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Herpes Simplex Virus Infections of the Central Nervous System
Encephalitis and Neonatal Herpes

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Contents

Summary Herpes simplex virus (HSV) infections are among the most commonly encountered in humans. Fortunately, the resulting diseases are more usually nuisances, such as recurrent fever blisters, rather than life threatening or morbidity inducing. Nevertheless, HSV can result in disease of the central nervous system (CNS) with attendant neurological complications. Examples of the latter include herpes simplex encephalitis (HSE) or neonatal HSV infection. The past decade has witnessed significant advances in our understanding of the pathogenesis of these 2 forms of disease and, even more importantly, their amenability to treatment. This review summarises our current understanding of the natural history, pathogenesis, presentation, and treatment of HSV infections of the CNS.

Because of the life-threatening nature of herpes simplex infections of the CNS, particular attention is paid to clinical presentation and differential diagnosis of confounding entities which mimic herpes simplex encephalitis. The controversy of brain biopsy versus alternative noninvasive diagnostic procedures is discussed. Clinical presentation and, importantly, the lack of uniform clinical presentation, as well as the value of intervention with appropriate antiviral drugs such as aciclovir and vidarabine (adenine arabinoside, ara-A) are stressed. The clinical outcome of herpes simplex virus infections of the CNS with therapy is particularly relevant. In spite of early intervention with selective and specific inhibitors of viral replication, return to normal function is not always achieved. At the conclusion of this review, the reader should be aware of the potential value of therapy as well as the problems encountered with diagnosis and management of patients with herpes simplex virus infections of the CNS.

1. History

The infectious nature of herpes simplex virus (HSV) was first delineated by demonstrating passage of the virus from lip and genital lesions of humans to either the cornea or the scarified skin of the rabbit (Gruter 1924). Goodpasture (1925) demonstrated that the inoculation of vesicular fluid from the lesions of herpes labialis onto scarified cornea of rabbits consistently produced herpes simplex encephalitis (HSE). Intranuclear inclusion bodies consistent with HSV infection were first demonstrated in the brain of a baby with encephalitis in 1941. Since HSV was isolated from brain tissue, this case provided important evidence that HSV can cause encephalitis in a newborn (Smith et al. 1941). The first adult case of HSE with similar findings, i.e. intranuclear inclusions in brain tissue and virus isolation, was described by Zarafonetis et al. (1944). The most striking pathological finding in this case was evidence of perivascular lymphocytic cuffing and numerous small haemorrhages localised to the left temporal lobe – a characteristic pathophysiological event in HSE.

In 1952, Zuelzer and Stulbery reviewed 8 cases of disseminated HSV infection in neonates, with involvement of most organs, including the brain (Zuelzer et al. 1952). Until this time it had been almost axiomatic that newborns were not susceptible to HSV infection. Their report was the first describing visceral lesions definitively attributable to HSV infection. They correctly implicated haematogenous spread of virus as the pathogenic mechanism. Furthermore, they postulated that maternal antibody was not protective, that infants born to mothers with herpetic lesions were at special risk, and that exposure after birth may lead to infection. Recognition of HSV as a cause of encephalitis progressed to such an extent that in a 1960 review of CNS viral syndromes (Meyer et al. 1960), HSV was the third most frequent cause of encephalitis.

In the mid 1960s, Nahmias and Dowdle demonstrated 2 antigenic types of HSV, HSV-1 and HSV-2. This distinction led to the definition of the epidemiology of HSV infections. Viral typing allowed demonstration that HSV-1 is primarily responsible for herpes infections 'above the belt' while HSV-2 causes herpes infections 'below the belt' (Nahmias & Dowdle 1968). Over the past 15 years, knowledge of the molecular biology of HSV has expanded, especially regarding the biochemistry of viral replication and associated gene products as

well as the epidemiology, natural history and pathogenesis of HSV infections. Future emphasis can now be on improved methods of diagnosis, treatment, and prevention.

2. *Herpes Simplex Encephalitis*

Herpes simplex virus infections of the central nervous system (CNS) are among the most severe of all human viral infections of the brain. The severity of HSE can be assessed by the outcome of patients with proven disease who have received no therapy or an ineffective antiviral drug (e.g. idoxuridine or cytosine arabinoside). Mortality exceeds 70% and only about 9.1% of surviving patients return to normal function following recovery from their illness (Boston Interhospital Virus Study Group 1975; Longson 1979; Longson et al. 1980; Whitley et al. 1977, 1981). Since diagnosis required brain biopsy with the isolation of HSV from tissue in these studies, it is likely that a broader spectrum of HSV infections of the CNS exists. One British study suggested milder forms of HSE which are associated with lower mortality and improved morbidity; serological evaluations were the basis for the diagnosis, a problem which will be discussed below (Klapper et al. 1984). Regardless, a spectrum of CNS disease caused by HSV must exist.

Although the clinical presentation, diagnosis and outcome of patients with HSE have been considered for some time, the reported studies indicate extreme variability in the methods of diagnosis, mortality, morbidity and the clinical course of disease. Studies performed in the United States by the National Institute of Allergy and Infectious Diseases (NIAID) Collaborative Antiviral Study Group (CASG) have resolved some of these issues. The clarification of many of these issues became possible because of a uniform diagnostic approach, namely brain biopsy and subsequent isolation of HSV from brain tissue. Unequivocal diagnosis often has created both practical dilemmas (Johnson et al. 1968; Meyer et al. 1960; Rappel et al. 1971) and intellectual controversies (Braun et al. 1980; Braza et al. 1980; Longson et al. 1980; Whitley et al. 1982a). This procedure has not been routinely employed in therapeutic, natural history or diagnostic investigations performed outside the United States for the prospective evaluation of patients with focal encephalitis. Through the NIAID studies, clinical presentation, the value of brain biopsy for diagnostic purposes as well as establishing alternative diagnoses which mimic HSE, and the relative value of therapy have all been identified. Because of its differing clinical presentation and outcome as well as special opportunity for disease prevention, neonatal herpes will be discussed separately (see section 3).

2.1 Epidemiology

Currently, HSE is estimated to occur in approximately 1 in 250 000 to 1 in 500 000 individuals per year (Whitley 1982). A similar incidence has been reported in Sweden and England (Longson 1975; Skoldenberg et al. 1984). In the United States, HSE is thought to account for as many as 10 to 20% of viral infections of the CNS (Corey & Spear 1986). The economic cost is considerable; the 1983 estimated medical costs of hospitalisation alone for the acute illness of adult HSE was over $100 million (National Academy of Sciences 1985; Straus et al. 1985), which grossly underestimates the total medical cost because of the long term care and support services required for most patients.

Herpes simplex encephalitis occurs throughout the year and in patients of all ages, with approximately one-third occurring in patients less than age 20 and one-half in those older than 50 years (Whitley et al. 1982b). Caucasians account for 95% of patients with proven disease. Women and men are equally affected.

2.2 Pathogenesis

The pathogenesis of HSE remains unclear. Both primary and recurrent HSV infections can cause disease of the CNS. From studies performed by the NIAID CASG, about one-third of the cases of HSE are the consequence of primary infection which occurred in patients less than 18 years of age. The remaining two-thirds of cases occurred in individ-

uals with pre-existing HSV antibodies. Only 6% of these patients had a history of recurrent HSV labialis. This latter group of patients was thought to have HSE as a consequence of reactivation of HSV (Nahmias et al. 1982).

The route of access of virus to the CNS in primary infection of humans has been discussed. While studies performed over 2 decades ago defined pathways for HSV access to the brain in animals, including both the olfactory and trigeminal nerves among others (Johnson 1984), it is not clear which of these nerve tracts uniformly leads to HSV infection of the CNS of humans. The anatomical distribution of nerves from the olfactory tract along the inferiomedial portion of the temporal lobe, the site of onset of HSE in humans, suggested that viral access to the CNS via this route was tenable. Reports in the literature, utilising electron microscopy, supported this concept (Dinn 1980; Ojeda et al. 1983; Twomey et al. 1979; Whitley 1990). Animal model data verified that the olfactory tract provided one neurological avenue for viral access to the CNS and resulted in localisation of the infection in the orbitofrontal region of the brain (Schlitt et al. 1986; Stroop & Schaefer 1986).

Reactivation of HSV, leading to focal HSE, is similarly confusing from the standpoint of pathogenesis. While it is possible to demonstrate latent virus infection within infected brain tissue (Rocket al. 1983), the likelihood of reactivation at that site remains purely hypothetical. Reactivation of virus peripherally, namely in the olfactory bulb or the trigeminal ganglion, has been suggested with subsequent neuronal transmission to the CNS (Davis & Johnson 1979; Griffith et al. 1967; Johnson 1984; Stroop & Schaefer 1986). Nevertheless, in spite of the frequency of recurrent HSV labialis, HSE is uncommon. Specifically, there are far more cases of recurrent HSV labialis than HSE. Furthermore, when patients with biopsy-proven HSE are compared to patients having other diseases which mimic HSE, there is a near equal frequency of both fever blisters (6%) and retrieval of virus from the oropharynx (11%) for the 2 groups (Nahmias et al. 1982). Certainly, HSE does not occur more frequently in immune-suppressed patients. These questions remain viable subjects for future investigations.

Patients with HSE can shed virus from a peripheral site such as the oro- or nasopharynx (Nahmias et al. 1982). Following primary infection, HSV accesses the CNS in a few patients. When the DNAs from both the peripheral and CNS isolates are compared by restriction endonuclease analyses, identity of the isolates can be expected. However, when disease occurs in individuals with HSV antibodies, namely recurrent infection, virus isolated from a peripheral site often is different from that retrieved from the CNS (Whitley et al. 1982a). Thus, the issue of reactivation of HSV directly within the CNS, the potential for enhanced neurotropism of certain HSV or the selective reactivation and access of one virus by the trigeminal route or other routes awaits further elucidation.

2.3 Pathology

The gross appearance of the brain in infected individuals shows acute inflammation, congestion, and softening, usually asymmetrically centered around the temporal lobes (Boos & Esiri 1986), but also involving adjacent areas. The meninges overlying the temporal lobes may appear clouded or congested. Acutely, petechiae or larger haemorrhages are visible. After approximately 2 weeks these changes proceed to frank necrosis and liquefaction, as shown in figure 1. The microscopic abnormalities associated with these changes have been previously described (Boos & Esiri 1986; Boos & Kim 1984; Garcia et al. 1984).

2.4 Immunity

Host immunity plays an important but as yet undefined role in the pathogenesis of HSE. The CNS may be particularly prone to HSV infection because intraneuronal spread may shelter the virus from defense mechanisms. A number of patients with cellular immune dysfunction and HSE have been reported. These patients may have an atypical presentation with a subacute but progressively deteriorating course (Barnes & Whitley 1986). Though

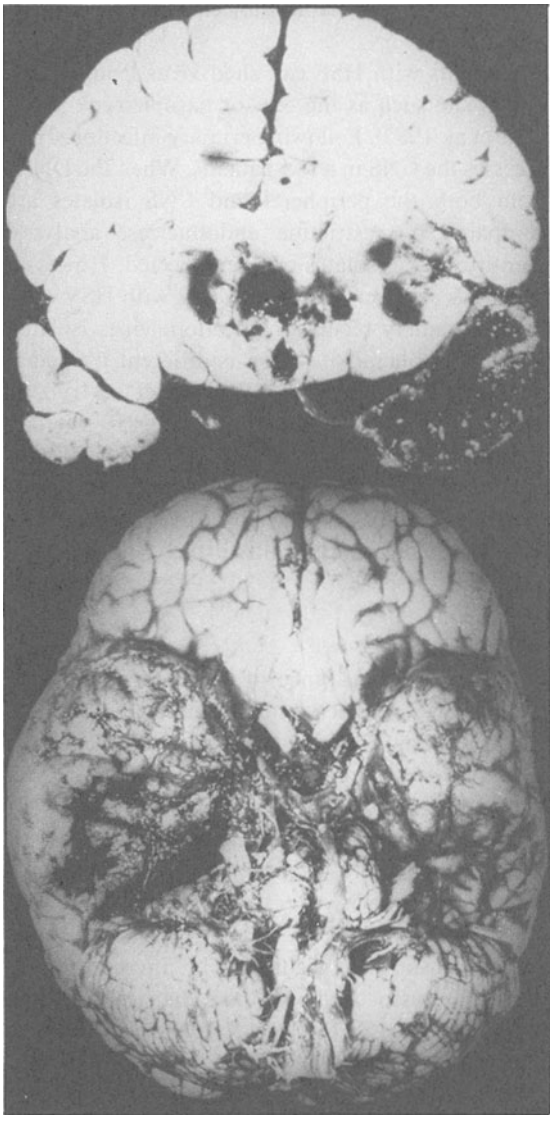

Fig. 1. Temporal lobe necrosis secondary to herpes simplex encephalitis.

mucocutaneous herpes infections are much more common and severe in immunocompromised hosts, the incidence of HSE in the absence of multiorgan disease is not significantly elevated in this patient population (Boos & Esiri 1986).

2.5 Diagnosis

Several aspects relating to the diagnosis of HSE merit discussion: the clinical presentation; the need for brain biopsy, conditions which mimic HSE, and the prospects of noninvasive diagnostic methods. Since the NIAID CASG required a positive brain biopsy for inclusion in its studies, a unique opportunity existed to evaluate clinical and neurodiagnostic characteristics of patients with positive or negative brain biopsies (Whitley et al. 1982a). All patients in these studies had clinical findings at outset compatible with HSE. Of 432 patients who were evaluated for HSE, HSV was isolated from brain tissue of only 193 patients. Four of the patients whose brain tissue failed to yield HSV had combinations of serological and clinical findings suggestive of HSE.

2.5.1 Clinical Presentation

Patients with biopsy-proven HSE presented with a focal encephalopathy, including fever, altered mentation and decreasing levels of consciousness with focal neurological findings, cerebrospinal fluid (CSF) pleocytosis and proteinosis, and focal electroencephalograph (EEG) and computed tomographic (CT) and/or technetium brain scan findings, as shown in table I. The use of magnetic resonance imaging (MRI) has not been adequately studied to date for HSE. The CSF failed to yield either fungal or bacterial pathogens. When comparing patients with HSE versus other diseases, only a higher frequency of headache and CSF occurred in patients with HSE. A higher frequency of ataxia occurred in patients having diseases which mimicked HSE. Nearly uniformly, patients with HSE presented with fever and personality change. Seizures, whether focal or generalised, occurred in approximately two-thirds of all patients with proven disease. Thus, the clinical findings alone of HSE are nonspecific and do not allow for empiric diagnosis predicated solely on presentation. This point must be stressed. While clinical evidence of a localised temporal lobe lesion is often thought to be HSE, other diseases mimic this condition (Whitley et al. 1989).

Table I. Comparison of findings in biopsy-positive and biopsy-negative patients with herpes simplex encephalitis (reproduced with permission from Whitley et al. 1982b)

Finding	Number of patients (%)[a]		
	positive (n = 207) [%]	negative (n = 243) [%]	p value
Historical findings			
Fever	192/207 (93)	203/243 (84)	0.003
Headache	151/207 (73)	134/243 (55)	<0.001
CSF pleocytosis	818/207 (87)	176/242 (72)	<0.001
Seizures	137/207 (66)	157/243 (65)	NS
Level of consciousness			
alert	7/205 (3)	11/240 (5)	
lethargic	81/205 (40)	78/240 (33)	0.45
semicomatose	54/205 (31)	73/240 (30)	
comatose	63/205 (31)	78/240 (33)	
Hemiparesis	68/207 (33)	68/243 (28)	NS
Akinetic mutism[b]	11/94 (12)	15/158 (9)	NS
Alteration of consciousness	193/207 (93)	218/243 (90)	NS
Findings at presentation (day 1)			
Dysphasia	91/128 (71)	91/135 (67)	NS
Ataxia	28/83 (34)	33/81 (41)	NS
Personality change	95/120 (79)	90/114 (79)	NS
Hemiparesis	78/190 (41)	79/214 (37)	NS
Seizures	82/205 (40)	107/234 (46)	NS
focal	49/82 (60)	38/107 (35)	0.002
general	17/82 (21)	35/107 (33)	
both	16/82 (19)	34/107 (32)	
Cranial nerve deficit	56/183 (31)	48/219 (43)	0.05
Papilloedema	28/193 (15)	15/231 (6)	<0.01

a Denominator varies according to ability to assess patient.
b Not available from prior trials.
Abbreviation: NS = not significant.

Noninvasive neurodiagnostic tests have been used to support a presumptive diagnosis of HSE. These tests have included the EEG and CT and technetium brain scan. More recently, MRI has been used for diagnostic purposes. Focality of the EEG is the most sensitive of the noninvasive neurodiagnostic procedures (Chien et al. 1977; Miller & Coey 1959; Radermecker 1956; Smith et al. 1975; Upton & Grumpert 1970). Characteristic EEG findings include spike and slow wave activity labelled as 'PLEDS' which arise from the temporal lobe. Early in the disease course, the abnormal electrical activity usually involves one temporal lobe but spreads to the contralateral temporal lobe as the disease evolves, usually over a period of 7 to 10 days. Sensitivity of the EEG has been defined as approximately 84%; but, unfortunately, a specificity of 32.5% has been demonstrated in the NIAID CASG trials. Technetium brain and CT scans initially show evidence of oedema localised to the temporal lobe which will progress to radiolucent lesions indicative of haemorrhagic necrosis and, then, a mid-line shift of CNS structures, including obliteration of lateral ventricles (Enzmann et al. 1978; Zimmermann et al. 1980). Bitemporal disease is common in the absence of

therapy, particularly late in the disease. When these neurodiagnostic tests are used in combination, the sensitivity is enhanced; however, the specificity is no better. Presently, none of these neurodiagnostic tests is uniformly satisfactory for diagnosing HSE; perhaps MRI will prove acceptable.

2.5.2 Brain Biopsy

The most sensitive and specific diagnostic method is the isolation of HSV from tissue obtained at brain biopsy. While this diagnostic approach is controversial, in our studies brain biopsy has not been associated with undue acute or chronic complications. The frequency of acute complications secondary to brain biopsy is approximately 3%, with the most common being poorly controlled cerebral oedema at biopsy or haemorrhage because of poor tissue visualisation. While long term complications have been thought to include seizure disorders, these have been uncommon in the experience of the NIAID CASG (Soong et al. 1990). It must be recognised that temporal lobe necrosis, as encountered with HSE, is an irreversible pathological process; thus, biopsy tissue must be considered nonviable and not amenable to recovery. Furthermore, the scarred tissue can be an epileptogenic focus.

2.5.3 Serology

Several strategies use antibody detection as a means of diagnosing HSE. Data from the NIAID CASG were analysed for comparison of serum and CSF antibody production in patients with proven disease (Nahmias et al. 1982). Since the majority of patients were seropositive for HSV prior to their illness, seroconversion was usually not helpful. A 4-fold rise in serum antibodies was neither sensitive nor specific enough to be useful. A 4-fold or greater rise in CSF antibodies occurred significantly more often in the month after onset of infection in patients with biopsy-proven HSE versus those with other diseases (85 *vs* 29%, respectively). However, earlier in the diease, such distinctions were not apparent. This test is useful only retrospectively for diagnosis. Using a serum-to-CSF antibody ratio of $\leqslant 20$ did not improve sensitivity during the first 10 days of disease.

Alternative noninvasive diagnostic procedures are in varying stages of development. One promising assay is the demonstration of antigens to glycoproteins gB, gD and gE in CSF of patients with proven disease (Lakeman et al. 1987). The CSF reveals antigens to HSV as early as 5 days after disease onset in 65 to 75% of specimens tested. The assay is nearly 100% specific and increases in sensitivity as the disease progresses. More recently, polymerase chain reaction has been employed to detect evidence of viral DNA. Applied to the detection of HSV, several reports have suggested the utility of this approach for diagnostic purposes (Hardy et al. 1990; Puchhammer-Stockl et al. 1990; Rowley et al. 1990). Conceivably, the availability of a CSF antigen detection assay will replace brain biopsy.

2.5.4 Diseases that Mimic HSE

From the NIAID CASG data, diseases which mimic HSE have been identified (Whitley et al. 1989) as shown in table II. 38 patients had diseases amenable to other forms of therapy, including brain abscess, tuberculosis, cryptococcal infection and brain tumour; 19 patients had diseases which were indirectly treatable; and 38 patients had alternative diagnoses established for which no current therapy exists. Usually these patients had infections caused by non-HSV viruses. The diagnosis of other treatable causes of encephalitis provides compelling support for brain biopsy of patients with suspected HSE. Future development of noninvasive diagnostic procedures must take into consideration alternative diseases which mimic HSE and require immediate medical intervention.

2.6 Therapy

The first antiviral drug evaluated and reported useful for HSE was idoxuridine (iododeoxyuridine) [Breeden et al. 1966; Illis & Merry 1972; Nolan et al. 1970, 1973; Rappel et al. 1971; Sarubbi et al. 1973]. In 1972, the NIAID CASG and the Boston Interhospital Viral Study Group demonstrated that

idoxuridine was both ineffective and toxic for patients with HSE (Boston Interhospital Virus Study Group 1975). Toxicity manifested as bone marrow suppression (neutropenia and thrombocytopenia) and secondary bacterial infection and occurred at purportedly effective dosages. Thus, the therapeutic index (ratio of efficacy to toxicity) was proven unacceptable and idoxuridine was no longer considered acceptable for the treatment of HSE.

Subsequent clinical trials suggested vidarabine (adenine arabinoside, ara-A) to be of value in the treatment of HSE (Whitley et al. 1977, 1981). In the first of a series of controlled studies of HSE, which used a double-blind, placebo-controlled study design, vidarabine therapy decreased mortality for patients with HSE from 70% to 28% at 1 month after disease onset and to 44% 6 months later. Because of small numbers, this study was followed by an uncontrolled trial to verify mortality and define long term morbidity. The follow-up study of nearly 100 patients with proven disease found a long term (3-year) mortality of 40%. In addition, it was proven that age and level of consciousness were the major determinants of outcome. Patients less than 30 years of age who were lethargic as opposed to comatose were more likely to return to normal function after HSE than older patients or those who were semicomatose or comatose, as displayed in figure 2. Older patients (greater than 30 years of age) whether comatose or semicomatose had mortality rates which approached 70% – a rate similar to that of placebo recipients in prior studies. For patients less than 30 years of age, a more acceptable outcome was achieved; the mortality rate was 25% and 40% of patients returned to normal function. An important lesson learned from these trials was that if therapy is to be effective, it must be instituted prior to the onset of haemorrhagic necrosis of a dominant temporal lobe which is associated with deterioration in the patient's level of consciousness.

More recently, the NIAID CASG has demon-

Table II. Alternative diagnoses made in patients biopsied for presumptive herpes simplex encephalitis (total biopsied 432) [from Whitley et al. 1989]

Treatable (n = 38)		Nontreatable (n = 57)	
Infection		**Nonviral** (n = 17)	
Abscess/subdural empyema		Vascular disease	11
bacterial	5	Toxic encephalopathy	5
Listeria	1	Reye's syndrome	1
fungal	2		
mycoplasma	2	**Viral** (n = 40)	
Tuberculosis	6	Togavirus infections	
Cryptococcal	3	St Louis encephalitis	7
Rickettsial	2	western equine encephalitis	3
Toxoplasmosis	1	California encephalitis	4
Mucormycosis	1	eastern equine encephalitis	2
Meningococcal meningitis	1	Other herpesviruses	
		Epstein-Barr Virus	8
Tumour	5	CMV	1
		Others	
Subdural haematoma	2	echo	3
		influenza A	4
Systemic lupus erythematosus	1	mumps	3
		adenovirus	1
Adrenal leucodystrophy	6	progressive multifocal leucoencephalopathy	1
		lymphocytic choriomeningitis	2
		subacute sclerosing panencephalitis	2

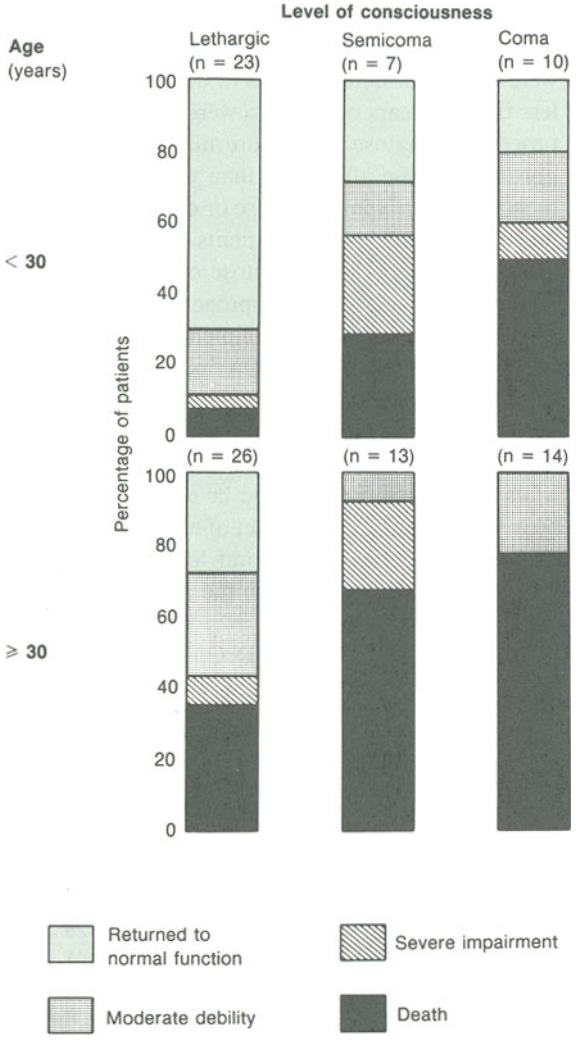

Fig. 2. Influence of level of consciousness and age on HSE mortality and morbidity (from Whitley et al. 1981).

strated that aciclovir is superior to vidarabine for the treatment of HSE (Whitley et al. 1986a,b). The design and mechanism of action of aciclovir have previously been discussed at some length (Gnann et al. 1983; O'Brien & Campoli-Richards 1989). Diagnosis involved isolation of HSV from brain biopsy tissue, a criterion somewhat different from that of a similar study performed in Sweden. The NIAID study demonstrated that aciclovir reduced mortality to 19% (compared with 50% for vidarabine recipients in the study or, historically, 70% in placebo recipients) 6 months after therapy, and 38% of patients irrespective of age returned to normal function. Scandinavian investigators defined similar outcome but in a smaller group of patients whose diagnosis was by a variety of methods (Skoldenberg et al. 1984). Both studies taken together indicate that aciclovir is superior to vidarabine for the treatment of HSE.

As displayed in figure 3, NIAID CASG data indicate a mortality rate of 50 and 50% at 6 and at 18 months after treatment with vidarabine; the corresponding mortality rate for aciclovir recipients was 19 and 24%, respectively. The mortality rate following vidarabine therapy in this study was greater than that of other trials because this group consisted of older individuals who had a lower level of consciousness. When populations were adjusted, differences in mortality remained significant (2-tail test, $p = 0.04$). Late deaths were not a consequence of either persistent or reactivated HSV infection of the CNS

The Glasgow coma score (GCS) was employed to rate patients according to motor, verbal and sensory responses. As shown in figure 4, scores which approached normal, predicted survival. When GCS and age were assessed simultaneously, as shown in

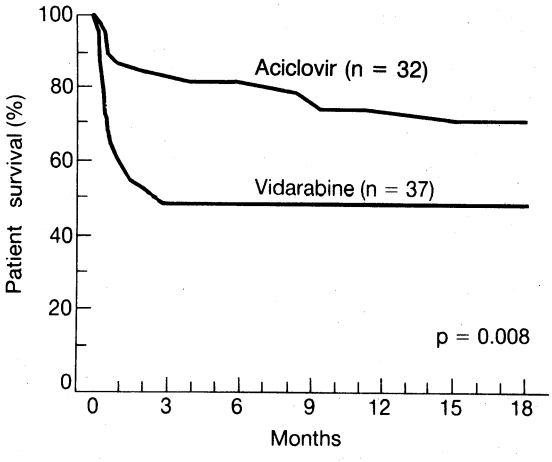

Fig. 3. Comparison of survival in patients with biopsy-proven herpes simplex encephalitis treated with vidarabine (ara-A) or aciclovir (from Whitley et al. 1986a).

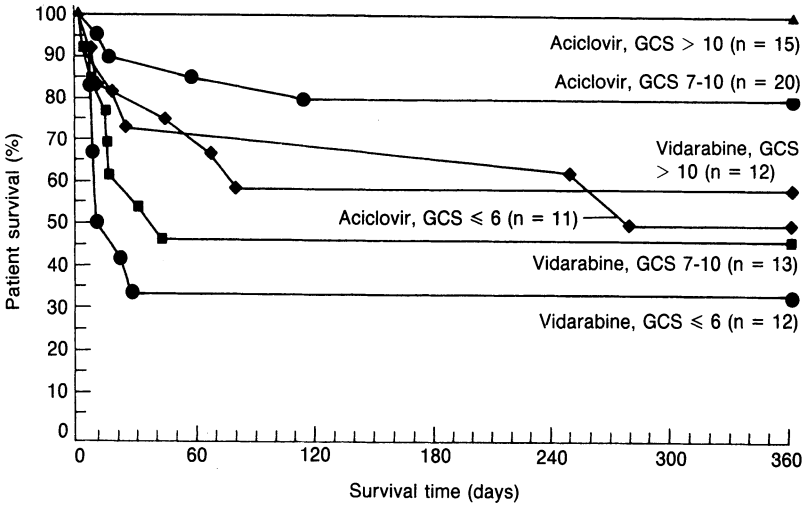

Fig. 4. Mortality after vidarabine or aciclovir treatment of biopsy-proven herpes simplex encephalitis, according to Glasgow Coma Score (GCS) [from Whitley et al. 1986a].

figure 5, a GCS less than or equal to 6 was associated with a poor outcome irrespective of the treatment or age of the patient (Whitley et al. 1986a).

Long term morbidity is important for patients with HSE and their families. Historically, the vidarabine studies indicated that approximately 15 to 20% of patients overall returned to normal following therapy of HSE. The current trial indicated that 13% of vidarabine recipients were left with no or minor sequelae, while 22% had moderate sequelae and 65% had severe sequelae or had died on follow-up. For aciclovir recipients, 38% of patients were normal or with minor impairment, 9% of patients had moderate sequelae, and 53% of patients were either left with severe impairment or were dead.

No patient entered into the current trial suffered a relapse. Relapse of HSE has been documented in a few patients following the administration of vidarabine (David & McLaren 1983; Dix et al. 1983), and was reported in a normal host after treatment with aciclovir (Van Landingham 1988). Demyelination syndromes have also been identified after successful treatment of HSE (Loenig et al. 1979).

Toxicity is not a significant problem in the treatment of HSE. As shown in table III, vidarabine recipients developed laboratory abnormalities during treatment more frequently than aciclovir recipients (50 versus 25%, p = 0.04). The most sig-

Table III. Abnormal laboratory values in 69 patients with biopsy-proven herpes simplex encephalitis (adapted from Whitley et al.)

Laboratory index[a]	No. of pts (%)	
	vidarabine group	aciclovir group
Platelets (< 100 000 cells/mm^3)	4 (11)	2 (6)
AST (> 250 U/dl)	5 (14)	1 (3)
BUN (> 50 mg/dl)	4 (11)	3 (10)
White cells (< 2500 cells/mm^3)	2 (6)	0 (0)
Total bilirubin (> 3 mg/dl)	1 (3)	0 (0)
Creatinine (> 3 mg/dl)	0 (0)	2 (6)
Combinations		
AST + bilirubin	1 (3)	0 (0)
White cells + platelets	0 (0)	0 (0)
BUN, platelets, + AST	1 (3)	0 (0)
Total	18 (49)	8 (25)

a To convert values for BUN to millimoles per litre, multiply by 0.357; to convert values for bilirubin and creatinine to micromoles per litre, multiply by 17.10 and 88.40, respectively.

Abbreviations: AST = serum aspartate amino transferase; BUN = blood urea nitrogen.

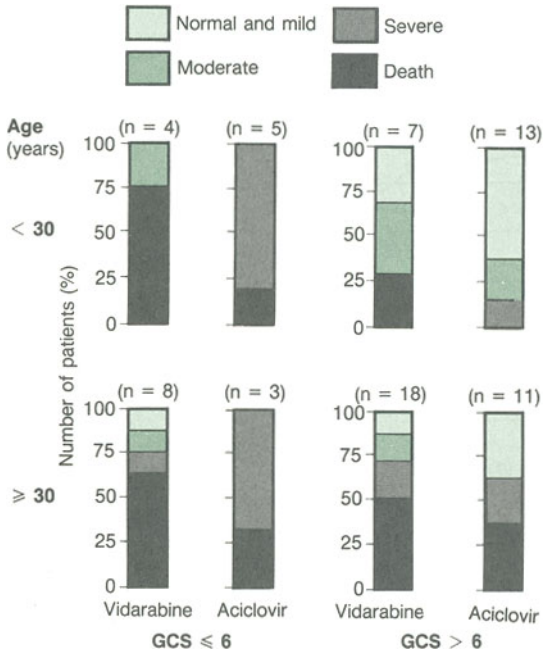

Fig. 5. Morbidity after vidarabine or aciclovir treatment of biopsy-proven herpes simplex encephalitis, according to age (< 30 *vs* > 30) and the Glasgow Coma Score (GCS) [< 6 *vs* > 6] (from Whitley et al. 1986a).

nificant laboratory abnormalities encountered among vidarabine recipients were a platelet count less than 100 000/mm^3 (11%), an elevated serum aspartate aminotransferase (AST) greater than 250U (14%), and an elevated blood urea nitrogen (BUN) in excess of 30 mg/dl (10.7 mmol/L; 11%). For aciclovir recipients, 10% experienced an elevated BUN and 6% developed a creatinine in excess of 2 mg/dl (177 μmol/L). It should be emphasised that the administration of both drugs was not associated with clinical evidence of toxicity.

2.6.1 Drug of Choice

These findings taken together indicate the therapy of choice for the management of HSE is aciclovir. A dosage of 10 mg/kg administered intravenously every 8 hours (total 30 mg/kg/day) for 10 to 14 days is suggested; however, certain circumstances may dictate a longer period of therapy, and clinical response and duration of fever should guide the physician in this regard.

2.7 Future Therapeutic Directions

Although aciclovir is the treatment of choice for HSE, mortality and morbidity remain problematic. Thus, alternative therapeutic approaches need to be developed. A longer duration of therapy with current agents and at current dosages may be beneficial. An alternative approach to the therapy of HSE is combination chemotherapy as in the management of malignancy and certain viral infections (De Vita et al. 1975; Rahal 1978). The application of combination therapy to the treatment of viral infections has been studied *in vitro* as well as in animal model systems (Ayisi et al. 1980; Biron & Elion 1982; DeClerq et al. 1980; Fischer et al. 1979; Schinazi et al. 1982b; Wigand & Hassinger 1980). In tissue culture experiments, aciclovir and vidarabine usually have an additive effect for reduction of replication of both HSV-1 and HSV-2 in Vero cells. Animal model data indicate that combination aciclovir and vidarabine therapy have additive if not synergistic effects for decreasing mortality. Similar animal model data have previously predicted the value of both aciclovir and vidarabine as single agents for treatment of HSE (Schinazi et al. 1982a).

Combination therapy may well have potential for decreasing the development of viral resistance. While resistant viral mutants can be generated easily *in vitro*, resistant HSV has not been a major problem in humans with HSE (Barry et al. 1985; Field 1983; Svennerholm et al. 1985; Wade et al. 1983).

3. Neonatal Herpes Simplex Virus Infections

While HSV infections of the CNS occur from ages of newborn to the adult, there are differences in pathogenesis, clinical presentation, diagnosis and outcome by age group. Neonatal HSV infection manifests as one of 3 forms: disseminated, encephalitis, or disease of the skin, eye, or mouth.

Because disseminated infection in the neonate usually involves the CNS and even isolated skin infections may have eventual CNS involvement, neonatal HSE must be discussed in the context of all neonatal HSV infections. The incidence of neonatal HSV infections is estimated to be 1 in 3000 to 5000 deliveries (Whitley 1982b). Neonates appear to have the highest frequency of visceral and CNS infection of any HSV-infected patient population (Corey & Spear 1986). Overall, two-thirds of children with neonatal HSV infection have involvement of the CNS regardless of whether disease is localised to the brain or becomes disseminated. These children are at exceedingly high risk for death or permanent neurological impairment. 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%.

3.1 Pathogenesis

3.1.1 Acquisition of Infection

Neonatal HSV infection is acquired at one of 3 times: *in utero,* intrapartum, or postnatally. The mother is the most common source of infection for the first 2 of these routes of transmission of virus to the newborn. A maternal source should be suspected when herpetic lesions are discovered after the birth of the child or when the baby's illness is caused by HSV-2.

Information about *in utero* infection is becoming increasingly available in the literature (Baldwin et al. 1989; Florman et al. 1973; Hutto et al. 1987; South et al. 1969). Originally, it was presumed that *in utero* infection resulted in either a totally normal baby or premature termination of gestation (South et al. 1969). It has become apparent that intrauterine infection can lead to symptomatology of congenital infection, mimicking clinical findings of diseases such as congenital cytomegalovirus infection, rubella, syphilis or toxoplasmosis.

The most common time of acquisition of infection is intrapartum, accounting for about 80% of cases. The infant comes into contact with infected genital secretions of the mother (Nahmias et al. 1971). The third route of transmission is postnatal acquisition (Brown et al. 1987; Dunkle et al. 19789; Hammerberg et al. 1983; Light 1979; Sullivan-Bolyai et al. 1983). Documented sources for such transmission include mother-to-child, including breast feeding from infected breasts (Dunkle et al. 1979; Kibrick 1979; Sullivan-Bolyai et al. 1983; Yeager et al. 1983), father-to-child (Douglas et al. 1983), and nosocomial transmission (Hammerberg et al. 1983; Linnemann et al. 1978). Even though HSV-1 has been associated with genital lesions, postnatal transmission of herpes simplex virus has been increasingly suggested because 20 to 30% of neonatal HSV infections are caused by this virus type (Nahmias et al. 1983). In fact, more recent data from the NIAID CASG indicate that the frequency of babies with neonatal HSV-1 infections has increased to nearly 30% (Whitley et al. 1982b). At each time of acquisition, the consequences for the fetus or infant are significant, and it is important to identify the factors governing transmission.

3.1.2 Factors Which Influence Transmission of Infection to the Fetus

Risk factors associated with intrauterine infection are not known; however, both primary and recurrent maternal infection can result in infection of the fetus *in utero.* Additionally, *in utero* infection can occur as a consequence of either transplacental or ascending infection.

Factors which influence intrapartum acquisition of infection are, among others: (a) type of maternal infection – namely, primary versus recurrent (Corey 1982; Corey et al. 1983); (b) maternal antibody status (Nahmias et al. 1983; Prober et al. 1987; Yeager et al. 1980; (c) duration of ruptured membranes (Nahmias et al. 1983); and (d) placement of fetal scalp monitor in a woman excreting virus (Kay & Dooling 1981; Parvey & Chien 1980). Primary infection is associated with larger quantities of virus replicating in the genital tract ($> 10^6$ viral particles per 0.2ml of inoculum) and a period of viral excretion which may persist for an average of 3 weeks. In contrast, virus is shed for an average of only 2 to 5 days and at lower concentrations (ap-

proximately 10^3 per 0.2ml of inoculum) in women with recurrent genital infection. Because of both the larger quantity of virus excreted and for a longer period of time, primary infection of the mother is associated with a higher rate of transmission to the fetus.

The mother's HSV antibody status at delivery appears to be an additional factor which can influence the severity of infection as well as the likelihood of acquisition. Transplacental maternal neutralising and ADCC antibodies appear to have a protective, or at least an ameliorative, effect on acquisition of infection for babies inadvertently exposed to virus (Kohl et al. 1989; Nahmias et al. 1983; Prober et al. 1987; Yeager et al. 1980).

Placement of a fetal scalp monitor in women excreting virus has been shown to infect the fetus. Monitor placement in this circumstance should be avoided.

The duration of ruptured membranes has become an indicator of risk for acquisition of neonatal infection. Prolonged rupture of membranes (greater than 6 hours) increases the risk of acquisition of virus, probably the consequence of ascending infection from the cervix (Nahmias et al. 1983; Vontver et al. 1982). Based on this observation, it is recommended that women with active genital lesions at the time of onset of labour be delivered by Caesarean section.

3.2 Pathology

Neonatal HSE, particularly in the setting of disseminated disease, typically diffusely involves the brain – consistent with haematological transmission of virus. Isolated encephalitis, however, may involve the brain focally (Whitley et al. 1982b). Gross examination of the brain frequently reveals encephalomalacia, hydranencephaly or extensive necrosis. Porencephaly, hydranencephaly and multicystic lesions are often sequelae in neonates who survive for several weeks or months. The microscopic appearance is characterised by a mononuclear inflammation, necrosis, haemorrhage and white matter gliosis (Singer 1981).

3.3 Immunity

A number of immune deficiencies in the neonate may make the newborn prone to severe infections (Kohl 1985). Unlike lymphocytes from adults, unstimulated lymphocytes from neonates are permissive for HSV replication, and the neonate to a large degree lacks the adult's macrophage barrier to viral spread. Other differences in the neonate include a delayed T-lymphocyte proliferative response, a defect in natural killer cell activity to HSV, and also less of a lymphocyte response to interferon as well as delayed interferon production.

3.4 Clinical Presentation

The clinical presentation of babies with neonatal HSV infection is a direct reflection of the site and extent of viral replication. Neonatal HSV infection is almost invariably symptomatic and frequently lethal. Although reported cases of asymptomatic infection in the newborn exist, they are most uncommon. Classification of newborns with HSV infection is mandatory for prognostic and therapeutic considerations. At the present time, babies with congenital infection should be identified within 48 to 72 hours following birth. As noted above, there are 3 disease categories, namely those with: (a) disease localised to the skin, eye or mouth; (b) encephalitis with or without skin, eye and/or mouth involvement; and (c) disseminated infection which involves multiple organs, including CNS, lung, liver, adrenals, skin, eye and/or mouth. As with studies of HSE, the NIAID CASG has studied this disease extensively. The presentation and outcome of infection varies by disease category.

3.4.1 Intrauterine Infection

Symptomatic intrauterine infection is apparent at birth, being characterised by skin vesicles or skin scarring, eye disease, and the far more severe manifestations of encephalomalacia or hydranencephaly. Often chorioretinitis alone or in combination with other eye findings, such as keratocon-

junctivitis, is a component of the clinical presentation. Chorioretinitis alone can be a presenting sign and should alert the paediatrician to the possibility of this diagnosis, albeit a less common cause than other congenital infections. The frequency of intrauterine infection is estimated to be between 1 in 100 000 and 1 in 200 000 deliveries (Baldwin et al. 1989).

A small group of children will have skin or eye lesions present at birth. These children are usually born to women who have had prolonged rupture of membranes. The babies have no other findings of invasive multiorgan involvement, specifically there is no chorioretinitis, encephalitis or evidence of other diseased organs.

3.4.2 Disseminated Infection

The principal organs involved with disseminated infection are the liver, CNS, and adrenals; however, infection can involve multiple other organs including the respiratory and gastrointestinal tracts, spleen, kidneys, pancreas and heart. Constitutional signs and symptoms include irritability, seizures, respiratory distress, jaundice, bleeding diatheses, shock, as well as a characteristic vesicular exanthem which is often considered pathognomonic for infection. The vesicular rash, as described below, is particularly important in the diagnosis of HSV infection. However, over 20% of children having disseminated infection will not develop skin vesicles during the course of their illness (Arvin et al. 1982; Whitley et al. 1988). In the absence of skin vesicles, the diagnosis becomes exceedingly difficult since the other clinical signs are often vague and nonspecific, mimicking those of neonatal sepsis. Mortality in the absence of therapy exceeds 80%; all but a few survivors are impaired. 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 utilised to define hepatic enzyme elevation [aspartate and aminotransferase (SGOT) and γ-glutamyl transferase], direct hyperbilirubinaemia, neutropenia, thrombocytopenia, and bleeding diatheses, among others. In addition, chest roentgenograms, abdominal x-rays, EEG and head CT all can be judiciously and serially employed to determine the extent of disease. The radiographic picture of HSV lung disease is characterised by a diffuse, interstitial pattern which progresses to a haemorrhagic pneumonitis. Encephalitis appears to be a common component of disseminated infection, occurring in about 60 to 70% of children. Cerebrospinal fluid examination and deployment of noninvasive neurodiagnostic tests, as defined below, will help assess the extent of brain disease.

3.4.3 Encephalitis

Infection of the CNS alone or in combination with disseminated disease presents with the findings indicative of HSE in the newborn. Brain infection can occur in one of 2 fashions; namely, either as a component of multiorgan disseminated infection or only as encephalitis with or without skin, eye and mouth involvement. Nearly one-third of all babies with neonatal HSV infection have only the encephalitis component of disease. The pathogenesis of these 2 forms of brain infection is likely different. Babies with disseminated infection probably seed the brain by a blood-borne route, resulting in multiple areas of cortical haemorrhagic necrosis. In contrast, babies who present with only encephalitis likely develop brain disease as a consequence of retrograde axonal transmission of virus to the CNS. Two pieces of data support this contention. First, babies with disseminated disease have documented viraemia and are hospitalised earlier in life than those with only encephalitis, 9 to 10 days versus 16 to 17 days. Second, babies with encephalitis are more likely to receive transplacental neutralising antibodies which may allow for only intraneuronal transmission of virus to the brain.

Clinical manifestations of either of the above types of encephalitis include seizures (both focal and generalised), lethargy, irritabillity, tremors, poor feeding, temperature instability, bulging fontanelle and pyramidal tract signs. While babies with disseminated infection often have skin vesicles in as-

sociation with brain infection, the same is not true for the baby with encephalitis alone. This latter group of children may only have skin vesicles in approximately 60% of cases at any time in the disease course (Arvin et al. 1982; Whitley & Hutto 1985; Yeager & Arvin 1984). Cultures of CSF yield virus in 25 to 40% of cases. Anticipated findings on CSF examination include pleocytosis and proteinosis (as high as 500 to 1000 mg/dl). Serial CSF examination provides a useful diagnostic approach as the infected child with brain disease will demonstrate progressive increases in the protein content. The importance of CSF examinations in all infants is underscored by the finding that even subtle changes have been associated with signficant developmental abnormalities. Electroencephalography and CT can be useful in defining the presence of CNS abnormalities (Mizrahi & Tharp 1981). Death occurs in 50% of babies with CNS disease who are not treated. With rare exceptions, survivors are left with neurological impairment (Arvin et al. 1982; Yeager & Arvin 1984).

3.4.4 Skin, Eye and/or Mouth Infection

Infection localised to the skin, eye, and/or mouth is associated with lower mortality, but it is not without significant morbidity. When infection is localised to the skin, discrete vesicles are the hallmark of disease. Clusters of vesicles often appear initially upon the part of the body which was in direct contact with virus during birth. With time, the rash can progress to involve other areas of the body. Vesicles occur in 90% of children. Children with disease localised to the skin, eye, or mouth generally present at about 10 to 11 days of life.

Skin vesicles usually erupt from an erythematous base, being 1 to 2mm in diameter or larger bullous lesions in some cases. Discrete vesicles on various parts of the body are usually encountered but crops and clusters of vesicles have been described. For most of these babies, the vesicular skin rash involves multiple and often distant cutaneous sites; however, a few babies have had infection of the skin limited to 1 or 2 vesicles and no further evidence of cutaneous disease. This group of babies warrants careful evaluation because many have developed encephalitis involvement in the absence of therapy. Another manifestation of skin involvement includes a zosteriform eruption (Musci et al. 1971).

Infection of the eye may manifest as keratoconjunctivitis or, later, chorioretinitis. The eye can be the only site of HSV involvement in the newborn (Whitley & Hutto 1985). These children present with keratoconjunctivitis or evidence of microphthalmia and retinal dysplasia. In the presence of persistent disease and no therapy, chorioretinitis can result, either caused by HSV-1 or HSV-2 (Nahmias & Hagler 1972; Nahmias et al. 1976; Reersted & Hansen 1979). Keratoconjunctivitis even with therapy can progress to chorioretinitis, cataracts and retinal detachment (Cibis & Burde 1971).

Neurological impairment has been encountered in children whose disease appeared localised to the skin, eye and/or mouth. The significant findings include spastic quadriplegia, microcephaly and blindness. Important questions regarding the pathogenesis of delayed onset neurological debility are raised by such clinical observations. Despite normal examinations, neurological impairment became apparent between 6 months and 1 year of life.

3.4.5 Diagnosis

Several aspects relating to the diagnosis of neonatal HSV should be emphasised, some of which have been previoulsy discussed. First, the clinical diagnosis of neonatal HSV infection has become increasingly difficult because of the apparent decrease in the incidence of skin vesicles as an initial component of disease presentation. Second, alternative diagnoses must be excluded, as a variety of infections of the newborn can resemble neonatal HSV infection. Third, virus isolation remains the definitive diagnostic method. In addition to skin vesicles, other sites from which virus may be isolated include the CSF, stool, urine, throat, nasopharynx and conjunctivae. It may also be useful in infants with evidence of hepatitis or other gastrointestinal abnormalities to obtain duodenal aspirates for HSV isolation. Only in 1 to 2% of cases of neonatal HSE will cultures be negative from all of these

sources. If suspicion for HSE is still high when cultures are negative, brain biopsy should be considered. because any positive culture in the neonate is an indication for treatment and since HSV can usually be retrieved, brain biopsy is rarely necessary in the neonate suspected of having HSE.

In contrast to other neonatal infections, serological diagnosis of HSV infection is not of great clinical value. Therapeutic decisions can not await the results of serological studies. Serial antibody assessment may be useful only if a mother without a prior history of HSV infection has a primary infection late in gestation and transfers little or no antibody to the fetus.

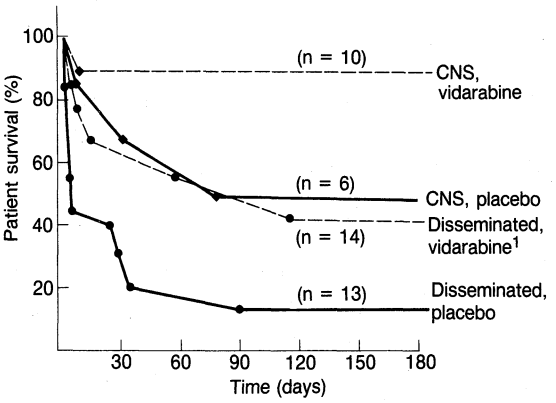

Fig. 6. Survival of vidarabine and placebo recipients according to disease duration. Survival in desseminated disease was significantly ($p = 0.042$) better with vidarabine than with placebo (Whitley et al. 1983).

3.5 Treatment

Of all perinatally acquired infections, the one most likely to be amenable to therapy is that caused by HSV. Since most babies acquire infection at the time of delivery or shortly thereafter, successful antiviral therapy should decrease mortality and improve long term outcome. Inherent in these presumptions is the recognition that diagnosis early after the onset of clinical illness is essential for adequate outcome. Importantly, the possibility of disease progression should weigh heavily in the physician's interpretation of decisions to institute therapy. It has been documented that children presenting with disease localised to the skin, eye and/or mouth can progress to either involvement of the CNS or disseminated infection in approximately 70% of cases (Whitley et al. 1980a). When such events occur, the likelihood of an adequate outcome, even with established drugs, is not optimal, as many of these children will either die or be left with significant neurological impairment.

As with adult HSE, only vidarabine and aciclovir have proven efficacy and acceptable therapeutic indices for the treatment of neonatal HSV infection. The NIAID CASG has evaluated 297 babies with neonatal HSV infection, including 102 with infection of the skin, eye and mouth, 101 with encephalitis, and 94 with disseminated infection. The demographic characteristics and changing disease presentation have been reported (Whitley 1988; Whitley et al. 1980b, 1983, 1966a,b, 1988).

3.5.1 Vidarabine Trials (1973 to 1983)

Vidarabine therapy (15 mg/kg/day for 10 days) of disseminated infection or encephalitis was associated with a decline in mortality rate from 75 to 40%. The lowest mortality rate was achieved in babies with either encephalitis or skin, eye, and mouth infection. As shown in figure 6, the mortality rate was decreased with therapy from 90% in babies with disseminated infection to approximately 70%. For babies with encephalitis, the mortality rate decreased from 50 to 15%. Approximately 30% of surviving children with either encephalitis or disseminated infection were reported as functioning normally at 1 year of age. Finally, with skin, eye and mouth infection, although there were no deaths, severe neurological impairment was decreased from 30% to 10% with therapy. No further decrease in mortality was achieved if the dose of vidarabine was increased to 30 mg/kg/day (Whitley et al. 1983). Nevertheless, the higher dose of vidarabine was associated with a decreased rate of progression to more serious disease.

3.5.2 Vidarabine Versus Aciclovir Trial (1983 to 1987)

The NIAID CASG has completed its evaluation of the relative value of vidarabine versus aciclovir for the treatment of neonatal HSV infection (Whitely et al. 1986a,b). Several aspects are worthy of discussion. First, the overall mortality rate for babies with encephalitis or disseminated infection 1 year after treatment is similar to that found in prior studies of neonatal HSV infection when only vidarabine was employed. There were no differences in either adverse effects or laboratory toxicity (Whitley et al. 1991a,b).

Secondly, regardless of the drug administered, there has been a significant increase in the number of babies who were developing normally. This can be accounted for largely by the changing presentation of babies with neonatal HSV infection. Specifically, over 48% of babies had disease localised to the skin, eye and mouth (Whitley et al. 1986a, b). This represented a 3-fold increase in the number of babies with skin, eye, and mouth involvement from previous studies and historical data ($p < 0.001$). The change in spectrum of disease presentation was related to earlier both diagnosis and intervention with therapy. The number of babies with encephalitis remained constant at approximately 30%, whereas the number of babies with disseminated disease decreased to 20%. The overall mortality rate was 19%.

Thirdly, while therapy was initiated an average of 3 days earlier, the mean duration of disease for all children (irrespective of disease classification) was 4 to 5 days. Thus, therapy can be instituted even earlier in the disease course. This 'window' for administration of treatment is significant if further advances in therapeutic outcome are to be achieved.

3.6 Prevention

There are both possibilities and problems for intervention in the management of pregnant mothers both with and without a history of genital herpes. On one hand, it is accepted practice that mothers with active herpetic lesions be delivered by caesarean section if delivery is within 4 hours of membrane rupture. Caesarean section is of unproven benefit if membranes have been ruptured for more than 4 hours. Nevertheless, infection of the newborn has occurred in spite of delivery by caesarean section, although most mothers (72%) of babies with neonatal herpes have no findings indicative of genital infection.

Current studies are underway to evaluate the benefit of uniform culture screening of mothers at delivery. The use of type specific antibody testing for HSV could reduce the population cultured at delivery. The prophylactic use of aciclovir in women who have a history of genital herpes is another strategy yet to be evaluated. The purpose of culture screening would be to identify those children delivered through an infected birth canal.

Additionally, since up to 30% of babies with neonatal HSV infection have disease caused by HSV-1, efforts to reduce postnatal acquisition must be employed. If family members, hospital personnel, etc., have orolabial or other herpetic infections, current recommendations must involve strict hand washing before touching the infant and, obviously, avoiding all contact the infant may have with lesions. Individuals with herpetic whitlow carry an especially high risk of viral shedding, and these individuals should be removed from the care of the infant if possible.

Though various strategies for prevention of neonatal infection must be instituted, eventual control of HSV infection is most likely to be achieved through vaccination. Several principles should be understood. First, it is unlikely that a vaccine will prevent infection; however, it must ameliorate if not prevent disease and decrease the potential for person-to-person transmission of infection (Corey & Spear 1986). Second, high serum HSV antibody levels do not protect humans from recurrent infection. Third, the presence of viral DNA in live or inactivated vaccines may be undesirable because of the potential oncogenicity of HSV *in vitro,* although this is highly improbable (Corey & Spear 1986). Conversely, live virus vaccines tend to induce more potent and durable hu-

Table IV. Therapies of herpes simplex virus infections of the central nervous system

Drug	Dosage	Duration (days)	Administration (standard IV fluid)	Laboratory toxicity parameters
Herpes simplex encephalitis				
Aciclovir[a]	10 mg/kg/8h IV over 1h	10-14	In approx. 100ml	CBC with differential and platelets BUN and creatinine
Vidarabine	15 mg/kg/day IV over 12h	10-14	At a conc. < 0.5 mg/ml	CBC with differential and platelets AST, ALT, BUN and creatinine
Neonatal herpes simplex virus infection				
Aciclovir[a]	10 mg/kg/8h IV over, 1h	10-14	Approx. 20ml	CBC with differential and platelets BUN and creatinine
Vidarabine	30 mg/kg/day IV over 12h	10-14	At a conc. < 0.5 mg/ml	CBC with differential and platelets AST, ALT, BUN and creatinine

a Treatment of choice.

Abbreviations: IV = intravenous; h = hours; CBC = complete blood count; BUN = blood urea nitrogen; AST = aspartate aminotransferase; ALT = alanine amino transferase.

moral and cellular immune responses (Straus et al. 1985).

Concern with the oncogenicity of viral DNA has prompted the evaluation of viral membrane extracts, envelope antigens, or purified viral proteins for use as vaccines. Recombinant DNA technology enhances the possibility that acceptable viral or subunit vaccines will be developed. For example, appropriate deletions or mutations may abolish the transforming capability of viral DNA, and, furthermore, could also abolish the ability of the virus to establish latency or to be activated from the latent state (Corey & Spear 1986). Genetically engineered deletion mutants of HSV-1 have been shown to induce immunity and protection in animal models, at times without establishing latency (Meignier et al. 1986; Yehiely et al. 1986). One recombinant viral vaccine may offer hope for an acceptable vaccine. Another current thrust is to prepare glycoprotein vaccines utilising recombinant DNA techniques. At least 3 types of recombinant vectors containing and expressing the type gD gene are under study (Straus et al. 1985).

4. Drug Therapy Recommendations (Table IV)

The recommended treatment of choice for HSE is aciclovir at a dosage of 10 mg/kg every 8 hours for a period of 10 to 14 days. It should be remembered, however, that some patients may have evidence of clinical relapse and therefore, may benefit from a more prolonged period of therapy. At present the value of prolonged therapy, namely to 21 days, is totally speculative.

In the management of neonatal HSV, aciclovir is again the treatment of choice. The dosage is the same as that for the management of HSE – 10 mg/kg every 8 hours. The dosage of aciclovir for babies with neonatal HSV infection should be reconstituted in a total volume and administered over a period of 1 hour. In contrast, the dosage for adults should be reconstituted in 100ml of standard intravenous solution and, similarly, administered over a period of 1 hour. The total duration of therapy for neonatal HSV infection is 10 to 14 days.

Continuing research efforts are attempting to define whether extending the period of therapy to 21 days or increasing the dosage as high as 60 mg/kg/day are of value in the management of neonatal HSV infection. The answers to these questions are currently unknown.

Alternatively, vidarabine can be administered in the treatment of either HSE or neonatal HSV infection. For HSE in older individuals, therapeutic outcome is not as acceptable as following the administration of aciclovir, therefore vidarabine must be considered a less than satisfactory alternative to aciclovir therapy. However, in the neonate, the administration of vidarabine is of equal value to aciclovir. The mediating difference between the 2 therapeutics is the ease of administration of aciclovir compared to vidarabine. Thus, the recommendation is for the administration of aciclovir to babies with neonatal HSV infection.

Should questions regarding the development of viral resistance or therapeutic value arise, the dosage of vidarabine in the treatment of HSE is 15 mg/kg/day given as a continuous intravenous infusion over a period of 12 hours in standard intravenous fluid. For babies with neonatal HSV infection the dosage is 30 mg/kg/day, again delivered as a continuous infusion over 12 hours. Duration of therapy for either HSE or neonatal HSV infection is 10 to 14 days.

5. Conclusion

The study of HSV infections of the CNS has evolved from disease descriptions, to carefully controlled studies, to answers for targeted questions. Clearly, treatment of individuals at all ages with these life-threatening and debilitating diseases has led to both improved outcome and quality of life. Nevertheless, the significant mortality and morbidity even in treated patients indicate that improvements in the therapeutic regimens are mandatory. Hopefully, the development of more sensitive and specific noninvasive diagnostic procedures, and, eventually, the development of vaccines to prevent HSV infection will improve the long term outcome.

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