

Neonatal Herpes Simplex Virus Infections in Israel

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Background: The incidence and the clinical characteristics of neonatal herpes simplex virus (NHSV) infection in Israel are unknown.

Methods: We reviewed the medical records of NHSV cases who were born between January 2001 and December 2007 in 5 medical centers located in central Israel. Cases were identified using International Classification of Diseases, 9th revision codes. In addition, parents of survivors were interviewed by telephone.

Results: In the 8-year study period, 22 cases of NHSV were identified (an incidence rate of 8.4 per 100,000 live births). Most patients (77.2%, 17 cases) manifested as skin, eye and/or mouth infection, 13.6% (3 cases) as localized central nervous system disease and 9.1% (2 cases) as disseminated disease. Most (76.4%) herpes viruses typed in our series were HSV-1. None of the mothers had documented intrapartum visible genital HSV lesions or a previous history of genital herpes. Ritual circumcision was the source of HSV-1 transmission in 7 infants (31.8% of cases).

Conclusions: The incidence of NHSV infection in Israel was found to be similar to the lower part of the scale reported in the United States, however higher than the incidence reported in Canada or in Europe. Similar to more recent reports, our series demonstrates the shift toward the predominance of HSV-1 in NHSV infection. In addition, none of the mothers in our series had a previous history of genital herpes. This study emphasizes the need for awareness of HSV infection in Israeli neonates.

Key Words: neonatal, herpes simplex virus, incidence

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Herpes simplex virus (HSV) infection can cause devastating disease in the newborn. Most (85%) neonatal HSV (NHSV) infections result from vertical transmission from mother to neonate at delivery.¹ Intrauterine infection occurs rarely, and approximately 10% of neonatal HSV infections are acquired postnatally.² One route of postnatal transmission, which is particularly relevant in Israel, occurs during ritual orthodox circumcision which involves sucking the wound with the mouth.³ HSV-2 has been reported to account for most NHSV cases, whereas HSV-1 seems to cause 30–50% of NHSV infections.⁴ NHSV may be classified into 3 main patterns which are important predictors of the outcome and occur with roughly equal frequency. Clinical presentation with only localized skin, eye and/or mouth (SEM) lesions is associated with an excellent prognosis when treated promptly and appropriately. However, up to 70% of infants with SEM disease will progress to the more severe forms of either central nervous system (CNS) or disseminated disease without

appropriate treatment.⁵ Intravenous acyclovir has reduced mortality from 85% to 31% among infants with disseminated disease and from 50% to 6% among infants with CNS disease.^{4–7}

The reported incidence of NHSV from several countries around the world varies widely between 1.6 and 60 per 100,000 live births.^{8–15} Some of the reasons for the differences in incidence among countries are due to difficulties in diagnosing maternal and neonatal herpes and variability in sexual behavior and in rates of maternal genital HSV infection.¹⁶ NHSV infection is not defined as a reportable disease in Israel, and its incidence and clinical characteristics are unknown. Data on the national incidence of NHSV infection, its outcome and morbidity and maternal and infant risk determinants are essential for adequate management of this serious infection in Israel.

The main objectives of this study were to estimate the incidence of NHSV during an 8-year period in central Israel, to describe the clinical spectrum of disease presentation and to assess adherence to clinical management guidelines.

MATERIALS AND METHODS

We reviewed the medical records of infants younger than 30 days of age who were born between January 2001 and December 2007 in 5 medical centers located in central Israel. In order to include all cases of NHSV infections, we used the following International Classification of Diseases, 9th revision codes for neonatal herpes: 771.2 (other congenital infections including congenital herpes simplex, listeriosis, malaria, toxoplasmosis and tuberculosis) and 054 (herpes simplex). Case definition included: any infant who presented with signs, symptoms and findings compatible with neonatal herpes and had an HSV-positive culture or polymerase chain reaction from vesicles, mucosal sites, cerebrospinal fluid or blood. Classification of cases as SEM, disseminated or CNS disease were determined according to the relevant organ involvement.

The study included all the hospitals in central Israel, and therefore we assumed that infants who were born in these hospitals will most likely be hospitalized later in 1 of these hospitals. Incidence rate of neonatal herpes was calculated by dividing the number of cases by the number of live births in the participating medical centers during the study period. Data regarding the number of live births were retrieved from the Israeli Ministry of Health registry.

Relevant demographic, clinical and outcome data were collected from the medical records. In addition, the parents of survivors were interviewed by telephone regarding recurrent outbreaks of herpes after the neonatal period, the child's long-term outcome and also regarding previous maternal history of genital herpes. The study was approved by the Ethical Committees of the participating Medical Centers.

RESULTS

Incidence

Twenty-two cases of neonatal HSV were identified from January 2001 until the end of 2007. A total number of 261,488 infants were born at the 5 participating medical centers during the 8-year study period. These figures yield an incidence rate of 8.4 per 100,000 live births.

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Maternal Demographic and Clinical Data

Maternal median age was 27 years (range 18–34 years) at delivery with most mothers (75%) being older than 25 years. None of the mothers had documented intrapartum visible genital HSV lesions. There was explicit exclusion of HSV genital lesions during delivery in the medical chart (8 cases) and by the mothers during telephone interviews (an additional 11 cases). None of the mothers in our series had past history of genital herpes.

Twelve infants (54.5%) were born after spontaneous vaginal delivery, whereas 8 infants were delivered with vacuum extraction and 2 infants (10%) by cesarean section. Birth complications included prolonged premature rupture of membranes (2 cases) and maternal fever (4 cases).

Neonatal Clinical Data

The clinical characteristics of infants with NHSV and their treatment are shown in Table 1. Most patients (77.2%, 17 cases) manifested as SEM infection, 13.6% (3 cases) as localized CNS disease and 9.1% (2 cases) as disseminated disease.

Five of the 22 cases presented with scalp vesicles within the first day of life but with no systemic involvement, and all of them were born after vacuum-assisted birth (patients no. 11, 12, 14, 15 and 16 in Table 1). Because HSV was recovered from scalp vesicles and not from intact skin, they were considered as SEM presentation. None of the infants had scalp electrodes during delivery.

All of the cases, except for 1 with disseminated disease, also had SEM involvement. NHSV diagnosis was confirmed by culture in 95.4% of the cases and by polymerase chain reaction alone in only 1 case. Thirteen neonates had HSV-1 disease, 4 neonates had HSV-2 disease and the viral type was unknown in 5 infants. Signs of infection appeared at the median age of 5.5 days (range 1–19 days). Fourteen infants (63.6%) presented with signs of infection within the first 1 week of life, whereas 45.4% of the cases (n = 10) had their clinical manifestations within the first 2 days of life. All infants (7 cases) who presented with delayed signs of neonatal infection (on days 14–19 of life) underwent orthodox circumcision a few days earlier (at the age of 8 days) and appeared with lesions involving the genital area. HSV-1 was isolated in all these cases. Five of the postcircumcision cases presented as SEM disease whereas the other 2 neonates developed CNS disease.

On 2 occasions, the same “mohel” performed the circumcision in 2 different infants: patients 4 and 7 and patients 18 and 20. The 3 other cases were circumcised by different “mohels.” Serologic data were available for all of the 7 mothers of the circumcision-associated cases. Four of them were negative for HSV antibodies (cases no. 5, 6, 17 and 20) and 3 mothers (cases no. 4, 7 and 18) had detectable anti-HSV-1 antibodies. Four of 5 “mohels” had serologic testing for HSV antibodies; all were positive for HSV-1 antibodies.

Treatment

All infants were treated with intravenous acyclovir. There was 1 infant for whom treatment duration was not mentioned. Only 8 of the 21 (38%) infants were treated according to the recommended guidelines. One patient received suboptimal acyclovir dosage, 8 patients were treated for inappropriate duration of intravenous acyclovir therapy, whereas 4 patients received therapy with both suboptimal dosage and duration (Table 1).

Outcome

Three families could not be reached, and in 1 case the parents refused to be interviewed. One of the infants died (a case fatality rate of 5%). This patient developed HSV-2 disseminated infection. One patient (case no. 7) developed HSV-1 encephalitis

TABLE 1. Clinical Characteristics of Infants With Neonatal Herpes Simplex Virus Infections

Year	Gender	Gestational age (wk)	Route of delivery	Age at presentation (d)	HSV type	Clinical presentation	Cutaneous recurrences	Dose (mg/kg/d)	Duration of IV acyclovir treatment (d)	Developmental delay
1	2001	M	39	1	1	CNS*	No	50	21	No
2	2001	M	39	2	Not typed	SEM†	Unknown	45	12	Unknown
3	2001	F	31	11	2	Disseminated	No	60	21	Died
4*	2001	M	40	15	1	SEM	Yes	60	14	No
5*	2002	M	40	15	1	SEM	Yes	60	10	No
6*	2002	M	39	14	1	SEM	Yes	50	13	No
7*	2002	M	40	16	1	CNS	No	60	21	yes
8	2002	M	39	1	Not typed	SEM	No	60	11 (+ PO acyclovir × 4 d)	No
9	2002	F	40	2	2	SEM	No	60	10 (+ PO acyclovir × 4 d)	No
10	2002	F	33	6	Not typed	SEM	Yes	60	Unknown	No
11	2002	F	39	1	1	SEM	No	60	9 (+ PO acyclovir × 2 d)	No
12	2002	F	41	1	Not typed	SEM	No	60	3 (+ PO acyclovir × 8 d)	No
13	2003	M	40	1	2	SEM	No	60	10 (+ PO acyclovir × 3 d)	Yes
14	2003	F	41	1	Not typed	SEM	Unknown	30	7 (+ PO acyclovir × 5 d)	Unknown
15	2003	F	37	1	1	SEM	Unknown	60	14	Unknown
16	2003	F	42	1	2	SEM	No	60	14	No
17*	2004	M	37	16	1	SEM	Yes	60	10	No
18*	2005	M	39	19	1	SEM	Unknown	15	8 (+ PO acyclovir × 6 d)	Unknown
19	2005	M	36	7	1	Disseminated	No	60	21	No
20*	2006	M	37	15	1	CNS	No	60	14	No
21	2006	F	38	6	1	SEM	Yes	60	14 (+ PO acyclovir × 14 d)	No
22	2007	M	36	5	1	SEM	No	60	14	No

*Cases associated with circumcision. Circumcision was performed at 8 days of age. IV indicates intravenous; PO, per os; M, male; F, female; SVD, spontaneous vaginal delivery.

followed by long-term brain damage manifested by seizures and infantile spasms, and 1 patient with SEM presentation (case no. 13) had mild gross motor and speech developmental delay. Fifteen patients were reported to have normal development (Table 1). Six infants experienced cutaneous recurrences of HSV; 5 of them suffered several recurrent episodes (cases no. 4, 5, 10, 17 and 21).

DISCUSSION

NHSV infection is a significant public health concern throughout the world. This is the first study that examines the NHSV incidence and clinical characteristics in Israel. Incidence of neonatal HSV has been reported from several countries around the world.⁸⁻¹⁵ The incidence rate of neonatal HSV infection in central Israel (8.4 per 100,000 live births) is higher than that reported in Switzerland (1.6 cases per 100,000 live births),¹² Denmark and Canada (6.5 and 5.9 cases per 100,000, respectively),^{8, 11} but seems to be similar to the lower part of the scale reported in the United States, where rates range from 8 to 60/100,000 live births.⁴

None of the mothers in our series had past history of genital herpes, and none had genital lesions at the time of delivery. Our results are in accord with previous studies that reported that most women who deliver infants with neonatal HSV had no lesions of HSV during delivery and no history of genital herpes either.^{8, 17}

At present, there is no known effective antepartum management to prevent vertical transmission between these mothers and their infants.

We found that the most frequent presentation was exclusive SEM (77.2%) followed by CNS infection (13.6%) and disseminated disease (9.1%). Similar distributions have been reported in other studies.⁸ SEM involvement was not presented only in 1 case (5%), less than reported previously by Kimberlin et al who reported that 17–39% of all patients had no skin vesicles throughout the course of their HSV disease.¹⁸

Most (76.4%) herpes viruses typed in our series were HSV-1. This is in contrast with a number of older reports that found HSV-2 to be more prevalent.^{19, 20} However, more recent studies showed an increasing proportion of HSV-1 as a cause of genital herpes infection.^{21, 22} A shift in the timing of acquisition of HSV-1 infections in women from younger to older ages due to improved standards of living together with changes in sexual behavior (increased rates of oral-genital contact) have resulted in increasing rates of HSV-1 sexual transmission, particularly in Western countries.²³

Moreover, studies performed in central Israel reported that the seroprevalence of HSV-2 in the Israeli population, including pregnant women, is in the lower range than that reported across Europe.^{24, 25}

Ritual circumcision that involves sucking of the wound with the mouth has been associated with neonatal HSV-1.^{26, 27} In our series, ritual circumcision seems to be a potential source of HSV-1 transmission in 7 infants (31.8% of cases). This route of postnatal transmission of HSV-1 is another possible explanation for the increased rate of HSV-1 SEM presentations in our series. However, even in the noncircumcision cases, HSV-1 was the predominant serotype (60% of the isolates serotyped). NHSV after circumcision is a unique presentation that occurs among Orthodox Jews. It is characterized by the appearance of lesions over the penis 7–11 days after the circumcision, and the causative virus was HSV type 1. In our series, the proportion of severe cases (disseminated or CNS) in postcircumcision cases was at least as high as the “regular” NHSV cases (28.5% versus 20%, respectively).

One infant in our series, who manifested with severe disseminated disease, died, which resulted in a case fatality rate of 5%. This rate is lower than that reported in previous studies.^{8, 28} The relatively improved prognosis in this series could result from the

higher incidence of HSV-1 that is associated with a better overall prognosis than HSV-2.²⁹

The adherence to the clinical management guidelines was not optimal, and 62% were treated with either suboptimal dosage or duration of acyclovir. This figure emphasizes the need for a better awareness of HSV infection in Israeli neonates.

The main limitations of our study are the small number of patients and its retrospective nature. In addition, the calculated incidence may be an underestimate because there is a lack of an International Classification of Diseases, 9th revision code specific for neonatal HSV. The coding problem was a limitation in other studies as well.^{12, 25}

In summary, this is the first description of NHSV epidemiologic and clinical features in Israel. The incidence of neonatal HSV infection was found to be similar to the lower part of the scale reported in the United States, however higher than the incidence reported in Canada or Europe. Similar to more recent series, our series demonstrates the shift toward the predominance of HSV-1 in NHSV infection. None of the mothers in our series had previous history of genital herpes. Our results emphasize the need for awareness of HSV infection in Israeli neonates.

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