

Inconsistent Management of Neonatal Herpes Simplex Virus Infections

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OBJECTIVES: The incidence of neonatal herpes simplex virus (nHSV) infections is monitored periodically in the Netherlands, yet management and outcome is unknown. Comprehensive national guidelines are lacking. We aim to describe management and outcome in the last decade to explore current diagnostic and therapeutic challenges. We aim to identify possible variability in management of patients with a suspected nHSV infection.

METHODS: We conducted a retrospective case series of management and outcome of nHSV infections at 2 tertiary care center locations in the Netherlands.

RESULTS: An nHSV infection was diagnosed in 1% (12 of 1348) of patients in whom polymerase chain reaction for HSV was performed. Of the patients with nHSV infection, 3 of 12 died, and 4 of 9 (44%) survivors suffered neurologic sequelae. Neurologic symptoms at presentation were seen in only 2 of 8 patients with nHSV encephalitis. A cerebral spinal fluid analysis was performed in 3 of 6 patients presenting with skin lesions. Only 3 of 6 patients with neurologic symptoms received suppressive therapy. nHSV infection was diagnosed in 8 of 189 (4%) patients who were empirically treated.

CONCLUSIONS: Management of nHSV infection, particularly when presented with skin lesions, is inconsistent. Many infants without a HSV infection are exposed to antiviral medication. There is substantial interhospital variation in diagnostic and therapeutic management of a suspected infection. Comprehensive guidelines need to be developed to standardize management of suspected nHSV infection.

ABSTRACT

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The incidence of neonatal herpes simplex virus (nHSV) infections, although low, has increased over the past 15 years in the Netherlands.¹ This problem is emerging because the herpes simplex virus (HSV) seroprevalence among adults is declining, resulting in a higher number of unprotected women of reproductive age and thus increasing the risk of nHSV disease.² The course of the disease ranges from skin lesions to severe neurologic disease or multiorgan failure.³ In progressed infection, substantial mortality and severe morbidity due to neurologic sequelae have been described.⁴

There are several difficulties in recognizing nHSV infection because >80% of maternal viral shedding is asymptomatic, and initial presentation is often nonspecific.^{5,6} International guidelines state contrasting recommendations, and in many countries, comprehensive national guidelines are lacking.^{7,8} In 2011, results of a trial revealed beneficial effects of prolonged 6-month treatment of proven neurologic nHSV infection.⁴ However, there is no consensus on what diagnostic testing is required in infants with a suspected nHSV infection to identify patients with indication for prolonged treatment.

We aimed to describe outcome and current management challenges and inconsistencies of nHSV infections in the Netherlands. Identification of these challenges supports the development of future national and international guidelines. We aim to identify possible variability in the diagnostic and therapeutic approach of patients with a suspected nHSV infection.

METHODS

We performed a chart review of all patients with nHSV admitted to 2 tertiary care centers in the northern region of the Netherlands from 2006 to 2017. We identified patients aged ≤ 60 days with a suspected nHSV infection (ie, sample collection for HSV polymerase chain reaction [PCR] testing) through a patient database query. We collected the following data: clinical data, HSV PCR testing results on any material, cerebral imaging results, residual symptoms, recurrent infections, and developmental delay. If available, Bayley Scales of Infant Development (BSID) scores

or Gross Motor Function Classification System (GMFCS) scores were documented. The BSID is used to score mental and motor development (range: 50–150; mean of 100). The GMFCS is used to categorize impairment in gross motor function of children with cerebral palsy (range: level 1–5).

We defined nHSV disease as an HSV (type 1 or 2) infection that was confirmed by PCR testing in a blood, cerebral spinal fluid (CSF), or skin and/or mucosal sample. PCR testing is performed in both tertiary care centers and is considered the primary diagnostic test in the Netherlands. Patients were categorized into 3 groups⁵: patients with skin, eye, and mouth (SEM) disease, patients with central nervous system (CNS) disease, and patients with disseminated disease. SEM disease is limited to a PCR test positive for vesicular SEM lesions on the skin and/or mucosal sample. CNS disease or HSV encephalitis is characterized by neurologic involvement and (1) a positive result on the PCR test of the CSF sample despite neurologic signs (seizures, hemiparesis, lethargy, abnormal neuroimaging, and CSF abnormalities) or (2) clinical signs of CNS involvement and a positive result on the PCR test of the blood or skin sample. In disseminated disease, signs of multiorgan involvement are present with any HSV-positive sample on the PCR test. Adequate therapy was defined as intravenous acyclovir at 60 mg/kg per day during 14 or 21 days for SEM and CNS and/or disseminated disease, respectively.³ Percentages were rounded to the nearest whole number.

This study was approved by the medical ethics review committee, and a waiver for the Medical Research Involving Human Subjects Act was provided.

RESULTS

A total of 1% of patients (12 of 1348) evaluated for an nHSV infection after clinical suspicion were included in the study with PCR-confirmed nHSV disease (8 of 1120 patients at the first center and 4 of 228 at the second center) (Fig 1). In 4% of patients (8 of 189) who were started on empirical acyclovir, a diagnosis of nHSV disease was confirmed (5 of 72 patients at the first center and 3 of 117 at the second center).

Table 1 reveals clinical course and management of the patients: 8 of 12 categorized as having CNS disease, 3 of 12 categorized as having SEM disease, and 1 of 12 categorized as having disseminated disease. Age at the onset of symptoms ranged from 0 to 30 days, with 5 of 12 patients presenting first symptoms at age 2 to 3 weeks. In total, 6 of 12 patients presented with SEM lesions, and only 2 of 12 presented with fever. Of all patients with CNS disease, 2 of 8 presented with seizures, whereas the remaining 6 patients presented with lesions or a subfebrile temperature. Of the patients with CNS disease without neurologic presentation, 3 of 6 developed neurologic symptoms during admission, whereas 3 patients did not have neurologic symptoms despite a PCR test on the CSF with positive results or MRI abnormalities. Delay in testing ranged from 0 to 12 days and counted ≥ 2 days in 5 of 12 patients. All patients with a delay in testing presented with nonspecific symptoms (irritability and poor feeding). In 2 patients, testing was delayed several days after presentation because of misdiagnosis of SEM lesions. Cerebral MRI was performed in 7 of 8 patients with CNS disease; all revealed hemorrhage or diffusion restriction in cortical parts of the brain. Two of 8 patients with CNS disease did not survive the infection. The only patient with disseminated disease, who was started on acyclovir after a delay of 7 days, died. Of the surviving patients with HSV, 4 of 9 (44%) developed neurologic sequelae in the following years (follow-up time: 1–12 years). On discharge, there were no residual symptoms in most of the patients who developed sequelae. History of maternal HSV was reported in 7 patients. Genital lesions during the last trimester were reported and treated in 2 patients.

HSV PCR testing on CSF was only performed in 3 of 6 (50%) patients presenting with SEM lesions. In this group, HSV PCR testing was performed on blood samples in 3 of 6 patients and on ocular and/or skin samples in 3 of 6 patients. Delay from onset of symptoms to initiation of adequate treatment was ≥ 2 days in this group. Adequate therapy was not initiated (according to treatment guidelines)⁴ in 3 of 12 patients presenting with SEM lesions. In

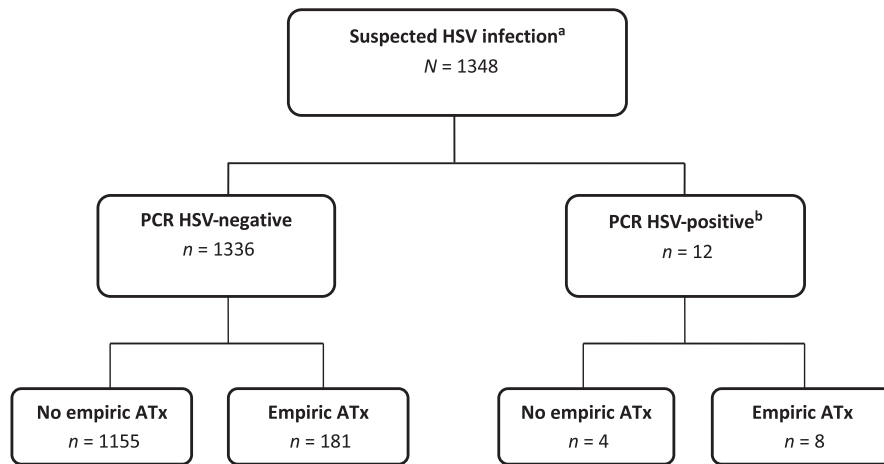


FIGURE 1 Patient inclusions. ^a PCR for HSV performed on any sample of blood, cerebral spinal fluid or skin/mucosal lesions of suspected patients. ^b ≥ 1 positive HSV PCR result on any sample. ATx, intravenous acyclovir therapy.

case 6, acyclovir was discontinued after 14 days despite neurologic involvement, and in case 7, the patient was switched to oral valacyclovir after 3 days because of a mild clinical course. In case 11, the patient presented with an HSV PCR test positive for SEM lesions, and initial treatment consisted of topical acyclovir cream; intravenous acyclovir was added after 4 days because of CSF pleocytosis and was stopped after 7 days when HSV PCR test results on the CSF were negative. This particular patient suffered neurologic sequelae and a recurrent HSV infection. In only 1 patient with CNS disease, the CSF was checked, and results were negative before therapy was ended.

Suppressive therapy was administered in 3 of 6 (50%) surviving patients with CNS disease. In 1 patient, suppressive therapy was given for 2 years because of recurrence, after which acyclovir resistance developed. In another patient, suppressive therapy was continued for 4 years because of recurrent SEM disease. The 3 remaining patients with CNS disease who survived the initial infection were not treated with suppressive therapy, 2 of whom developed late sequelae.

DISCUSSION

Our results reveal that mortality and morbidity rates of nHSV disease, CNS disease in particular, are high. HSV CNS disease often presents without neurologic symptoms. Also, we found substantial

interhospital variation in diagnostic and therapeutic management of suspected nHSV infection, particularly in patients presenting with skin lesions. The incidence rate is in line with the latest Dutch monitoring study, which revealed an incidence of 4.8 per 100,000 births.¹ Comparable morbidity rates have been described in earlier studies revealing normal development in only 30% to 35% of patients with CNS disease.^{4,9}

Moreover, we found a nonspecific presentation to be common, such as in patients with nHSV CNS disease without neurologic signs at presentation or during admission. A nonspecific presentation is likely to lead to variation in management and to treatment delay in the absence of uniform guidelines. Practice variation was particularly substantial in PCR testing of patients presenting with SEM lesions. Reluctance to perform a CSF analysis is understandable given the invasive nature of a lumbar puncture and the rarity of the disease. Yet without a CSF analysis, a proportion of nHSV CNS cases will remain unrecognized, and antiviral medication will be incorrectly withheld. Inadequate treatment of neurologically involved patients often leads to lifelong disabilities and increased health care costs.⁴ Additionally, end-of-treatment reassessment of CSF HSV PCR testing was rarely performed. Despite the international opinion that neurologic involvement cannot be excluded on the basis of clinical presentation, not all guidelines state clearly when a CSF

analysis is indicated to rule out neurologic infection or to confirm treatment effect.⁷

The most important dilemmas remain: What characteristics should prompt a clinician to perform PCR testing, and which justify empirical acyclovir? Despite reported adverse effects of acyclovir, some experts suggest a low threshold to empirical treatment.¹⁰ All proven patients with nHSV disease from our cohort identified from 2016 forward (patients 1–5) were treated on the same day that testing was performed, whereas 4 of 7 patients^{6–12} before 2016 had treatment initiated at least 2 days after testing. Gaensbauer et al¹¹ suggest a tendency toward increasing empirical acyclovir treatment in HSV-negative patients beyond the neonatal age in more recent years. However, the risks of overtreating infants should be taken into consideration in low-incidence countries, and cost-effective benefits of empirical treatment in cases of suspected nHSV infection has not been proven. Because our study was not designed to address tendencies in empirical acyclovir treatment in the HSV-negative neonates, this might be an interesting objective for future research.

Ours and earlier studies reveal interhospital variation in the diagnostic and therapeutic approach to suspected nHSV infection in the Netherlands.¹² This reflects the lack of national consensus, which has also been underlined in other countries.^{13,14} The American Academy of Pediatrics gives some practical guidance on PCR testing, although precise testing and treatment indications are lacking.³ The Dutch guideline on febrile infants advises to only treat empirically in cases of neurologic symptoms.¹⁵ This is in contrast to the Canadian guidelines, which advise treatment with empirical acyclovir in all unwell infants <6 weeks who are suspected of having sepsis.⁷ Additional characteristics to prompt empirical therapy have been mentioned, such as vesicular lesions or pleocytosis.^{12,13} Because prospective trials are limited by the low incidence and required follow-up time, larger-scale observational studies should be focused on the value of clinical characteristics in identifying patients

TABLE 1 Characteristics, Management, and Outcome of nHSV Infection Cases

Year	HSV Classification	Comorbidity	Presenting Symptoms	HSV Contact	HSV-Positive Sample	Age at Symptom Onset	Age at Sample Collection	Age at Start of Acyclovir Therapy	Acyclovir Therapy Length	Outcome	Suppressive Therapy	Sequelae After Discharge	Recurrence of HSV Infection	BSID and/or GMFCS ^a
1	2017 CNS HSV-2	—	Temperature 37.9°C	No	CSF	16	17	17	4	Deceased	—	—	—	—
2	2017 CNS HSV-2	—	Temperature 37.8°C	Maternal, other	CSF, plasma	16	18	18	4	Deceased	—	—	—	—
3	2017 CNS HSV-1	—	Lesions	Maternal	CSF	16	28	28	21	Recovery	Yes	No	3 times, SEM	Unknown
4	2017 CNS	—	Temperature 38.2°C, seizures	No	CSF	Unknown	38	38	21	Recovery	No	Abnormal moving pattern, on AEDs	No	Unknown
5	2016 SEM	—	Lesions, temperature 37.0°C	Other	Skin	10	12	12	14	Recovery	No	No	2 times, SEM	Unknown
6	2014 CNS HSV-2	Prematurity, 27 wk	Lesions	Maternal	CSF, plasma	0	0	3	14	Recovery	Yes	Hemiparesis	>3 times, SEM	BSID: 94; GMFCS 1
7	2013 SEM	—	Lesions, temperature 36.8°C	No	Plasma	9	12	12	21	Recovery	No	No	No	Unknown
8	2010 CNS HSV-1	SGA	None	Maternal	CSF, sputum	—	1	4	21	Recovery	No	No	No	Unknown
9	2007 SEM	—	Lesions, temperature 37.0°C	Maternal	Skin	18	18	20	14	Recovery	No	No	No	Unknown
10	2006 CNS	—	Seizures	Other	CSF, plasma	17	17	17	21	Recovery	No	Diplegia	No	Unknown
11	2006 CNS HSV-2	Prematurity, 31 wk	Lesions, temperature 37.2°C	Maternal, other	Skin, ocular	30	30	34	7	Recovery	Yes	Epilepsy, on AEDs, PM retardation, vision impairment	>3 times, SEM	GMFCS: 5
12	2006 Disseminated disease	—	Temperature 39.0°C	Maternal	Plasma	5	13	13	4	Deceased	—	—	—	—

AED, antiepileptic drug; HSV-1, herpes simplex virus type 1; HSV-2, herpes simplex virus type 2; PM, psychomotor; SGA, small for gestational age; —, not applicable.
^a BSID scores ranged from 50 to 150 (mean of 100), and GMFCS scores ranged from level 1 (no impairment) to level 5 (severe impairment).

requiring CSF testing and empirical therapy to develop evidence-based guidelines.

This study is limited by its retrospective nature, and completeness of data was dependent on medical records because there is no national registry on long-term outcomes available in the Netherlands. Prospective studies on nHSV disease are limited because of the low incidence and the required follow-up time. Although it is likely that follow-up would be conducted at the treating tertiary care centers, cases of long-term sequelae could have been missed. Also, follow-up time differs between cases, and further disabilities might become apparent in the future. Although a small sample size was inevitable, it prevented us from analyzing differences between subgroups. We tried to minimize the selection bias by identifying infants through a query of both patients in whom HSV PCR testing was performed and patients who were started on acyclovir. The search in the pharmacy database was merely done to decrease the chance of missing potential inclusions because of incomplete reporting. All patients who were treated with acyclovir were PCR tested.

Our data provide insight in the clinical course and outcome of nHSV disease. This case series underlines the current management challenges and the need for uniform national guidelines to improve recognition and management of suspected nHSV infection.

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