Inconsistent Management of Neonatal Herpes Simplex Virus Infections

Maya W. Keuning, MD, a Martijn van der Kuip, MD, PhD, a Jarne M. van Hattem, MD, b Dasja Pajkrt, MD, PhD, MBA a

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.
The incidence of neonatal herpes simplex virus (nHSV) infections, although low, has increased over the past 15 years in the Netherlands. 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. The course of the disease ranges from skin lesions to severe neurologic disease or multiorgan failure. In progressed infection, substantial mortality and severe morbidity due to neurologic sequelae have been described.

There are several difficulties in recognizing nHSV infection because >80% of maternal viral shedding is asymptomatic, and initial presentation is often nonspecific. International guidelines state contrasting recommendations, and in many countries, comprehensive national guidelines are lacking. In 2011, results of a trial revealed beneficial effects of prolonged 6-month treatment of proven neurologic nHSV infection. 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.

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 (6 of 72 patients at the first center and 3 of 117 at the second center).
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. Comparable morbidity rates have been described in earlier studies revealing normal development in only 30% to 35% of patients with CNS disease.4,5 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 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.8 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 patients6,12 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 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>
<thead>
<tr>
<th>Year</th>
<th>HSV Classification</th>
<th>Comorbidity</th>
<th>Presenting Symptoms</th>
<th>HSV Contact</th>
<th>HSV-Positive Sample</th>
<th>Age at Symptom Onset</th>
<th>Age at Sample Collection</th>
<th>Age at Start of Acyclovir Therapy</th>
<th>Acyclovir Therapy Length</th>
<th>Outcome</th>
<th>Suppressive Therapy</th>
<th>Sequelae After Discharge</th>
<th>Recurrence of HSV Infection</th>
<th>BSID and/or GMFCS&lt;sup&gt;a&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>2017</td>
<td>CNS HSV-2</td>
<td>—</td>
<td>Temperature 37.9°C</td>
<td>No</td>
<td>CSF</td>
<td>16</td>
<td>17</td>
<td>17</td>
<td>4</td>
<td>Deceased</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2017</td>
<td>CNS HSV-2</td>
<td>—</td>
<td>Temperature 37.8°C</td>
<td>Maternal, other</td>
<td>CSF, plasma</td>
<td>16</td>
<td>18</td>
<td>18</td>
<td>4</td>
<td>Deceased</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2017</td>
<td>CNS HSV-1</td>
<td>—</td>
<td>Lesions</td>
<td>Maternal</td>
<td>CSF</td>
<td>16</td>
<td>28</td>
<td>28</td>
<td>21</td>
<td>Recovery</td>
<td>Yes</td>
<td>No</td>
<td>3 times, SEM</td>
<td>Unknown</td>
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<tr>
<td>2017</td>
<td>CNS</td>
<td>—</td>
<td>Temperature 38.2°C, seizures</td>
<td>No</td>
<td>CSF</td>
<td>Unknown</td>
<td>38</td>
<td>38</td>
<td>21</td>
<td>Recovery</td>
<td>No</td>
<td>Abnormal moving pattern, on AEDs</td>
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<tr>
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<td>SEM</td>
<td>—</td>
<td>Lesions, temperature 37.0°C</td>
<td>Other</td>
<td>Skin</td>
<td>10</td>
<td>12</td>
<td>12</td>
<td>14</td>
<td>Recovery</td>
<td>No</td>
<td>No</td>
<td>2 times, SEM</td>
<td>Unknown</td>
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<td>2014</td>
<td>CNS HSV-2</td>
<td>Prematurity, 27 wk</td>
<td>Lesions</td>
<td>Maternal</td>
<td>CSF, plasma</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>14</td>
<td>Recovery</td>
<td>Yes</td>
<td>Hemiparesis</td>
<td>&gt;3 times, SEM</td>
<td>BSID: 94; GMFCS 1</td>
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<tr>
<td>2013</td>
<td>SEM</td>
<td>—</td>
<td>Lesions, temperature 36.8°C</td>
<td>No</td>
<td>Plasma</td>
<td>9</td>
<td>12</td>
<td>12</td>
<td>21</td>
<td>Recovery</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Unknown</td>
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<tr>
<td>2010</td>
<td>CNS HSV-1</td>
<td>SGA</td>
<td>None</td>
<td>Maternal</td>
<td>CSF, sputum</td>
<td>—</td>
<td>1</td>
<td>4</td>
<td>21</td>
<td>Recovery</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Unknown</td>
</tr>
<tr>
<td>2007</td>
<td>SEM</td>
<td>—</td>
<td>Lesions, temperature 37.0°C</td>
<td>Maternal</td>
<td>Skin</td>
<td>18</td>
<td>18</td>
<td>20</td>
<td>14</td>
<td>Recovery</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Unknown</td>
</tr>
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<td>CNS</td>
<td>—</td>
<td>Seizures</td>
<td>Other</td>
<td>CSF, plasma</td>
<td>17</td>
<td>17</td>
<td>17</td>
<td>21</td>
<td>Recovery</td>
<td>No</td>
<td>Diplegia</td>
<td>No</td>
<td>Unknown</td>
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<td>2006</td>
<td>CNS HSV-2</td>
<td>Prematurity, 31 wk</td>
<td>Lesions, temperature 37.2°C</td>
<td>Maternal, other</td>
<td>Skin, ocular</td>
<td>30</td>
<td>30</td>
<td>34</td>
<td>7</td>
<td>Recovery</td>
<td>Yes</td>
<td>Epilepsy, on AEDs, PM retardation, vision impairment</td>
<td>&gt;3 times, SEM</td>
<td>GMFCS: 5</td>
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<td>2006</td>
<td>Disseminated disease</td>
<td>—</td>
<td>Temperature 39.0°C</td>
<td>Maternal</td>
<td>Plasma</td>
<td>5</td>
<td>13</td>
<td>13</td>
<td>4</td>
<td>Deceased</td>
<td>—</td>
<td>—</td>
<td>—</td>
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</tr>
</tbody>
</table>

<sup>a</sup> BSID scores ranged from 50 to 150 (mean of 100), and GMFCS scores ranged from level 1 (no impairment) to level 5 (severe impairment).
REFERENCES


11. Gaensbauer JT, Birkholz M, Pfannenstein K, Todd JK. Herpes PCR testing and empiric acyclovir use beyond the neonatal period. Pediatr Infect. 2014;134(3). Available at: www.pediatrics.org/cgi/content/full/134/3/e651


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