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Mini-review

Herpes simplex encephalitis: Adolescents and adults

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Dedicated to Prof. Erik De Clercq on the occasion of reaching the status of Emeritus-Professor at the Katholieke Universiteit Leuven in September 2006.

Abstract

Herpes simplex encephalitis (HSE) remains one of the most devastating infections of the central nervous system despite available antiviral therapy. Children and adolescents account for approximately one third of all cases of HSE. Clinical diagnosis is suggested in the encephalopathic, febrile patient with focal neurologic signs. However, these clinical findings are not pathognomonic because numerous other diseases in the central nervous system can mimic HSE. Neurodiagnostic evaluation can provide support for the diagnosis by the demonstration of temporal lobe edema/hemorrhage by magnetic resonance image scan and spike and slow-wave activity on electroencephalogram. In the current era, the diagnostic gold standard is the detection of herpes simplex virus (HSV) DNA in the cerebrospinal fluid by polymerase chain reaction (PCR). Although PCR is an excellent test and preferable to brain biopsy, false negatives can occur early after disease onset. Acyclovir is the treatment of choice and is administered at 10 mg/kg every 8 h for 21 days. Even with early administration of therapy after the disease onset, nearly two thirds of survivors have significant residual neurologic deficits. Current investigative efforts are assessing the prognostic value of quantitative PCR detection of viral DNA at the onset of therapy as well as at the completion of therapy and the contribution of prolonged antiviral therapy to improved neurologic outcome.

Keywords: Herpes simplex encephalitis; Cerebrospinal fluid; Polymerase chain reaction

Contents

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1. Introduction

Since the discussion of herpes simplex encephalitis (HSE) by the Mathewson Commission in 1926 (Mathewson Commission, 1929) and subsequent description of the histopathologic changes (Smith et al., 1941) herpes simplex virus (HSV) infection of the brain has become recognized as the most common cause of sporadic fatal encephalitis in the United States (Meyer et al., 1960). Intranuclear inclusion bodies consistent with HSV infection were demonstrated first in the brain of a neonate with encephalitis by Smith et al. (1941). Virus subsequently was isolated from brain tissue (Smith et al., 1941). The first adult case of HSE providing similar proof of viral disease (i.e. intranuclear inclusions in brain tissue and virus isolation) was described by Zarafonetis et al. (1944). The most striking pathologic findings in this patient's brain were apparent in the left temporal lobe, in which perivascular cuffs of lymphocytes and numerous small hemorrhages were found. This temporal lobe localization subsequently has been determined to be characteristic of HSE in individuals older than 3 months of age.

In the mid-1960s, Nahmias and Dowdle (1968) demonstrated two antigenic types of HSV. Viral typing allowed the demonstration that HSV-1 was responsible primarily for infections "above the belt" (including brain disease in adults), whereas HSV-2 was responsible primarily for infections "below the belt" and brain disease in neonates, although this epidemiologic paradigm has changed significantly in the 21st century as HSV-1 has become an increasingly frequent cause of genital herpes. Notably, recent studies indicate that either virus can infect the mouth or genital tract. However, essential to all observations is that HSE nonetheless is caused by HSV-1 in virtually all patients. Indeed, frank encephalitis attributed to HSV-2 has been reported only in a few cases in the world's literature (Whitley et al., 1982a,b).

2. Pathology and pathogenesis

The pathologic changes induced by replicating HSV include ballooning of infected cells and the appearance of chromatin within the nuclei of cells followed by degeneration of the cellular nuclei. Cells lose intact plasma membranes and form multinucleated giant cells. As host defenses are mounted, an influx of mononuclear cells can be detected in infected tissue. HSE results in acute inflammation, congestion, and/or hemorrhage, most prominently in the temporal lobes and usually asymmetrically in adults (Boos and Esiri, 1986) and more diffusely in the newborn. Adjacent limbic areas also show involvement. The meninges overlying the temporal lobes may appear clouded or congested. After approximately 2 weeks, these changes proceed to frank necrosis and liquefaction of the involved brain tissue.

Microscopically, involvement extends beyond areas that appear grossly abnormal. At the earliest stage, the histologic changes are not dramatic and may be non-specific. Congestion of capillaries and other small vessels in the cortex and subcortical white matter is evident; other changes, including petechiae, also are evident. 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 findings after the second week (Kapur et al., 1994; Boos and Kim, 1984). The microscopic appearance becomes dominated by evidence of necrosis and, eventually, inflammation; the latter is characterized by a diffuse perivascular subarachnoid mononuclear cell infiltrate, gliosis, and satellitosis-neuronophagia (Garcia et al., 1984; Boos and Esiri, 1986). 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 findings, 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 most often are visible in the first week of infection. Intranuclear inclusions (Cowdry type A inclusions) are characterized by an eosinophilic homogeneous appearance and often are surrounded by a clear, unstained zone beyond which lies a rim of marginated chromatin.

2.1. General observations on the pathogenesis of human disease

Fundamental to the development of HSE is the source of virus that causes disease in the central nervous system (CNS). Indeed, access of virus to the brain or, alternatively, reactivation of virus in the temporal lobe are not well-understood phenomena. Although more is known about human disease and its pathogenesis, our understanding is incomplete. The pathogenesis of human disease, particularly primary infections depends on intimate, personal contact of a susceptible individual (namely, one who is seronegative) with someone excreting HSV. The virus must come in contact with mucosal surfaces or abraded skin for infection to occur. With viral replication occurring at the site of infection, the de-enveloped capsid is transported by neurons to the dorsal root ganglia, where, after another round of viral replication, latency is established. These events have been demonstrated in a variety of animal models, as reviewed (Hill, 1985). Transport of the virion is by retrograde axonal flow (Cook and Stevens, 1973). 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 proliferation and shedding at mucocutaneous sites appearing as skin vesicles or mucosal ulcers. Occasionally, primary infection can become systemic, affecting other organ systems besides the central and peripheral nervous systems. Such circumstances include disseminated neonatal HSV infection with multi-organ involvement, multi-organ disease of pregnancy, and infrequently dissemination in patients undergoing immunosuppressive therapy. Multi-organ disease likely is the consequence of viremia in a host not capable of limiting replication to mucosal surfaces.

Infection with HSV-1 is transmitted by respiratory droplets or through direct contact (to a susceptible individual) with infectious secretions (such as virus contained in orolabial vesicular fluid). Acquisition of HSV-2 infection usually is the consequence of transmission via genital routes. Under these circum-

stances, virus replicates in the vaginal tract or on penile skin sites, with seeding of the sacral ganglia.

2.2. Pathogenesis of encephalitis

The pathogenesis of HSE in older children (>3 months of age), adolescents, and adults is only partially understood but likely is similar for all age groups. Both primary and recurrent HSV infections can cause disease of the CNS. Studies performed by the National Institute of Allergy and Infectious Diseases (NIAID) Collaborative Antiviral Study Group (CASG) indicate that 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 of age. 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 pre-existing antibodies are thought to have HSE as a consequence of reactivation of HSV (Nahmias et al., 1982). When the DNA from the peripheral (labial) and CNS isolates are compared by restriction endonuclease analysis, the isolates usually are identical; however, such is not always the case. The virus isolated from the peripheral site can be different from that retrieved from the CNS (Whitley et al., 1982a,b). Thus, the issue 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 require further elucidation.

The route of access of virus to the CNS in primary infection, especially in humans, is a subject of debate. Classic studies defined pathways for access of HSV to the brain in animals and include both the olfactory and trigeminal nerves among others (Johnson et al., 1968). However, which of these nerve tracts more commonly 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. In patients with HSE, electron microscopic evidence has demonstrated herpes virus particles along the olfactory tract in some individuals (Whitley, 1986; Twomey et al., 1979; Ojeda et al., 1983; Dinn, 1980). 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 (Stroop and Schaefer, 1986; Schlitt et al., 1986). Definitive proof for 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 (Rock and Frasher, 1983); 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 (Stroop and Schaefer, 1986; Johnson et al., 1968; Griffith et al., 1967; Davis and Johnson, 1979). Nonetheless, a relevant observation is that with recurrent herpes labialis, whereby reactivation of virus from the trigeminal ganglia occurs, HSE is a very uncommon event.

Host immunity plays an important, but as yet 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 occurs no more frequently 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 (Barnes and Whitley, 1986).

3. Clinical presentation of HSE

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 in 250,000 to 1 in 500,000 individuals per year. At the University of Alabama at Birmingham, the diagnosis of HSE was confirmed by brain biopsy in an average of 10 patients per year for an incidence of approximately 1 in 300,000 individuals, an incidence similar to those in Sweden and England (Longson, 1984; Skoldenberg et al., 1984). In the United States, HSE is thought to account for as many as 10–20% of all encephalitic viral infections of the CNS (Corey and Spear, 1986) before the occurrence of West Nile Virus encephalitis.

The economic cost of HSE is considerable, being estimated in 1983 for hospitalization alone of adolescents and adults to be more than $500 million (Straus et al., 1985; Khetsuriani et al., 2002). The total medical cost is considerably higher because of the long-term care and support services required for many of the survivors, resulting in estimates in excess of $1 billion.

HSE occurs throughout the year and in patients of all ages, with approximately one-third of cases occurring in patients younger than age 20 years but older than 6 months of age and approximately one-half in patients older than 50 years (Whitley et al., 1982a,b). Caucasians account for 95% of patients with diseases confirmed by either biopsy or polymerase chain reaction (PCR). Both sexes are affected equally.

The severity of disease is determined best 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, the mortality rate is in excess of 70%; only approximately 2.5% of all patients with confirmed disease (9.1% of survivors) returned to normal function after recovering from their illness (Whitley et al., 1977; Whitley et al., 1981; Longson, 1979; Longson et al., 1980; Boston Interhospital Virus Study Group and the NIAID Sponsored Cooperative Antiviral Clinical Study, 1975). 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, indicating a very limited spectrum of disease as defined in the series of patients undergoing brain biopsy (Tyler, 2004).

4. Diagnosis

Several aspects relating to the diagnosis of HSE merit discussion particularly in relation to disease: (1) the clinical presentation with regard to the sensitivity and specificity of various clinical characteristics in children and adolescents; (2) the historical use of brain biopsy to establish the diagnosis; (3) conditions that mimic HSE; and (4) non-invasive means of diagnosis. Data from the NIAID CASG compare presentation and outcome for patients with positive brain biopsies and those with negative brain biopsies (Whitley et al., 1982a,b). These data provide the only definitive comparisons of patients with confirmed disease versus other clinical entitles that mimic HSE. Of 432 patients who were evaluated for HSE because of focal neurologic findings, HSV was isolated from brain tissue of only 195 (45%) (Whitley et al., 1989). Only three of the remaining patients (non-biopsy-proven patients) had combinations of serologic and clinical findings that were suggestive of HSE. These patients subsequently were shown by PCR to have HSV DNA in their cerebrospinal fluid (CSF). Approximately one-third of these patients were children and adolescents (<18 years of age). Thus, in this series, focal neurologic findings predicted HSE and did so irrespective of age.

As shown in Table 1, most patients with HSE confirmed by biopsy presented with a focal encephalopathic process, including (1) altered mentation and decreasing levels of consciousness with focal neurologic findings, (2) CSF pleocytosis and proteinosis, (3) the absence of bacterial and fungal pathogens in the CSF, and (4) focal electroencephalographic (EEG), computed tomographic (CT), and/or technetium brain scan findings (Whitley et al., 1982a,b). Although magnetic resonance imaging (MRI) is a more sensitive diagnostic tool and has, for the most part, replaced CT scans, definitive studies have not been reported (Zimmerman et al., 1987; Sener, 2001; Sener, 2002; Schlesinger et al., 1995).

Table 1
Comparison of findings in "brain-positive" and "brain-negative" patients with herpes simplex encephalitis (Whitley et al., 1982a,b)

	Number (%) of patients	
	Brain-positive ($n = 113$)[a]	Brain negative ($n = 85$)[a]
Historical findings		
Alteration of consciousness	109/112 (97)	82/84 (98)
CSF pleocytosis	107/110 (97)	71/82 (87)
Fever	101/112 (90)	68/85 (78)
Headache	89/110 (81)	56/73 (77)
Personality change	62/87 (71)	44/65 (68)
Seizures	73/109 (67)	48/81 (59)
Vomiting	51/111 (46)	38/82 (46)
Hemiparesis	33/100 (33)	19/72 (26)
Memory loss	14/59 (24)	9/47 (19)
Clinical findings at presentation		
Fever	101/110 (92)	84/79 (81)
Personality change	69/81 (85)	43/58 (74)
Dysphasia	58/76 (76)	36/54 (67)
Autonomic dysfunction	53/88 (60)	40/71 (56)
Ataxia	22/55 (40)	18/45 (40)
Hemiparesis	41/107 (38)	24/81 (30)
Seizures	43/112 (38)	40/85 (47)
Focal	28	13
Generalized	10	14
Both	5	13
Cranial nerve defects	34/105 (32)	27/81 (33)
Visual field loss	8/58 (14)	4/33 (12)
Papilledemia	16/111 (14)	9/84 (11)

[a] Of 202 patients assessed.

The frequency of headache and CSF pleocytosis is higher in patients with confirmed HSE than in patients with diseases that mimic HSE. With near uniformity, and irrespective of age, patients with HSE present with fever and changes in personality. Seizures, whether focal or generalized, occur in only approximately two-thirds of all patients with confirmed disease. Thus, the clinical findings of HSE are non-specific and do not allow for empiric diagnosis of disease predicated solely on clinical presentation. Although clinical evidence of a localized temporal lobe lesion often is thought to indicate HSE, a variety of other diseases can mimic this condition (Whitley et al., 1989).

Examination of the CSF is indicated in patients with altered mentation, provided it is not contraindicated because of increased intracranial pressure. It is essential to both assess biochemical parameters and perform an HSV PCR. In patients with HSE, CSF findings are non-diagnostic, being similar in patients with confirmed disease and those with diseases that mimic HSE (Whitley et al., 1989). Both the CSF white blood cell count (lymphocytes predominance) and CSF protein become elevated as the disease progresses. The average CSF white blood cell 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. Approximately 5–10% of patients have a normal CSF formula on first evaluation. This later observation is especially the case in children, in whom presentation includes fever, encephalopathy, altered mentation, and an initially normal CSF examination. However, repeating the CSF examination even within 24 h will, in most cases, reveal abnormalities.

Non-invasive neurodiagnostic studies support a presumptive diagnosis of HSE. These studies have included EEG, CT, and MRI scans. Focal changes of the EEG are characterized by spike and slow-wave activity and periodic lateralized epileptiform discharges, which arise from the temporal lobe (Upton and Grumpert, 1970; Smith et al., 1975; Radermecker, 1956; Miller and Coey, 1959; Ch'ien et al., 1977). 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 during a period of 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 (Zimmerman et al., 1980; Enzmann et al., 1978). Bitemporal disease occurs commonly in the absence of therapy, particularly late in the course of the disease. 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 before CT demonstration (Schlesinger et al., 1995).

A sensitive and specific means of diagnosis is the isolation of HSV from tissue obtained at brain biopsy. However, PCR detection of HSV DNA in the CSF has replaced routine brain biopsy for diagnostic purposes (see below). Brain biopsy is of value in clinical presentations that are confusing; complications, either acute or chronic in nature, occur in approximately 3% of patients. Fears of potentiating acute illness (by incising the brain in a diseased area) or of causing chronic seizure disorders have not been substantiated by follow-up studies performed by the NIAID CASG.

4.1. Serologic evaluation

Several strategies utilizing antibody production as a means of diagnosing HSE have been utilized (Cesario et al., 1969). Because most encephalitic patients are HSV-seropositive at presentation, seroconversion per se usually is not helpful as fever alone can reactivate labial herpes, resulting in antibody elevations. A four-fold rise in serum antibody was neither sensitive nor specific enough to be useful. A four-fold or greater rise in CSF antibody occurred significantly more often within a month after onset of disease in patients with biopsy-proven HSE as opposed to those with other diagnosis: 85% versus 29%, respectively. By 10 days after clinical presentation, however, only 50% of brain-biopsy-positive patients had a four-fold rise in CSF antibody. Thus, 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.

4.2. PCR detection of viral DNA

PCR detection of HSV DNA in the CSF has become the diagnostic method of choice (Shoji et al., 1994; Sakrauski et al., 1994; Rowley et al., 1990; Puchhammer-Stockl et al., 1993; Lakeman et al., 1995; Fodor et al., 1998; DeBiasi and Tyler, 1999; Aurelius et al., 1991; Aurelius et al., 1993). Data from the NIAID CASG defined the sensitivity and specificity as 94% and 98%, respectively. These CSF specimens were obtained from patients with biopsy-confirmed or negative disease. Notably, the specificity would have been higher except that some tissue specimens were fixed in formalin, which killed infectious virus, before attempts at isolation in cell culture were made. HSV DNA persists in 80% of tested specimens for 1 week or more despite antiviral therapy.

More recently, real-time PCR has been applied to evaluation of CSF specimens from patients with HSE. Virus load in the CSF appears to correlate directly with clinical outcome. In an initial study, the quantity of virus (copies of viral DNA/mL) correlated statistically with decreased level of consciousness, the presence of a lesion detected by either CT or MRI, and a poor neurologic outcome (Domingues et al., 1997; Domingues et al., 1998a,b).

5. Differential diagnosis

In a compilation of the NIAID CASG data, 193 of 432 (45%) patients undergoing brain biopsy for a focal encephalopathic process had HSE (Whitley et al., 1989). As shown in Table 2, the remaining patients were evaluated for diseases that mimic HSE (Whitley and Gnann, 2002). Thirty-eight patients 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.

Table 2
Diseases that mimic herpes simplex encephalitis

Treatable diseases ($N=46$)[a]		Non-treatable diseases ($N=49$)[a]	
Abscess/subdural empyema		Vascular disease	11
Bacterial	5	Toxic encephalopathy	5
Listeria	1	Reye's syndrome	1
Fungal	2	Viral ($N=40$)	
Mycoplasma	2	Arbovirus infection	
Tuberculosis	6	St. Louis encephalitis	7
Cryptococcal	3	Western equine encephalitis	3
Rickettsial	2	California encephalitis	4
Toxoplasmosis	1	Eastern equine encephalitis	2
Mucormycosis	1	Other herpesviruses	
Meningococcal meningitis	1	Epstein-Barr virus	8
Other viruses[b]		Other viruses	
Cytomegalovirus	1	Mumps virus	3
Influenza A	4	Adenovirus	1
Echovirus infection	3	Progressive multifocal	1
Tumor	5	Leukoencephalopathy (JC virus)	
Subdural hematoma	2	Lymphocytic choriomeningitis	1
Systemic lupus erythematosus	1	Subacute sclerosing panencephalitis	2
Adrenal leukodystrophy	6		

[a] Of 432 patients assessed.
[b] Drug therapy under investigation.

Importantly, the diagnoses of other types of encephalitis, particularly enterovirus and Epstein-Barr virus, CNS disease were established more commonly in children and adolescents than in older individuals. In addition, adrenal leukodystrophy occurred only in children.

6. Associated neurologic syndromes

HSV obviously involves areas of the nervous system other than the brain. Primary and recurrent genital herpes have been associated with neuritis localized to one extremity or even transverse myelitis. Neuritis evident in such patients can be associated with altered sensation of the lower extremities, as can dysesthesias, shooting pain, and motor impairment.

Urinary and fecal incontinence have been reported in a few patients. An aseptic meningitis syndrome also is a common finding, frequently being associated with a Mollaret syndrome, and not without complications (Tyler, 2004). These findings have not been limited solely to adults, as reports in children have occurred (Tyler, 2004).

Guillain-Barré syndrome and localized dermatomal rashes associated with acute neuritis also have been attributed to HSV infections. Similarly, benign recurrent lymphocytic meningitis or Mollaret syndrome has been associated with both HSV-1 and HSV-2 infection (Tedder et al., 1994; Picard et al., 1993). Acute retinal necrosis has been reported as a long-term complication of HSE (Kim and Yoon, 2002).

7. Therapy

The first antiviral drug reported as efficacious therapy of HSE was idoxuridine; however, in a controlled clinical trial it proved to be both ineffective and toxic (Boston Interhospital Virus Study Group and the NIAID Sponsored Cooperative Antiviral Clinical Study, 1975). Subsequent therapeutic trials defined vidarabine as an efficacious medication for the management of biopsy-proven HSE (Whitley et al., 1977; Whitley et al., 1981); however, it has been replaced by acyclovir in the physician's armamentarium. During these studies, the variables of age, duration of disease, and level of consciousness at the onset of therapy proved to be major determinants of clinical outcome. Patients younger than 30 years of age and with a more normal level of consciousness (lethargic as opposed to comatose) were more likely to return to normal function than were older patients, especially those who were semicomatose or comatose. Notably, 90% of individuals younger than 30 years of age were children and adolescents. From these data, older patients (older than 30 years of age), 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 of significant deterioration of consciousness. Acyclovir is superior to vidarabine for the treatment of HSE (Whitley et al., 1986). The mechanisms of action of acyclovir have been discussed at length (Gnann et al., 1983). Acyclovir decreases the mortality rate to 19% 6 months after therapy. Importantly, 38% of patients, irrespective of age, return to normal function. However, conversely, most patients are left with significant neurologic impairment.

The NIAID CASG study defined a mortality rate of 55% at 6 and 18 months after the onset of treatment for vidarabine recipients versus 19% and 28%, respectively, for the acyclovir-treated 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. The mortality rate is somewhat lower in children and adolescents but not statistically different than older individuals. As noted above, 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 score (GCS). Scores that approached normal predicted enhanced survival. When GCS and age were assessed simultaneously, a GCS of 6 or less predicted a poor therapeutic outcome, irrespective of the agent administered or of the age of the patient (Whitley et al., 1986).

Regarding morbidity, the vidarabine studies indicated that approximately 15–20% of patients overall would develop normally after receiving therapy for HSE on long-term follow-up. The only comparative trial indicated that 13% of vidarabine recipients were left with no or minor sequelae, whereas 22% had moderate or severe sequelae and 65% died during follow-up. For acyclovir recipients, 38% of patients were normal or had minor impairment, 9% of patients had moderate sequelae, and 53% of patients were left with severe impairment or died. No patient entered into the NIAID trials suffered a relapse after completion of therapy. Relapse of HSE has been reported, although not well documented, in a few patients after receiving vidarabine (Wang et al., 1994; Davis and Mclaren, 1983) and acyclovir (Wang et al., 1994; Vanlandingham et al., 1988). 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. These findings indicate that the current therapy of choice for the management of HSE is acyclovir rather than vidarabine. Acyclovir is administered at a dosage of 10 mg/kg every 8 h (30 mg/kg/day) for a period of only 14–21 days.

8. Future considerations

Several considerations are in order. First, in the management of HSE in children, adolescents, and adults, we do not have PCR evidence of disease persistence as occurs in the newborn. Stated more simply, these studies have not been performed. Such information may be important in gauging duration of therapy, as appears to be the case in the management of neonatal disease. However, definitive data remain lacking. Second, no controlled clinical trial to date has relied solely on PCR confirmation of disease to understand either the natural history of disease or the neurologic outcome independent of brain biopsy. Currently, the NIAID CASG is performing a clinical trial to assess these outcome events as well as the contribution of viral load and quantitative MRI extent of involvement to long-term prognosis. Third, the role of long-term therapy of HSE with orally bioavailable therapeutics after intravenous therapy remains to be seen, and it currently is being studied to determine its contribution

to overall morbidity. Fourth, the application of proteomics and microarrays to biologic specimens obtained from patients with HSE may further elucidate disease pathogenesis and offer novel therapeutic interventions (i.e. anti-inflammatory agents or monoclonal antibodies directed against selected cytokines).

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