Changing Patterns of Neonatal Herpes Encephalitis and Current Treatment Guidelines

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Herpes simplex virus (HSV) infections are among the most commonly encountered infections in human beings. A pool of 30 million HSV infected patients exist in USA. Two types of HSV infections have been identified HSV-1, which usually causes orolabial disease, and HSV-2, which is associated more frequently with -genital and newborn infections. Usually, HSV causes mild and self-limited disease of the mouth and lips or at genital sites. However, on occasion, the disease can be life threatening. Neonatal herpes infections occur in infants at a mean age of 14 days, but can happen up 10 1`011:- to six weeks after birth. Clinical manifestations of neonatal infection can be localized to the slain, eye or mouth (SEM) or to the central nervous system (CNS), such as encephalitis with or without skin lesions. They can also present as disseminated sepsis. Furthermore, in the immunocompromised host, severe infection has been encountered and is a source of morbidity. Even in the iminunoeompetent host, frequent recurrences, particularly those of the genital tract, can be debilitating. Because HSV does cause genital ulcerative disease, it is associated with an increased risk of acquiring a human immunodeficiency virus infection.

This article will summarize the natural history of neonatal HSV encephalitis and will describe recent developments in neonatal HSV disease management.

Epidemiology

Neonatal herpes simplex virus (HSV) infections may be caused by either herpes sin,piex virus type-I (HSV-1) or frel;pes simplex virus type-2 (HSV-2). In the United States, HSV-2 is responsible for 75% of genital and neonatal infections, while HSV-1 causes the rest. HSV-1 more commonly affects the oropharynx, the eyes and the central nervous system._.'- A pool of 30 million HSV infected patients exist it- USA. With 600,000 new cases occur each year.[3] Sero prevalence has increased steadih from 16.49io (1976-80) to 21.7% (1989-90). It is estimated that 20 to 30% of sexually active adults are seropositive for HSV-%.* The majority of subjects with HSV infections .host likeiv have unrecognized symptomatic infection.'[6] Sixt\- to eivlltv. percent of children with neonatal herpes are boll to :vOmel with no known history of genital herpes.' Arnoas tllc: women who deliver a HSV infected baby only 25° t, - 3,3°,:, are symptorrlatic at delivery and or,!„ _;`/t - 19% have a: history of HST,'°. In the largest epi;iernio!o lcal stad„ o 70i?h? pregnant women approximately':% acquired HSV tth?'illg pregnancy 1 0 Postnatal acquisition o newborn d:Seasc is rare but t? us occurred from :?asp:tat persol?l7el and ofleg. caregivers with orolabial herpes.'" Among the women ;1vho deliver a HSV infected baby only 25-33% are syrlptolnatic at delivery and only 13-19% have a history of HSV in the largest epidemiological Stttdy of 7,000 pregnant women approximately ?% acquired HSV during pregnanc-,•.' recent study has shown that about 3% Of i17Othefs _, o susceptible to acquiring prltuary genltai HSV 4afCatiorr during pregnancy._° Among tl- : s 3º/<„ if the infection iv acquired near the time of iabor, the risk of transn? Ion d=uring birth call reach 5000. A _)regnant ws =hart ,+ id? a primary genital HSV-2 infection who has HSV-1 antibodies in her blood may have partial protection against HSV-2 vertical. transmission (risk of about 2i)`ioi,I yIi)i:hers recurrent episodes of genital HSV have the lowest risk of transmission between 0% to 5%.[2,13] The reported rate of neonatal herpes infection varies in the United States between 20 to 50 cases per 100,000 live births, while in the United Kingdom and Australia it is about two or three cases per 100,000 live births. Seroprevalence of HSV infection is also high in Canadian surveys, [4,5]

Pathophysiology

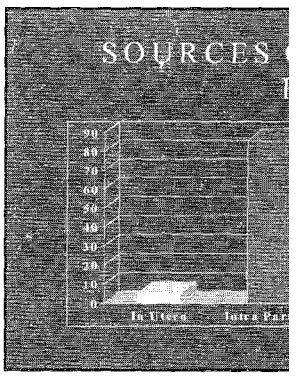
Viral lipid envelope fuses with host cell membrane for infection to occur. It takes up to an hour to gain entry into the host cell, hence interventions like soap or alcohol can prevent the infection during this time. It has been reported that HSV has affinity (tropism) for neural tissues. At the site of cell damage additional cell replication produces vesicles, which contain millions of virions. HSV completes a complete neural arc to produce mucocutaneous lesions. Mature immune system responds within hours to HSV infection. First line of body defense including Natural Killer (NK) cells and interferons are produced in first few days. Antibody production starts at about 5-7 days followed by T memory cells by 2 weeks Even in an irnmunocompetent host first line of defense is incapable to eliminate latent infection in nerve ganglions These viruses reside in nerve ganglions in a latent state for life in the host.

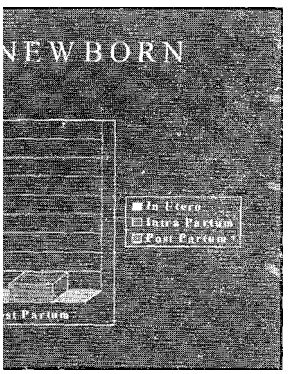
The immune altered neonate

Newborns are relatively immuno suppressed as too active immune system in utero can lead to a graft -Vs- host reaction. They have weak NK and interferon activity hence poor first line defense. If mom is sero positive baby can have some protection, but if infection is too close to birth, there mialit not be sufficient antibodies available to be effective.. Most antibodies cross placenta in last month of pregnancy, hence premature babies are more vulnerable for infections. Newborns can sometimes aspirate HSV from infected birth canal, which can cause Pneumonia, which is an easy access for the vascular compartment.

Sources of newborn HSV

HSV disease of the newborn is acquired in I of 3 time periods: intrauterine, peripartum, or postpartum. Of infants with HSV infection, approximately 85%-88% acquire it in the peripartum period, 10%-12% acquire it postnatally and 3 0-5% acquire it in utero.! 6





Clinical manifestations

HSV Infection can manifest in three forms in a neonate.

SEM disease

Disease is limited to skin. or mucus !ne!nbranes only. 30-40% of patients with neonatal herpes have localized disease. Sites include: skin, mouth and eyes. Usually presents in first two weeks of life (Mean, day 11). Skin lesions are typically papulo vesicular, they often have erythernatous base and pustular appearance (86%). Fever is uncommon (14%). Chest ?Cray, liver function tests (LFTs) and cerebrospinal fluid (CSF) analysis are normal. There is no evidence of CNS or visceral organ involvement. Positive culture or Fluorescein Antibody (FA) usually nnakes diagnosis for HSV.

Prognosis

If left untreated 75% will progress to disseminated or CNS disease. Progression from local infection with skin lesions to CNS or disseminated disease decreases from -70% to 5-20% with early treatment.!?

Disseminated Neonatal Herpes Infection

Disseminated neonatal herpes is the most lethal form of the iesion.Ts Twenty five to 50% of infants with neonatal herpes suffer from this type of neonatal disease. It presents usually at 9-11 days of age, but can also appeal as late as 4 weeks of age. This is a multi System disease involvitiL, Liver (100%), CNS (65%) and lungs (48°%), Adrenals, Kidneys, Spleen and Heart may also be affected. Mortality is still very high (50% - 65%). Symptoms include Sepsis like picture, as Fever. Lethargy and Hypotonia. It can also present as pneumonitis, hepatitis, disseminated intravascular coagulation, with or without encephalitis, exanthem, or kerato-conjunctivitis. Other symptoms include irritability, seizures, respiratory distress, jaundice, bleediriL,.. shock, and a characteristic vesicular rash. Ten to 50G~ o^`. Patients may not develop skin lesions during the course of their illness. 1 Encephalitis is common (,60 to '%5°'b).

Prognosis

Mortality v"ithout treatment is >80%, with treatment 57%'0. AN:orma r!eu=.olcgical status develops at one year in 92% untreated patients and 86⁄6 in treated patients with disseminated disease

Central Nervous S'vstein Herpes in the Neonate

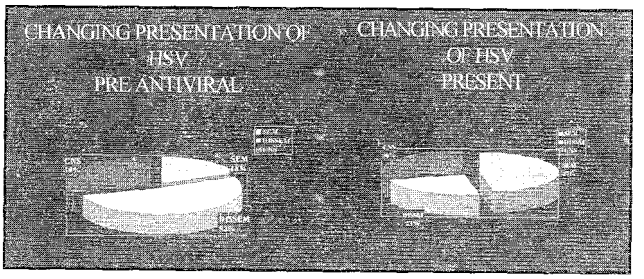
((Herpes c n.^ eph€=la S:

of infants with neonatal herpes (including those witit disseminated/CNS disease).!s It presents in the second to third week of life (Mean. day 1 7). CNS involvement is documented by abnormal CSF results, (Lynphocytic Pleocytosis and Increase in Protein count. positive CSF PCR) or changes in MRI or CT scan of the head, in conjunction with positive surface cultures. Clinical manifestations of encephalitis, either alone or in association

with disseminated disease, include seizures (both focal and generalized), lethargy, irritability, tremors, poor feeding, temperature instability, and bulging fontanelle. Of those infants with CNS disease without visceral dissemination, between 60 ⅟₁ and 70% have associated skin vesicles at any given point in the disease course.

Changing presentation of HSV

Since the introduction of anti viral therapy, the incidence of SEM disease has increased Nvith a decrease in the systemic form of HSV in neonates.



D iagnosis

Diagnosing neonatal herpes infection is more difficult in absence of slain lesions.eb''s Forty percent of infants with HSV encephalitis do not show skin lesions.9 In the presence of skin lesions, other causes of exanthems should be excluded, such as varicella-zoster, enteroviral disease, and disseminated cytornegalovirus. Serologic specimens and other viral cultures should be obtained to exclude toxoplasmosis., rubella and syphilis , 9 On the other hand early diagnosis and prompt treatment are essential to increase the chance of survival and limit disabilities in HSV infections. Scrapings from the base of skin lesions may show multinucleated giant cells, or cells with nuclear inclusions. Identification of virus can be made by isolation in tissue cultures. Vesicular fluid has the highest yield.'-i Ca alginate swabs should not be used for this purpose. Also detection of HSV antigen or DNA allows rapid diagnosis. PCR is especially useful in the detection of HSV in CSF. CT scans and NIRI can demonstrate areas of hemorrhage and calcification. EEG is usually abnormal in CNS disease. Conjugated hyper bilirubinernia, elevated LFT'S and coagulopathy are other features present.

Use of PC'R for Diagnosis

The diagnosis of neonatal HSV infections has been revolutionized by the application of PCR technology to clinical specimens, including CSF'-'- and blood. The reported sensitivity of PCR testing in the diagnosis of CNS disease has ranged from 75 ⅟₁ to 100⅟₁.=, While this broad range can be explained at least in pat, by differences in the methodologies of the individual studies, many of which involved retrospective PCR analysis of stored biologic specimens, the variability in performance of PCR between. laboratories warrants consideration.

Standards to ensure that identical specimens processed in 2 different laboratories will yield identical results are largely nonexistent. ·Without such standards, determination of the sensitivity and specificity of each. laboratory's PCR assay for HSV cannot be accomplished. In addition, the performance of PCR analysis in any laboratory is highly dependent on the manner in which the specimen was collected and maintained before reaching the laboratory. Given these considerations, physicians must interpret PCR test results cautiously. It is mandatory that file test result be correlated with the patient's clinical presentation and disease course before deciding the extent to which it confirms or refutes a diagnosis of HSV disease.

Treatment

During tne past 2 decades, selective and specific inhibitors of f"SV replication have been developed. These agents, acyclovir, valaciclovir, and famciclovir, all accelerate the events of healing and decrease the probability of excreting the virus when they are taKen in a suppressive fashion.

Acyclovir 60 mg/kg/day IV, in three divided doses for 14 to 21 days'-, should be initiated as soon as suspicion of HSV is raised. Any skin lesion suggestive of HSV should be treated promptly as (70⅟/0) untreated SEMI can lead to CNS/DISS disease. If maternal history and phvsicai examination is consistent wit!) primary herpes empirical antiviral therapy is indicated. Therapy should be considered in culture negative sepsis, DIC, thrombocytopenia and lymphocytic pleocytosis in CSF, or newborns bon? to a mother with recurrent HSV and active lesions, or where an infant has skin or scalp rash, especially of vesicular lesions. intravenous acyclovir should be initiated at birth after HSV tests have been obtained in an infant whosc mother has primary genital herpes at the tune of delivery.x

Prognosis

Improvements in morbidity rates followim, disseminated or CNS HSV disease have no, been as dramatic as improvements in mortality. In the early placebo controlled study discussed above., 50⅟₁ of untreated survivors with disseminated disease developed normally at I year of age.'-, With the use of HD ac;~clovir for 21 da'Nlse this percentage increased to 83°/1.'-, Of the untreated patients with CNS disease, 33⅟₁ develop normally at I year of age, while 31 ⅟₁ of patients given HD acyclovir develop normally at 1 year today. While these differences are not dramatic, it is important to note that as more neonates survive HSV disease (based on the mortality data presented above), the total number of patients who **subsequently**

Table. Prognostic factors identified by multivariate analyses for neonates with HSV infection.

	Relative risk	
	Mortality	Morbidity
'total group (N = 202)		
Extent of disease		
S EM	l	l
CNS	3.8*	4.4*
Disseminated	33*	2.t*
Level of consciousness		
Alert or lethargic	i	NS
Semicomatose or comatose	j.2*	NS
DIC	3.8*	NS
Prematurity	3.7*	NS
Virus type		
HSV-1	2.31.	l
HSV 2	l	4.9*
Seizures	NS	3*
infants with disseminated disease (n =46)		
DIC	3.5*	NS
Level of consciousness		
Alert or lethargic	l	I
Semicomatose or comatose	3.9*	4*
I'ncumonia	3.6*	NS
Infants with CNS involvement (n = 71)		
Level of colisclouszess		
Alert or lethargic	i	NS
Semicomatose or comatose	6.1*	NS
prenlattlrit)	5.2'	NS
Seizures	NS	3.4*
lntants with SIAM infection (n = 85)		
Number of skin vesicle recurrences		
.,	N A	l
?'= 3	NA	21*
Virus type		
HSV-I	NA	l
HSV-2	NA	l 4',

HSV, herpes simple; virus; SEM, disease affecting skin, eyes, and/or mouth; NS. not statistically significant (P > .05), DIC, disseminated ilitravasctliar coagulopaYlty. NA. not applicable (no infant evitl~ disease con tined to the stain_ eyes, and/or mouth died).

*P < .01.

'-p < .05.

:, Because of the correlation between virus type and skin vesicle recurrence, virus type was not significant in the nudtivariate model; however, it was significant as a single factor.

develop normally is higher today even while the percentage of survivors with normal development is not dramatically different. Prognostic factors associated with increased risk of morbidity, in addition to category of disease involvement, are listed in the table.

Mortality among patients with CNS disease

Mortality is 50% in untreated and 10~'/n-15c,e treated babies with localized CNS disease. UnfortunateIN large number of survivors have psychomotor retardation. often with: microcephaly, hydranencephaly, porencephalic cysts, spasticilty blindness, or learning disabilities. Abnormal neurological status at one year decreased from 83% to 50% in patients with local CNS disease.

Therapeutic challenges

A recent comparison between 2 periods (1981-19&~ and 1949-1997) spanning 16 years suggests that no progress has been made since 1981 in decreasing the time interval between onset of symntotrs and initiation of antiviral therapy. i' Given the *highly* effective antiviral therapies that currently exist for the management of neonatal HS"., disease, the most ineaningf°ul and immediate manner in which the outcome of neonatal HSV disease can be rapidly altered is to raise awareness of this infection. and by so doing, decrease the time to diagnostic evaluation for neonatal HSV disease and initiation of appropriate antiviral therapy.[24]

While it is not necessary to add acyciovir routinely to standard antibiotic therapy for neonates admitted to role out sepsis, HSV infection should be considered in the differential diagnosis of acutely ill infants younger Churt 1 month. If the presentation is compatible with neonatal HSV disease, appropriate laboratory specimens should be obtained and then acyciovir therapy initiated. This is especially true if the results of the patient's bacterial cultures are negative at 48 to 72 amours acid the neonate has not inioroved clinically.

Management of pregnant women with HSV

All pregnant women with primary active genital HSV disease should undergo Caesarian section (C/S) within 4 hours of ruplire c:= ?yet:~'Jrattes. Controversy exists in case of recurrent HSV at-u treatment with prophylactic acyciovir vs. -'S , y ..:'delivery. Some authorities suggest that oral acyc._ : .~~te DFegnancy with secondary disease is more cos; elective as compared to C'S. Oral acyciovir in pregnancy isas been shoavn to be safe for both mother and newborn. C/S f'or recui-rent Herpes require 386 women with recurrent HSV to Undergo C/S to prevent ONE neonatal infection, also a cost of 1.3 million dollars per neonatal infection and a cost of 3 million dollars per neonatal death prevented.

Prevention

For neonatal HSV infection, prevention is a challenge as it implies prevention of genital herpes simplex infection in adults. Neonatal herpes infection is a rare complication *of* a common infection in mothers, for which there is a treatment but no cure. Although research is underway to develop an effective prophylactic vaccine, more studies need to be done. The best prospect for a vaccine will be to prevent acquisition of primary infection with a potential to reduce the severity, frequency of recurrences, viral shedding and transmission of genital herpes simplex infection"- [5,6] successful counseling of mothers and their sexual partners on the chronic aspects *of* the disease, recurrences, anti-viral therapy, transmission and risk of neonatal infection, safer sex practices, especially during the last trimester *of* pregnancy, and the risk of specific genital sexual practices; the ability to identify women at high risk of acquiring a primary HSV infection and the management of high-risk women and their newbornS, [27]

For comprehensive genital HSV prevention strategies, further research needs to be done to explore: the benefits *of* type-specific serology for screening, in high-risk population and pregnant women, and for diagnosis.

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