prior studies of neonatal HSV infection that used lower doses [200]. There are no differences in either adverse effects or laboratory toxicity.

Second, irrespective of the therapeutic modality employed, there has been a significant increase in the number of babies who returned to normal function. This can be accounted for largely by the introduction of therapy before the development of encephalitis or disseminated disease [200]. Of the babies entered in a controlled trial comparing vidarabine with acyclovir in neonatal herpes simplex virus infection (Whitley, et al.), more than 48 % have disease localized to the skin, eye, and mouth [200]. This represents a threefold increase in the number of babies with skin, eye, and mouth involvement, when compared with that of previous studies and historic data ($p < .001$). The change in spectrum of disease presentation is most likely related to earlier diagnosis. The number of babies with encephalitis has remained fairly constant at approximately 30 %, whereas the number of babies with disseminated disease has decreased to 22 %. Nevertheless, improved morbidity by disease classification is unchanged for encephalitis.

Third, available data indicate that therapy has not been initiated any earlier in the most recent neonatal HSV studies [201] as compared to earlier studies [200]. However, the mean duration of disease for all children (irrespective of disease classification) entered into these studies was 4–5 days; therapy can, therefore, be instituted even earlier in the disease course. This "window" for earlier administration of therapy is significant if further advances in therapeutic outcome are to be achieved.

The existing database from the NIAID CASG has provided insight into those factors that influence outcome [202]. Those factors that have a major impact on outcome include disease classification, level of consciousness, time of initiation of therapy, virus type, and the virus type and frequency of skin recurrences for babies whose disease is localized to the skin, eye, and mouth. Our understanding of these

data implies that limitation of disease before there has been extensive multiorgan involvement or disease of the CNS is associated with the best prognosis. This information will be useful in developing therapeutic strategies and in counseling parents of children with neonatal HSV infection.

6.11.2 Long-Term Suppressive Therapy with Oral Acyclovir

The use of oral acyclovir therapy for prolonged periods for 6 months has recently been shown to improve neurologic outcome such that over 60 % of children with CNS disease returned to normal function. This finding implies the chronic replication of HSV in the brain [203].

6.11.3 Long-Term Follow-Up

Children with neonatal HSV infection require frequent and detailed long-term follow-up. Children with CNS or disseminated disease are at risk for neurologic impairment. Management of resultant seizure disorders is standard. Even children with skin, eye, and/or mouth disease are at risk for neurologic impairment and must be followed carefully.

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