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# Characteristics of neonatal herpes simplex virus infections in Germany: results of a 2-year prospective nationwide surveillance study

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## ABSTRACT

**Objective** To assess incidence and burden of neonatal herpes simplex virus (HSV) infections and to explore possible transmission routes.

**Methods** A 2-year prospective nationwide surveillance study performed in 2017 and 2018. All German paediatric departments (n=464 in 2017, n=441 in 2018) were contacted on a monthly basis to report potential cases of neonatal HSV infections. Infants with a postnatal age of  $\leq 60$  days and a positive HSV PCR or HSV culture from skin, mucous membrane, vesicles or conjunctival smear, blood or cerebrospinal fluid were included in the study.

**Results** 37 cases were analysed. 29 patients who exhibited no or only mild clinical symptoms were discharged home without organ damage or neurological abnormalities. Four patients showed significant neurological impairment, one patient required liver transplantation and two patients died during in-patient treatment. The 2-year incidence of neonatal HSV infections was 2.35 per 100 000 live births (95% CI 1.69 to 3.02) and disease-specific mortality was 0.13 per 100 000 live births (95% CI 0.04 to 0.21). Data on possible transmission routes were available in 23 cases. In 20 cases, an orofacial HSV infection was present in one or more family members. An active maternal genital HSV infection was reported in 3 cases.

**Conclusion** Neonatal HSV infections are rare in Germany. Most infants have a benign clinical course, but some infants are severely affected. Postnatal HSV exposure may account for a considerable number of neonatal HSV infections.

## INTRODUCTION

Neonatal herpes simplex virus (HSV) infections are rare. In the USA and Canada, the incidence has been estimated to be around 6–10 cases per 100 000 live births.<sup>1,2</sup> It is commonly assumed that about 85% of infants become infected in the intrapartum period, 10% postnatally and 5% in utero.<sup>3</sup> However, in many cases, the exact mode of transmission cannot be determined.<sup>2</sup> Neonatal HSV infections are usually apparent before 14 days of life, but later manifestations have been described.

The two specific types of HSV, HSV-1 and HSV-2, both cause neonatal infections.<sup>4</sup> Mother-to-child transmission is significantly increased in primary versus recurrent maternal infections, during vaginal delivery versus caesarean section and in infection with HSV-1 versus HSV-2.<sup>5</sup> Maternal

## What is already known on this topic?

- ▶ Neonatal herpes simplex virus (HSV) infections are rare but associated with a high morbidity and lethality.
- ▶ Maternal genital HSV infection is the most common source of infection.

## What this study adds?

- ▶ Horizontal transmission via mothers and family members may be a possible source of neonatal HSV infection.
- ▶ Neonates treated for asymptomatic or skin/mucous membrane HSV infections have a favourable outcome, while neonates presenting with disseminated disease or eye infection are at high risk for sequelae.
- ▶ An urgent need exists for extended HSV serology and direct virus detection in mothers, neonates, and family members to assess perinatal or postnatal HSV transmission.

HSV type-specific serology allows risk-adapted treatment in cases with a high risk of transmission.<sup>6</sup> In Germany, estimates of HSV seroprevalence in adults are about 78%–83% for HSV-1 and 10%–13% for HSV-2.<sup>7–9</sup> Although seroprevalence has tended to decrease over the past two decades, this decrease may pose a threat to neonates because, concomitantly, susceptibility to HSV infection may increase in the perinatal period.<sup>5,9,10</sup>

Three major disease manifestations of neonatal HSV infection occur: (1) skin, mucosa and conjunctival disease; (2) central nervous system (CNS) disease; (3) disseminated disease with multiple organ involvement. Neonatal HSV infections may present with classic symptoms (herpetic skin and mucosal lesions, seizures), but symptoms may also be nonspecific (fever, poor drinking, lethargy) or absent.<sup>11</sup> Timely diagnosis is challenging but crucial to avoid a delay in the initiation of antiviral therapy. Neonatal HSV infections can have a high morbidity and mortality. Delayed initiation of therapy has been associated with poorer outcomes.<sup>12,13</sup> The actual incidence of neonatal HSV infections in Europe, especially in Germany, is insufficiently evaluated. There are also limited data available



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on disease burden, routes of transmission and the frequency of nosocomial neonatal HSV infections. The aim of this study was to assess incidence and burden of neonatal HSV infections and to explore possible transmission routes.

## METHODS

### Design

This 2-year prospective nationwide surveillance study was performed in 2017 and 2018. All German paediatric departments (n=464 in 2017, n=441 in 2018) were contacted on a monthly basis to report potential cases of neonatal HSV infections. Data were collected via the German Paediatric Surveillance Unit for Rare Diseases (ESPED—in German: Erhebungseinheit für Seltene Pädiatrische Erkrankungen in Deutschland), a voluntary reporting system that covers all German paediatric departments. Following each initial case report, a detailed clinical questionnaire was sent out to the reporting department by ESPED.

The questionnaire included perinatal characteristics, clinical symptoms, diagnostic findings and outcome data. In addition, the questionnaire asked about possible routes of transmission (active maternal genital HSV infection: first or recurring; active non-genital HSV infection: mother, father, siblings, other household members).

### Case definition/ inclusion criteria

Infants with a postnatal age of  $\leq 60$  days and a positive HSV PCR or HSV culture from skin, mucous membranes, vesicles or conjunctival smear, blood or cerebrospinal fluid (CSF) were included in the study.

### Secondary data sources

To assess underreporting in the incidence of neonatal HSV infections, an additional dataset was generated using the validated hospital discharge records (coded by the respective ICD-10 code P35.2) reported to the German Federal Statistical Office by the statutory health insurances as the second source. An inquiry was performed for the frequency of the prespecified diagnosis P35.2 “congenital infection due to herpes viruses” in infants with a postnatal age of  $\leq 1$  year in the years 2017 and 2018 (data requested from <https://www.gbe-bund.de/gbe/>; 11 September 2020).

### Statistical analysis

Data entry, cleaning and evaluation were performed using IBM SPSS Statistics V.25. Characteristics of the patients and their mothers were expressed by means for continuous variables and by relative and absolute frequencies for discrete variables.

To estimate the extent to which the ESPED sample was representative, we planned a two-source capture–recapture calculation. Because one of the underlying basic assumptions of a capture–recapture calculation was violated, the distribution of some characteristics was compared with the health insurance data. The numbers of patients were extrapolated to the German live born infants in 2017 and 2018 (Federal Statistical Office, Wiesbaden 2020), and the 2-year incidence of neonatal HSV infections per 100 000 live born infants for the years 2017 and 2018 was calculated with 95% CI. For comparison with the data of our cohort study, we also present the incidence of neonatal HSV infections per 100 000 live born infants with the health data reported to the German Federal Statistical Office by the statutory health insurances companies.

**Table 1** Perinatal characteristics of neonates with HSV infection in Germany 2017–2018

Infant's characteristics	N
Total	37
Sex	
Male	20
Female	17
Gestation	
Term	29
Preterm	7
N/A	1
Age at onset of symptoms*	
Day of life, median (min, max)	10 (0, 52)
Days between onset of symptoms and start of antiviral treatment*	
Days, median (min, max)	2 (0, 13)
<b>Mother's characteristics</b>	
Total†	36
Maternal age, years	
20–35	30
>35	2
<20	4
Birth mode	
Vaginal	22
Vaginal-instrumental	4
Caesarean section	4
N/A	6
Rupture of membranes >18 hours before birth	
Yes	2
No	16
N/A	18

\*Available for the 27/37 infants that were symptomatic.

†Total number is 36 for the mothers since a pair of twins was included in the survey. For child-related factors, this mother is included in the calculations for each child individually.

HSV, herpes simplex virus; N/A, not applicable.

## RESULTS

### Incidence

There were 48 initially reported cases in 2017 and 2018. The case definition was not fulfilled in three cases, and in another eight cases the questionnaires were not sent back. Thus, a total of 37 affected infants, including one pair of twins, were analysed. Perinatal characteristics are presented in table 1. The 2-year incidence of neonatal HSV infections was 2.35 per 100 000 live births (95% CI 1.69 to 3.02). This result was in line with the health data reported to the German Federal Statistical Office by the statutory health insurance companies. Retrospective analysis of the period from 2017 to 2018 resulted in 60 cases with a diagnosis of “congenital infection due to herpes viruses”. This corresponded to an incidence of 3.83 per 100 000 live births.

### Distribution of HSV subtypes

In most cases (18 infants), infection with HSV type 1 was present. Type 2 was detected in four infants, and mixed infection with HSV types 1 and 2 occurred in two infants. In the remaining 13 cases, no subtype determination was performed, or the result was unknown. HSV subtype 2, which is associated with genital herpes, CNS infection or disseminated infection in adults, was exclusively detected in infants with eye infection. HSV subtype 1 was present in all types of infections.

### Antiviral therapy

Therapy of all neonatal HSV infections was with acyclovir, with doses ranging from 13 to 70 mg/kg/day. In two infants, the doses were not reported. The duration of therapy ranged from 4 to 205 days, with a median of 14 days. In two infants, the duration of therapy was not reported.

### Hospital stays

Most infants (28) were solely treated on general paediatric wards while 8 infants received treatment in intensive care units. The median duration of hospital stay was 14 days, with a minimum of 2 days and a maximum of 73 days. Length of hospital stays and inpatient assignment were not reported for two patients each.

### Possible transmission routes and risk factors

Data on possible transmission routes were available for 23 infants. In 20 cases, an orofacial HSV infection was present in one or more family members (mothers in 15 cases, fathers in 3 cases, both parents in 1 case and a sibling in 1 case). Labial herpes was reported in 17 cases, one mother was affected by nasal herpes and another had periorbital herpes. In one case, a mother of affected twins had labial herpes.

An active genital HSV infection was reported from three mothers. Twenty-six mothers definitely did not reveal symptoms of a genital HSV infection, while the status was unknown in seven mothers. None of the mothers was reported to have been treated with acyclovir before or during delivery to prevent transmission of the herpes virus.

**Table 2** Virological profiles of affected infants, mothers and other household members

Case number	Onset of symptoms (DOL)	Hospitalisation since birth	Localisation of HSV detection*	HSV subtype	HSV copies/mL	Active maternal or household HSV infection
1	6	No	CSF	2	N/A	Mother, labial herpes
2	5	No	CSF	1	N/A	None reported
3	30	No	CSF	1	N/A	Mother, labial herpes
4	N/A	Yes	Mucocutaneous	N/A	N/A	Mother, labial herpes
5	5	No	CSF	2	N/A	None reported
6	1	Yes	Blood	1	$5.8 \times 10^2$	Mother, labial herpes
7	18	No	Blood	N/A	N/A	None reported
8†	N/A	Yes	Mucocutaneous	N/A	N/A	Mother, labial herpes
9†	N/A	Yes	Mucocutaneous	N/A	N/A	Mother, labial herpes
10	N/A	Yes	Mucocutaneous	N/A	N/A	Mother, various mucocutaneous lesions
11	6	No	Blood	N/A	N/A	None reported
12	N/A	Yes	Mucocutaneous	N/A	N/A	Mother, labial herpes
13	19	No	Blood	N/A	N/A	Father, labial herpes
14	3	Yes	Blood	1	$5 \times 10^6$	None reported
15	2	Yes	Mucocutaneous	1	N/A	Father, labial herpes
16	34	No	Blood	1	N/A	Mother, labial herpes
17	7	No	Mucocutaneous	1	N/A	Mother, labial herpes
18	21	No	CSF	1	$4.3 \times 10^2$	None reported
19	13	No	Mucocutaneous	1	N/A	Father, labial herpes
20	9	No	Mucocutaneous	1	N/A	Mother, labial herpes
21	52	No	Mucocutaneous	N/A	N/A	Sibling, labial herpes
22	3	No	CSF	2	N/A	None reported
23	2	Yes	Blood	1	$4.5 \times 10^6$	None reported
24	6	No	Mucocutaneous	1	N/A	None reported
25	9	No	CSF	2	$5.7 \times 10^3$	None reported
26	21	No	Mucocutaneous	1	N/A	None reported
27	0	Yes	Mucocutaneous	1	N/A	None reported
28	8	Yes	Blood	1	N/A	None reported
29	N/A	Yes	Mucocutaneous	1	N/A	Mother, genital herpes
30	N/A	No	Mucocutaneous	1	N/A	Mother, labial herpes
31	14	No	Mucocutaneous	1	$6.7 \times 10^3$	Mother, labial herpes
32	N/A	No	Mucocutaneous	N/A	N/A	Mother, various mucocutaneous lesions
33	N/A	No	Mucocutaneous	1 and 2	N/A	Mother, genital herpes
34	N/A	No	Mucocutaneous	N/A	N/A	Mother, labial herpes
35	12	No	Mucocutaneous	N/A	N/A	None reported
36	35	No	Mucocutaneous	N/A	N/A	Mother, labial herpes
37	25	No	Blood	1 and 2	N/A	Mother, genital herpes

\*All tests performed via PCR.

†Twins.

CSF, cerebrospinal fluid; DOL, day of life; HSV, herpes simplex virus; N/A, not available.

**Table 3** Clinical and diagnostic characteristics of neonates with HSV infection in Germany 2017–2018

Category of disease	Number of infants*
Mucocutaneous	21
Eye	8
CNS	2
Disseminated	4
Not reported	2
<b>Clinical symptoms</b>	
No symptoms	10
Mucocutaneous herpes blisters	10
Poor feeding	7
Circulatory problems	7
Body temperature >38.0°C	5
Seizures	6
Dyspnoea or tachypnoea	6
Apnoea	5
Lethargy	4
Unspecific symptoms	6
<b>Laboratory findings</b>	
No abnormal findings	21
Elevated liver enzymes	10
Leucocyte count >15/nL	7
Thrombocytopenia <150/nL	5
Abnormal coagulation	4
CRP >15 mg/L	4
CSF cell count >20/nL (0–28 DOL), >9/nL (29–60 DOL)	3
CSF glucose <40 mg/dL	2
Leucocyte count <5/nL	1
<b>Diagnostics</b>	
Cranial ultrasound	
Normal	23
Abnormal	4
Not performed/unknown	10
Cranial MRI	
Normal	3
Abnormal	5
Not performed	29
EEG	
Normal	2
Abnormal	6
Not performed	29

\*Multiple answers possible.

CNS, central nervous system; CRP, C reactive protein; CSF, cerebrospinal fluid; DOL, day of life; EEG, electroencephalogram; HSV, herpes simplex virus.

Table 2 summarises the virological profiles of the affected infants and their families.

### Clinical symptoms and outcomes

During the study period, two deaths associated with neonatal HSV infection were reported. One of those infants was also diagnosed with an inborn error of metabolism, likely contributing to the fatal outcome. The two deaths resulted in a case fatality rate of 5.4% (95% CI 1.37 to 6.97) and a disease-specific mortality rate of 0.13 per 100 000 live births (95% CI 0.04 to 0.21).

Ten infants were asymptomatic. Fifteen infants presented with one isolated symptom and 12 infants presented with a combination of two to five symptoms. Details on disease manifestation and symptoms are given in table 3.

Twenty-nine infants were healthy at discharge, while five infants had significant sequelae. Four of them showed significant neurological impairment, and one had a liver transplant. In one case, the outcome was unknown, as the infant was transferred to another hospital without further information available. Half of the infants who presented with disseminated disease had sequelae, as did 37.5% of those with eye infection. Almost all (97.3%) infants with a skin or mucous membrane lesion and all asymptomatic infants were healthy at discharge.

### DISCUSSION

The incidence of neonatal HSV infections has been previously estimated to range from 1.4 to 4.7 per 100 000 live births in Switzerland, Australia and the Netherlands<sup>14–17</sup>; and up to 5.9, 8.4 and 12.1 per 100 000 live births in Canada, Israel and the USA.<sup>2 18 19</sup> Globally, the incidence is estimated to be around 10 per 100 000 live births.<sup>20</sup> We report an incidence at the lower end of this spectrum for Germany (2.35 per 100 000). The different study results appear comparable, even though study designs and definitions of neonatal HSV infection vary across studies. Differences between regions and countries are largely unknown but are likely attributable to cultural differences or differences in primary healthcare settings. Compared with other studies, reporting case fatality rates of 19% to 26%, death from neonatal HSV infection was low in our study.<sup>17 21</sup>

It is commonly assumed that most neonatal HSV infections occur in the intrapartum period and that postnatal transmissions are rare incidents.<sup>3 14 22</sup> However, HSV transmission routes have been insufficiently evaluated in prospective studies. As with incidence, transmission routes may also vary significantly between countries and regions. In our study, symptoms of maternal genital HSV infections were rarely reported, while non-genital HSV infections of household members were frequent among affected neonates. Possible postnatal transmission of HSV via household members has been suggested in various case reports<sup>23–28</sup> and also in one large study from Jones *et al.*<sup>17</sup> Our study supports this suggestion, but cannot definitely prove this mode of transmission due to lack of molecular testing. Future studies will need to incorporate comprehensive maternal antibody testing and molecular genetic techniques to explore preventive factors and to further elucidate sources of neonatal HSV infections.

HSV-1 was detected in the majority of infections. This is in contrast to high maternal and neonatal HSV-2 infection rates in other parts of the world.<sup>20</sup> These results indicate regional differences in the epidemiology of neonatal HSV infections. In Germany, it appears that awareness of maternal genital HSV infections is high, and that prenatal care may have improved over time, while postnatal HSV exposure may be more common. However, vertical transmission may have been underestimated in this study since transmission occurring in the birth canal is also possible in the absence of active genital HSV lesions.<sup>29</sup> HSV shedding around birth can also occur with asymptomatic reactivation and only be estimated adequately, if direct virus monitoring is performed in particular on the basis of previously reported episodes of genital HSV.<sup>4</sup>

Our study adds evidence to the possibility of postnatal HSV exposure. Neonates are at risk of acquiring HSV infections from family members or others with skin or mucous membrane infections. More research is needed to evaluate strategies of empirical antiviral therapy of exposed infants, including those with no or mild symptoms. Based on the available evidence, families should receive comprehensive counselling, and preventive measures, especially

avoidance of contact with herpetic blisters, should be liberally implemented.<sup>30</sup>

We found seven infants with serious adverse outcomes. Our findings that infants with skin/mucous membrane infection commonly had good outcome at discharge, but that many infants with disseminated disease had sequelae, warrant further confirmatory investigations. However, we suggest that parents of infants presenting with no or only mild symptoms and who are on antiviral treatment may be reassured.

In summary, neonatal HSV infections are rare in Germany. The vast majority of infections are skin/mucous membrane infections with a mild clinical course and very good outcome. Nevertheless, HSV infections can be extremely severe in individual cases and cause permanent severe impairment. Horizontal infection within the family may be a possible transmission route. Neonatal HSV infection is for both mothers and infants, as well as family members, an interdisciplinary diagnosis. Inclusion of specific maternal and infant virological data is a prerequisite for urgently needed multi-national studies to increase our knowledge on recognition and prevention of neonatal HSV infections.

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