



MARCH 2009: VOLUME 6, NUMBER 7

Update on Neonatal Herpes Simplex Virus Infections



In this Issue...

Herpes simplex virus (HSV) infections in neonates have been recognized for nearly 75 years. However, neonatologists and other pediatricians struggle to accurately diagnose and manage neonatal HSV disease. The vesicular rash characteristic of HSV infections may not be present in an infected neonate. The absence of this important diagnostic finding may hamper clinicians' efforts to distinguish this disease from other disorders (eg, bacterial sepsis, inborn errors of metabolism) that present in the neonatal period with signs and symptoms of multi-organ failure or encephalopathy. The sequelae of severe neonatal HSV infections are devastating, however, as they involve significant neurologic morbidities that can impair long-term functioning and survival.

In this issue, the problems associated with identifying both the baseline incidence of neonatal HSV in the United States, and specific signs and symptoms that distinguish this disease from other neonatal infections will be examined. The neuroradiographic and neurodevelopmental complications of neonatal HSV infections, particularly a newer imaging technique (diffusion-weighted magnetic resonance imaging [DW-MRI]) that may provide further insight into the central nervous system (CNS) damage caused by HSV, will be reviewed.

Program Information

- [CE Info](#)
- [Accreditation](#)
- [Credit Designations](#)
- [Intended Audience](#)
- [Learning Objectives](#)
- [Internet CME/CNE Policy](#)
- [Faculty Disclosure](#)
- [Disclaimer Statement](#)

Length of Activity

1.0 hour Physicians
1 contact hour Nurses

Release Date

March 26, 2009

Expiration Date

March 24, 2011

Next Issue

April 16, 2009

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At the conclusion of this activity, participants should be able to:

- Describe the difficulties involved in ascertaining the annual incidence of neonatal herpes simplex (HSV) infections in the United States
- Discuss novel maternal and neonatal characteristics, signs, and symptoms that potentially identify infants with HSV infections in the absence of dermatologic findings
- Review neuroimaging findings in, and neurodevelopmental sequelae of, neonatal HSV central nervous system infections

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- **Mary Terhaar, DNSc, RN** has indicated no financial relationship with any commercial supporters.
- **Anthony Bilenki, MA, RRT** has indicated no financial relationship with any commercial supporters.

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THIS ISSUE

- [IN THIS ISSUE](#)
- [COMMENTARY](#) from our [Guest Authors](#)
- [INCIDENCE AND PREVALENCE OF NEONATAL HSV INFECTIONS](#)

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■ [MATERNAL AND INFANT CHARACTERISTICS ASSOCIATED WITH HSV INFECTIONS](#)

■ [COMPARISON OF IMAGING MODALITIES IN NEONATAL HSV ENCEPHALITIS](#)

■ [NEUROPSYCHOLOGIC OUTCOMES IN CHILDREN WITH NEONATAL HERPES ENCEPHALITIS](#)

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In this audio interview Dr. Golden discusses why a diagnosis of neonatal HSV can be so difficult, how these patients present, and if there are any special considerations for premature infants. Dr. Golden then looks at this information in the context of several case studies.

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COMMENTARY

In 2001, Kimberlin and colleagues¹ compared the diagnosis and management of neonates with HSV infections during 2 time periods in the “acyclovir era.” These researchers from the National Institute of Allergy and Infectious Diseases (NIAID) Collaborative Antiviral Study Group (CASG) concluded that no progress had been made (from 1981 to 1988 and from 1989 to 1997) in reducing the interval between onset of HSV symptoms and administration of antiviral therapy.¹ They further maintained that appreciation by pediatricians of the significance of neonatal HSV infections and application of available diagnostic and therapeutic modalities, such as polymerase chain reaction (PCR) and use of high-dose acyclovir (60 mg/kg/day), represented the only available means of reducing infection-associated morbidity and mortality. Although the techniques for viral detection and strategies for management of primary and recurrent HSV infection continue to evolve, clinicians still fail to include HSV in the differential diagnosis of the ill neonate, as demonstrated in a small survey of British pediatricians in 2004.² Thus, HSV infections still remain an underappreciated cause of neonatal disease.

The characteristics of neonatal HSV infections have been further delineated since their initial descriptions by Batignani³ and Hass⁴ in the mid-1930s. The classifications of infection (based on the CASG-derived system) are disseminated disease (25% of all cases⁶) involving the liver, respiratory tract, adrenal glands, and CNS, isolated HSV CNS disease (nearly 30% of all cases⁶), and infection localized to the skin, eye, and/or mucous membranes (SEM disease, approximately 45% of all cases).⁶ Morbidity and mortality from neonatal HSV infections can be predicted based on this classification scheme.⁷ Most infections present between 1 and 3 weeks of age, with HSV encephalitis presenting later (average, 16 to 19 days of age) than SEM or disseminated disease (10 to 12 days of age).^{1,8} Infants with disseminated disease have higher rates of mortality¹ but have demonstrated the most dramatic improvement in survival with the evolution of antiviral therapy, with a reduction in mortality from 85% (no acyclovir therapy) to 29% (high-dose acyclovir).^{6,9} Furthermore, some infants with SEM disease manifest evidence of CNS infection (as detected by retrospective PCR analysis¹⁰), suggesting a continuum of the 3 disease types mediated by maternal and neonatal factors.

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Despite the definition of the clinical entity, incidence data on neonatal HSV infections in the United States are not uniform, making it difficult for clinicians to recognize the frequency of the disease. The best data evolved from a large prospective analysis of nearly 60,000 live births at 7 hospitals in the Seattle area, revealing an estimated incidence of neonatal HSV of 1 in 3200 live births¹¹. With approximately 4 million live births annually in the United States, this estimate translates into 1500 HSV cases per year. However, this number may be misleading. As noted in their retrospective analysis summarized in this newsletter, Xu and associates maintain that the higher incidence of neonatal HSV disease in their Northwest cohort (the states of Washington and Oregon) relative to their California cohort may be due to a greater number of non-Hispanic white residents, who are more likely to be seronegative for HSV.^{12,13} Primary maternal HSV infection in pregnancy is a known risk factor for vertical transmission and neonatal infection.^{6,14} Thus, data from the prospective trial may reflect numbers of neonatal HSV cases in an at-risk population, resulting in an overestimation of the national incidence. Further attempts at prospective incidence determination are currently limited, since as of January 2008, only 8 US states and New York City have mandated the reporting of neonatal herpes infections to public health authorities (as noted in the Whitley et al. article reviewed herein and by others).¹⁵

Retrospective determination of neonatal HSV incidence has remained equally difficult. Three articles discussed in this review analyzed archived clinical and laboratory databases to identify the incidence/prevalence of neonatal HSV infections. In addition to known problems with disease documentation using retrospective analysis (ie, incorrect coding, missing laboratory or clinical data), several other problems with documentation of neonatal HSV infections were highlighted. Most importantly, as noted by Whitley and coworkers in this issue, no specific ICD-9 code exists for neonatal HSV infections. The studies by Xu et al. and Whitley et al. (discussed herein) relied on a combination of billing codes for all HSV infections (0.54.xx series) and nonspecific HSV-associated diagnoses (encephalitis, viremia) to screen for and identify cases, although as noted by Xu and coworkers, the positive predictive value of the 2 most commonly used codes was low. These studies calculated a higher (Whitley et al.) or lower (Xu et al.) incidence compared with the aforementioned prospective analysis.¹¹ Xu and collaborators attributed these discrepancies to differences in study methodology (prospective vs retrospective), the previously mentioned population differences in HSV seroprevalence,^{12,13} and other maternal and neonatal factors. Finally, prevalence data from the single-center study by Caviness and associates were complicated by limited viral analysis performed in the infants evaluated.

An equally prominent barrier to the diagnosis of neonatal HSV infections is the paucity of disease-specific symptoms in the newborn in the absence of dermatologic findings. Of neonates with HSV infections, approximately 70% of mothers¹⁶ have no history of genital HSV disease. In the NIAID natural history study,¹ no single set of signs and symptoms identified all newborns with HSV infections, and only 61% of all neonates with disseminated disease (who often present with nonspecific signs/symptoms of illness) developed skin lesions before, during, or after study enrollment. In an older study, fever was reported at equal rates in neonatal HSV and bacterial infections.¹⁷ However, in the aforementioned article by Caviness and colleagues reviewed herein, neonates with HSV infections were less likely than those with bacterial infections to be febrile at presentation. In an additional article by Caviness and coworkers, reviewed in this issue, the authors identified 3 independent risk factors (1 maternal, 2 neonatal) associated with HSV infection in infants without a rash. However, the small number of cases over the study period weakened the statistical strength of these factors, thus limiting the applicability of these characteristics alone or in combination in rendering a diagnosis of neonatal HSV infection.

Despite these epidemiologic and diagnostic limitations, recent investigations into the diagnosis and outcomes of neonates with HSV CNS infections have provided important information for clinicians. Morbidity in cases of neonatal HSV encephalitis has not improved even with the introduction of high-dose acyclovir.¹⁸ The sobering reality of complications of neonatal HSV CNS disease is well reflected in the study by Engman and coworkers, reviewed in this newsletter, who comprehensively describe the neuropsychologic deficits observed in their small cohort. This study, and the work by

Vossough and colleagues, also document the limitations of routine computerized tomography (CT) in the diagnosis and prognosis of HSV infections. The data from the Vossough study also demonstrates that DW-MRI, which identifies tissue abnormalities based on the diffusion of water molecules, may identify CNS injury in the neonate that is routinely missed by CT or conventional MRI. Thus, routine DW-MRI imaging, coupled with accurate PCR analysis of the cerebrospinal fluid (CSF), may identify cases of neonatal HSV before the results of viral cultures are available, allowing for rapid case identification and immediate, appropriate management.

In conclusion, neonatal HSV infections must be considered in any infant with signs and symptoms of systemic organ failure or encephalopathy in the presence or absence of a rash. A key point to recognize is the small total numbers of cases included in most studies of the disease. Thus, a national reporting system is urgently needed to identify all potential cases of neonatal herpes infections, facilitating better understanding of the pathogenesis and diagnostic/prognostic factors of the illness. Whitley et al. (in the article reviewed herein) and others¹⁹ have previously proposed such reporting of neonatal herpes. Until then, neonatologists and other clinicians must maintain continued vigilance for HSV disease in neonates, using physical examination findings, available laboratory and diagnostic imaging tests, and a high index of suspicion.

Commentary References

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INCIDENCE AND PREVALENCE OF NEONATAL HSV INFECTIONS

Whitley R, Davis EA, Suppapanya N. **Incidence of neonatal herpes simplex virus infections in a managed-care population.** *Sex Transm Dis.* 2007;34(9):704-708.

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Xu F, Gee JM, Naleway A, Zangwill KM, Ackerson B, Eriksen E, et al. **Incidence of neonatal herpes simplex virus infections in two managed care organizations: implications for surveillance.** *Sex Transm Dis.* 2008;35(6):592-598.

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Caviness AC, Demmler GJ, Almendarez Y, Selwyn BJ. **The prevalence of neonatal herpes simplex virus infection compared with serious bacterial illness in hospitalized neonates.** *J Pediatr.* 2008;153(2):164-169.

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Whitley and colleagues sought to determine the incidence of possible neonatal herpes infections over a 5½-year period in a large managed care population representing 7 United States census regions (predominately in the mid-Atlantic and Northeast). The investigators conducted a retrospective cohort analysis on medical and pharmacy claims, using International Classification of Diseases, 9th Edition (ICD-9) codes for herpes infections or other conditions (unspecified viremia, other congenital infections, defibrination syndrome, or dermatologic findings) suggestive of HSV infection.

Among 233,487 infants born in the study period, 178 were given an ICD-9 code at <30 days of age that indicated the possible presence of neonatal HSV, yielding an incidence of 0.08% (or 1 in 1312 live births). The most common ICD-9 codes used in infants diagnosed with presumed neonatal HSV were 771.2 (other congenital infection), 054.9 (herpes simplex without mention of complication), 790.8 (viremia, unspecified), and 695.1 (erythema multiforme). Among the identified infants, 26 (15%) of the mothers had a history of HSV, with 13 (7%) receiving antiviral medication in pregnancy, and 7 (4%) receiving medication and undergoing a cesarean section at delivery. Similar percentages were noted in infants <90 days of age.

The authors concluded that the incidence of neonatal HSV is higher than previously reported. While acknowledging the potential overdocumentation or underdocumentation of cases (based on diagnostic codes used), they emphasized that these findings are reported during a period of high genital herpes prevalence in the United States. The researchers further recommended the reporting of neonatal herpes infections, the

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documentation of maternal HSV status, and the treatment of at-risk mothers as measures with the potential to curtail the incidence of neonatal HSV disease.

Xu and associates sought to determine the incidence of neonatal herpes infections and to assess the utility of surveillance methods for neonatal herpes in 2 regions (Oregon/Washington and southern California) of a managed care plan in the United States. A standardized medical chart review was conducted over a 5-year period. Cases were identified using the standard ICD-9 codes for herpes (0.54.xx) and other congenital infections (771.2), as well as 13 other codes for meningitis/encephalitis (viral or nonspecific), cutaneous or neurologic signs/symptoms associated with herpes, and diseases presenting in a similar fashion to disseminated herpes. Of 270,703 neonates born in both cohorts studied in the time frame, 737 potential cases were identified by ICD-9 data, with 95% of the patients' charts subsequently reviewed.

The group identified 24 recorded cases (incidence of 8.9 cases per 100,000 live births) using a standard definition for a confirmed neonatal HSV infection (a neonate with signs/symptoms of HSV and a positive culture, PCR, or direct fluorescent antibody [DFA] test for HSV). When probable cases (neonates with signs/symptoms of HSV, but a negative or absent HSV-specific laboratory test) were included, the incidence increased to 12.9 per 100,000 live births (35 total cases). The incidence (using total cases) was greater in the Northwestern US cohort than in the California cohort. The discharge ICD-9 codes 054.xx or 771.2 identified 31 of the 35 total cases, with the herpes codes shown to be more sensitive identifiers than the congenital infection code and with a low positive predictive value for both codes.

The authors aptly recognized differences in HSV incidence between their work and prior studies. The prospective study by Brown and coworkers yielded an incidence of 31 cases per 100,000 live births, whereas the Whitley paper (described above) calculated an incidence of 76 cases per 100,000 live births. Xu and colleagues noted that the differences may be due to methodology or variation in maternal HSV seroprevalence among the populations studied. They also emphasized the need for strategies for national surveillance for neonatal herpes in order to reduce morbidity and mortality.

Caviness and associates sought to determine the prevalence of HSV infection (relative to other viral infections and serious bacterial infections [SBIs]) in neonates admitted to a tertiary-care children's hospital from the emergency department (ED). This 5-year retrospective study identified 5817 neonates (median age, 15 days; median length of stay, 3 days). Infected infants were identified based on positive HSV testing (culture, PCR, DFA) and medical record review (for HSV infections), viral testing (for non-HSV viral infections), or culture and medical record review (for SBIs).

Non-HSV viral infections were the most common type of infection (8.4% of neonates), followed by SBIs (4.6%) and HSV infections (0.2%). Neonatal HSV infections were most prevalent in the second week of life (0.6%) and less likely in febrile (temperature $>38.0^{\circ}\text{C}$) infants (0.3%, vs 16.9% for non-HSV viral infections and 14.3% for SBIs). Febrile HSV-infected infants were more likely to present with a mononuclear CSF pleocytosis. Additionally, HSV infection was as statistically prevalent (0.2%) as bacterial meningitis (0.4%). Of the 6 confirmed cases who presented with a chief complaint of rash, 5 had a confirmed vesicular rash in the ED.

This study indicates that the prevalence of HSV does not differ statistically from that of bacterial meningitis but is lower than that of all SBIs (4.6%). The authors acknowledged that the prevalence may be underestimated due to a lack of prospective testing (<30% of all infants had viral cultures performed) and the absence of laboratory testing from outside hospitals. However, they suggested that HSV infection should be considered in the differential diagnosis of neonates being evaluated for SBIs or presenting with a vesicular rash or "sepsis-like" syndrome in the second week of life.

One underlying theme in all these studies is the lack of documentation of neonatal HSV disease. As a result, retrospective analysis may overestimate or underestimate the incidence/prevalence of disease, based on insufficient laboratory testing in at-risk neonates, inadequate coding that documents a diagnosis of neonatal HSV disease, and other maternal and neonatal factors. The comparable prevalence of neonatal HSV infections and bacterial meningitis, as determined by Caviness and colleagues, indicates

that clinicians must maintain a high index of suspicion for herpes infections in this patient population. Inclusion of testing for HSV infection in the evaluation of any ill neonate may lead to better identification of disease risk factors and improved outcomes with early therapy.

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MATERNAL AND INFANT CHARACTERISTICS ASSOCIATED WITH HSV INFECTIONS

Caviness AC, Demmler GJ, Selwyn BJ. **Clinical and laboratory features of neonatal herpes simplex virus infection: a case-control study**. *Pediatr Infect Dis J*. 2008;27(5):425-430.

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Caviness and colleagues conducted a retrospective case-control study of neonates with and without HSV infection admitted to an urban tertiary-care children's hospital over a 14-year period. The authors sought to identify independent features of neonatal herpes infections, as well as characteristics associated with HSV infection in neonates without vesicular rash.

Of neonates admitted to the hospital via the ED or transferred from another facility, 6559 had at least one in-house laboratory test (PCR, antigen detection, or culture) that could have identified HSV infection. After review of laboratory and medical records, 40 infants were identified as HSV cases (based on a positive test) and were categorized based on NIAID criteria as having SEM, CNS, or disseminated disease. Four neonates admitted for nonsurgical reasons with a negative HSV test (2 presenting within 2 weeks prior to the case, 2 presenting within 2 weeks after the case) were matched to each HSV-infected infant.

The study verified the traditional characteristics associated with neonatal HSV infection, including maternal primary HSV infection, prematurity, cutaneous rash, seizures, lethargy, hypothermia, elevated hepatic enzymes, CSF pleocytosis, respiratory distress, and thrombocytopenia.¹⁻⁹ Delivery by cesarean section was protective but did not reach statistical significance. Additionally, multivariate analysis (adjusting for delivery method, prematurity, and post-gestational age) demonstrated that maternal fever, respiratory distress requiring mechanical ventilation, and CSF pleocytosis were associated with neonatal HSV infection in infants without a vesicular rash. However, the sensitivity of each of these 3 individual factors for diagnosing neonatal HSV was low (maternal fever, 42.9%; mechanical ventilation, 47.6%; CSF pleocytosis, 63.6%), likely due to the small sample size. Factors not associated with neonatal HSV infection included neonatal fever, total peripheral white blood cell count, and red blood cells in the CSF.

The authors emphasized that maternal fever may be a marker for occult primary HSV infection, a known risk factor for neonatal HSV infection. They further claimed that neonatal fever and red blood cells in the CSF are not helpful in identifying patients with HSV infection. Finally, they highlighted the applicability of the data to all patients admitted to tertiary-care centers, and the potential use of respiratory distress, maternal fever, and thrombocytopenia as additional criteria for identifying patients with neonatal HSV infections.

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COMPARISON OF IMAGING MODALITIES IN NEONATAL HSV ENCEPHALITIS

Vossough A, Zimmerman RA, Bilaniuk LT, Schwartz EM. **Imaging findings of neonatal herpes simplex virus type 2 encephalitis.** *Neuroradiology*. 2008;50(4):355-366.

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Vossough and colleagues assessed the computed tomography (CT) and magnetic resonance imaging (MRI) findings in neonatal HSV-2 encephalitis. In this retrospective analysis over an 8-year period, 12 infants (8 female, 4 male) with HSV documented by enzyme-linked immunosorbent assay (ELISA), culture, immunoglobulin titers, or PCR were identified. Of those evaluated, 1 patient had a congenital infection and 1 had recurrent disease at 3 months of age; the remaining infants presented with symptoms of disease between 8 and 42 days of age. Among those studied, 1 infant had disseminated HSV infection; the remainder had HSV CNS disease alone. Only 2 infants had a maternal history of HSV in pregnancy or at delivery. In addition, only 2 neonates had a vesicular rash suggestive of herpes.

All patients underwent non-contrast CT scans (first study in 11 of 12 patients) and MRI imaging (sagittal and axial T1, axial and coronal FLAIR and T2, gadolinium-enhanced T1), with an initial imaging study performed within 48 hours of presentation. Diffusion-weighted MRI (DW-MRI) was performed in 10 of the 12 patients. The CT images were reviewed for areas of hypoattenuation or hyperattenuation, and to identify calcifications and hemorrhages. MR images were reviewed for T1 and T2 signal abnormalities, including the presence of hemorrhage or calcification, the presence of contrast enhancement, and areas of restricted diffusion. The authors (who were all radiologists) were unblinded to the findings of other imaging examinations in the same patient.

Of the 12 infants evaluated, 8 (67%) had multifocal CNS disease and the remaining 4 (33%) demonstrated disease localized to the temporal lobes or brainstem. A total of 8

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patients had temporal lobe involvement, 8 showed some degree of hemorrhage, and 7 had deep gray matter injury. Conventional MRI showed more extensive abnormalities than CT scan in 9 of 11 patients. Additionally, 7 of 10 patients who underwent DW-MRI had new lesions or more extensive damage detected (relative to conventional MRI or CT scan). Furthermore, 4 patients had restricted diffusion and infarcts in watershed areas remote from the site of infection. Follow-up imaging demonstrated encephalomalacia, infarctions, calcifications, and cystic changes. Per chart review, none of the infants experienced a hypotensive or hypoxemic event in the acute stages of disease.

The authors point out the findings of neonatal HSV disease on CT scans (early white matter hypointensity, gyriform cortical hyperdensities or enhancement) and MRIs (T1 hypointensities, T2 hyperintensities, loss of gray-white matter differentiation, leucomalacia). As the higher water content of the neonatal brain may limit the differentiation of infected vs normal brain on conventional MRI, the researchers also indicate that DW-MRI may better detect abnormalities. According to the authors, the use of DW-MRI revealed early changes in the damaged brains of their cohort before any changes were detected by CT or conventional MRI. However, they admit that DW-MRI did not provide any additional data in approximately one-third of their patients. They also describe the pathologic basis of findings of hemorrhage, temporal and frontal lobe involvement, and deep gray matter injury seen in HSV encephalitis in their cohort, which contrasts with data from prior studies. Finally, the authors emphasize that their manuscript is the largest case series reported in the imaging literature, but that the frequency and types of lesions may differ in larger studies.

NEUROPSYCHOLOGIC OUTCOMES IN CHILDREN WITH NEONATAL HERPES ENCEPHALITIS

Engman ML, Adolfsen I, Lewensohn-Fuchs I, Forsgren M, Mosskin M, Malm G. **Neuropsychologic outcomes in children with neonatal herpes encephalitis.** *Pediatr Neurol.* 2008;38(6):398-405.

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Engman and colleagues examined the neuropsychologic profiles of a cohort of Swedish children with a history of neonatal herpes central nervous system (CNS) infections. Over a 12-year period, 19 of 267,690 infants born in metropolitan Stockholm were diagnosed with neonatal HSV infections (documented by virologic testing). Of this group, 9 patients (between the ages of 2.5 and 13 years at study enrollment) were evaluated in childhood. As infants, 7 of these children had had HSV disease limited to the CNS, and 2 had had disseminated neonatal HSV disease, including CNS involvement. Two children were born to mothers with primary HSV infections; 2 children were born prematurely (at 29 and 36 weeks' gestation, respectively). Of the children examined, 7 presented with seizures in the neonatal period. All but 1 child had a positive HSV PCR of the CSF in the neonatal period. A total of 6 neonates had a documented positive HSV PCR at the time of infection, whereas 2 had positive results documented only by retrospective analysis of stored CSF. One infant had a positive PCR at diagnosis and upon retrospective analysis. Of the 9 infants evaluated, 8 had cerebral palsy, as classified by the Surveillance of Cerebral Palsy in Europe. A majority of the children had been placed on prophylactic acyclovir therapy for at least 6 months.

The children underwent a battery of neuropsychologic assessments matched to his or her developmental level and ability to cooperate. Components of the Griffiths Mental Development Scales I and II (Hearing and Speech, Eye and Hand Coordination, Performance, Practical Reasoning), the Wechsler Intelligence Scale for Children (Verbal and Performance Intelligence Quotient), and the Snijders-Oomen Non-Verbal Intelligence Test were used in assessments. Standardized tests were used for the assessment of memory and executive function. Expressive language, concentration, social skills, and

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well-being of the children were evaluated by clinical observations of the investigators, as well as by interviews with parents and school staff.

Results of the study demonstrated that only 2 of the 9 children tested had average intellectual ability (IQ 85 to 115), with 5 of the 9 children diagnosed as mentally retarded. One child had a recurrence of HSV CNS disease, with a profound loss of abilities between his second and fifth birthdays. Major deficits in attention (7 of 9 children) and expressive speech (8 of 9 infants) were also noted. However, social interaction was affected in only 2 children. Of the 9 children evaluated, 2 had a decreased level of well-being. A total of 4 of the 9 children attended special schools/preschools; of the remaining 5 children, 4 required extra support in the classroom. Four additional children identified originally but refusing neuropsychologic assessment were also discussed in the study, with 75% of them having cerebral palsy and 1 requiring extra educational support in a regular classroom.

Of the children completing neuropsychiatric testing, 8 had imaging performed between 7 and 28 days after the onset of illness (7 CT, 1 MRI). The neuroradiologic findings in these infants showed bilateral cerebral involvement, with one side more severely affected and with preferential frontal and parietal lobe involvement. Of children with follow-up imaging after 28 days from onset of illness, 5 of 6 had progression of the lesions. Furthermore, the degree of cerebral damage visualized by the initial CT scan did not correlate with neurodevelopmental outcomes.

The authors concluded that HSV CNS infections in neonates are associated with significant neurodevelopmental handicaps. To mitigate the complications of neonatal HSV CNS disease, they encourage neuropsychologic testing to identify deficiencies and provide external interventions/adaptations in affected children. They also encourage the investigation of other modalities (MRI or DW-MRI, acyclovir prophylaxis) and improved vigilance by clinicians, especially in infants with neonatal seizures, in order to prevent or minimize neonatal HSV CNS infections.

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