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# Long-term Outcomes of Neonatal Herpes Simplex Virus Infection and Treatment

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# LONG-TERM OUTCOMES OF NEONATAL HERPES SIMPLEX VIRUS INFECTION AND TREATMENT

by

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## ABSTRACT

The prevalence of herpes simplex virus (HSV) infection globally is high, and although there is no cure for it, the antiviral drug acyclovir is used to alleviate symptoms. There are two types of HSV: HSV-1, which typically infects the oral area, and HSV-2, which is associated with genital infections. A mother who carries the infection may transmit it to a neonate in different ways, most commonly via vaginal delivery in the presence of active lesions. There are three types of HSV disease that affect newborns: skin, eyes or mouth (SEM) disease, central nervous system (CNS) disease, or disseminated disease. The purpose of this study was to examine the long-term effects of the infection and the treatment used in neonates infected with HSV. Data collection consisted of original case reports published in Medline, CINHAL, and Google Scholar. Two case reports were found, and this narrative review compares the cases, which report recurrences and outcomes of HSV infection identified in the three databases. Both cases were consistent with recurrence of CNS disease, and one showed signs of a slight developmental delay that may have been related to the CNS insult.

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# INTRODUCTION

Herpes simplex viruses type 1 and 2 (HSV-1 and HSV-2) are double-stranded, DNA viruses commonly transmitted sexually leading to infections that can affect the oral (HSV-1) or genital (HSV-2) areas. Although no cure has been found yet, the infection can be treated with the antiviral drug acyclovir. The treatment of a first outbreak in adults consists of 400 mg of acyclovir orally, three times a day for seven to ten days (Whitley, 2007). For adults with recurrent outbreaks, meaning that they have had an initial treatment, the drug dose is 400 mg taken orally twice a day for seven days. This is important to know because it is the treatment that a mother who has been infected would receive to minimize the duration of outbreaks and to prevent recurrent viral shedding. It is recognizable when an expectant mother has an outbreak because lesions appear in the infected areas. A typical lesion is an ampulla or blister that may bleed or ooze a limited amount of fluid, and the outbreak area may present with pruritus or a burning sensation.

Adults infected with HSV, regardless if it is type 1 or 2, may transmit the virus to a newborn in three different ways. First, it may be transmitted during birth through the vaginal canal with an active outbreak. Second, the neonate may be exposed to HSV when the amniotic sac ruptures. Third, a caregiver with an active infection may transmit it to the newborn. A baby born to a mother with a first-time lesion has 25% to 60% risk of infection, whereas a baby born to a mother who has a recurring infection is less likely to be infected (i.e., 2% rate) (Harris & Holmes, 2017). It has been recommended that pregnant women who are aware of their infection, even if they do not have lesions at

the time, start acyclovir therapy at 36 weeks of gestation (Harris & Holmes, 2017). This therapeutic approach does not prevent virus transmission, rather, it decreases the number of outbreaks that the mother may have when getting closer to labor and birth.

If the newborn is infected with HSV during birth, they may present the first signs and symptoms between the moment of birth up to two months after. Some of the symptoms, such as fever and infection, may resemble other conditions and may be misdiagnosed as a bacterial infection. Assuming that both the provider and mother are aware of the mother's existing infection, the first step after the baby is born is to test the newborn for HSV within 24 hours of birth (Harris & Holmes, 2017). Nevertheless, there are cases were the mother is unaware of her infection because it has been dormant until labor. If this is the case and the neonate show signs of infection, they must be tested for HSV as well.

A neonatal HSV infection may manifest in three ways. First, when the infection involves the skin, eyes, and mouth (SEM), it usually manifests around the fifth to eleventh day of life, with lesions around the mouth and the skin, without involvement of the central nervous system (CNS) or the internal organs. Just like in adults, the therapy of preference to treat this virus is acyclovir, nevertheless the route of administration and the strength of the dosage is different. For neonates, the treatment of HSV is intravenous acyclovir 60 mg/kg/day every 8 hours, three times a day, for 14 days (Pinninti et al, 2018). If the SEM disease is not treated in time or if it is mistreated or mistaken for a bacterial infection, it may progress and develop into CNS or disseminated disease. Health care providers try to avoid this progression because out

of the three types of disease, SEM disease is the least dangerous and aggressive (Harris & Holmes, 2017).

A second form of the disease is the CNS disease, which generally manifests around the eighth to seventeenth day of life. Before manifestation of this form of the disease, the neonate is most likely asymptomatic, unless the disease arises from an untreated SEM disease, or the mother was unaware that she is a carrier of the HSV virus, so the baby was not tested during their first 24 hours of life. Symptoms mirror neonatal bacterial infections, therefore a test on the cerebrospinal fluid (CSF) must be conducted to verify if the neonate has indeed a bacterial or a viral infection. According to Harris and Holmes, “a total of 50% of neonates who are diagnosed with a localized CNS disease will die, and the ones [who] survive will have severe neurologic sequelae” (2017, p. 89). Just like in the SEM disease, the treatment for the CNS disease is acyclovir 60 mg/kg/day three times a day, but in this case, therapy duration is 21 days.

Last, neonatal HSV infection may manifest as disseminated disease, which involves various internal organs, such as the lungs, liver, CNS, and/or adrenal glands (Pinninti et al, 2018). Typically, neonates with disseminated disease appear with fever, renal and/or lung failure, and may experience disseminated intravascular coagulopathy (Harris & Holmes, 2017). It has been shown that “nearly 30% of newborns with disseminated disease die even with treatment” (Harris & Holmes, 2017, p.89). As with the previous forms of neonatal HSV disease, newborns who have been infected are treated with intravenous acyclovir 60 mg/kg/day every 8 hours for 21 days.

Herpes simplex virus infection may be asymptomatic for years or may manifest with symptoms immediately after the infection. If a pregnant woman knows that she has an HSV-2 infection or if her healthcare professional suspects the infection, the newborn must be tested for HSV within 24 hours after birth. If the neonate tests positive, they must be treated in a timely manner. Some studies “recommend giving oral acyclovir therapy at a dose of 300 mg three times a day for six months after completion of [intravenous] therapy” (Bhatta et al., 2018, p. 690). Nevertheless, it has been shown that long-term use of acyclovir can lead to neutropenia, which can lead to increased vulnerability to other infections. Neutropenia may be self-limited following treatment with acyclovir but monitoring of neutrophil count is still recommended during treatment (Whitley, 2007).

After reviewing the different types of neonatal syndromes associated with HSV infection and understanding the treatment for infected adults and neonates, it is evident that there is a gap in the literature for the long-term effects of both the neonatal HSV infection and its therapy. Thus, this study aims to describe the long-term effects reported for neonatal HSV infection and its treatment in children with congenital HSV infection.

# METHODS

## Study design

A narrative literature review was the design of choice for this study to critically review the literature on neonatal HSV infection and its long-term outcomes. In this study, congenital herpes infection was defined as a newborn who showed the presence of the virus between the fifth and seventeenth days of life. This study focused on finding the effects of the HSV infection in patients who were initially diagnosed within their first month of life.

## Data sources and search strategy

Data search was conducted among original publications in English without date limits in PubMed, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Google Scholar. **Table 1** showcases the keywords and phrases related to HSV that were used to conduct multiple searches.

**Table 1.** Keywords used for data search

| Search on PubMed and CINAHL | Search on Google Scholar |
|---|---|
| Neonatal and HSV and effects | Adult survivors of herpes at birth |
| Herpes simplex virus and neonatal and long-term effects | Antiviral therapy for HSV |
| Herpes simplex virus and mother-to-child transmission | Neonatal viral simplex infection and acyclovir |
| HSV and neonatal prognosis or outcome | Incidence of congenital hsv infection |
| Congenital herpes and treatment or intervention and effects or consequences | |

## Study selection

Articles were selected if they contained original reports of long-term outcomes of neonatal HSV infection or therapy. Articles that did not report original data or that did not discuss the long-term outcomes of the infection or therapy were discarded.

## Data extraction

Articles meeting the inclusion criteria were retrieved and read in full by the author. After reviewing the reports, key demographic variables on the cases were extracted in a matrix, namely: age, gender, time of initial HSV infection, HSV type, course of treatment received, and long-term outcomes.

# RESULTS

The purpose of this study was to investigate the long-term side effects of neonatal HSV infection and treatment. The search in all three databases identified four records matching the keyword search, published between 2009 and 2017. Two publications were excluded: one was a commentary on the dearth of studies on the long-term outcomes of neonatal HSV infection (Melvin et al., 2015) and one was a review on the treatment of neonatal HSV infection, without reporting long-term outcomes (Jones et al., 2009). Thus, two studies reporting original data remained in this analysis (Henderson et al., 2015; Kato et al., 2017). **Table 2** presents the key findings extracted from these reports, followed by a summary of each case.

**Table 2.** Summary of the characteristics of the case reports reviewed.

| **Study** | **Kato et al., 2015** | **Henderson et al., 2017** |
|---|---|---|
| Country | Japan | Not specified |
| Sex | Boy | Girl |
| Age at initial infection | 12 days old | 10 days old |
| Treatment at initial infection | Intravenous acyclovir 20 mg/kg every 8h for 21 days | Intravenous acyclovir 60 mg/kg per day for 21 days |
| Type of virus and disease | HSV-2 with CNS disease | HSV-2 with CNS disease |
| Age at recurrence | 7 months old | 7 years old |
| Treatment at recurrence | Intravenous acyclovir 15 mg/kg every 8h for 21 days | Intravenous acyclovir for 21 days |
| Long-term outcomes reported | Delayed in development | Not specified |

Case report 1 (Kato et al., 2015)

A 12-day-old boy was vaginally delivered by a mother with previous history of HSV-1, without history of HSV-2. For his first 11 days of life, he showed no signs or symptoms of an infection (no fever, lesions, vomiting, etc.) All laboratory results for the boy were within range. Nevertheless, a magnetic resonance imaging (MRI) showed brain hemorrhage. After a spinal tap, the baby was diagnosed with neonatal HSV

infection with CNS disease. The treatment prescribed was intravenous acyclovir 20 mg/kg per dose every eight hours for 21 days. After completing the intravenous treatment, the blood and CSF laboratory results came back negative for HSV infection and the patient was prescribed oral valacyclovir for six months.

Nevertheless, he was brought back to the hospital with fever 14 days after completing the oral therapy. A spinal tap showed presence of HSV in the cerebrospinal fluid (CSF), so he was started once more on intravenous acyclovir for 21 days. Following this, he was administered oral therapy for a year. When the second oral suppressive therapy ended, a standardized developmental test showed slight delay in his development. No recurrences were reported proceeding the last round of oral therapy, this after being followed up for a year.

Case report 2 (Henderson et al, 2017)

A 7-year-old girl presented with headaches, dizziness, and signs of vomiting. She had a history of neonatal HSV-2 infection with CNS disease at 10 days of age. After the diagnosis, she received intravenous acyclovir for 21 days, and after this, she followed an oral therapy of acyclovir for six months. The patient did not show any symptoms of HSV infection until seven years later.

During the recurrent episode, all laboratory results for HSV infection were within range, except for the CSF test, which was positive for HSV-2. This confirmed a diagnosis of HSV-2 meningitis. She received intravenous acyclovir for 21 days, resolving her symptoms by the third day on treatment. After completing the treatment, laboratory results were negative for HSV-2 infection, and she was discharged with oral

acyclovir for 12 months. After completing the oral treatment for a year, she showed no recurrence.

## DISCUSSION

The aim of this narrative review was to describe reports on the long-term outcomes of neonatal HSV treated with acyclovir. Only two case reports met the inclusion criteria and were included. Both cases reported recurrence of HSV in patients previously diagnosed and treated for HSV with CNS involvement during the neonatal period. Neither case ever showed signs of skin lesions or rashes suggesting that the CNS disease did not progress from SEM disease. Treatment was the same for both cases when they were first diagnosed (i.e., intravenous acyclovir for 21 days), followed by antiviral suppressive therapy of oral valacyclovir or acyclovir for six months.

One of the differences between the two case reports was the time between the recurrences. While the male patient had a recurrence approximately seven months after the initial insult, the female patient experienced an interval of seven years between outbreaks. One potential reason for this difference is that the male patient was treated with oral valacyclovir as the suppressive therapy, and the female patient was prescribed acyclovir for the same purpose. Nevertheless, both case reports explain that a shortened course of therapy can be a big factor in the sequelae of the disease, explaining why after the intravenous therapy, there’s an oral suppressive therapy for a longer period.

Another of the differences found was the age of recurrence. The boy had a CNS recurrence at 7 days of age, whereas the girl had a CNS recurrence at age 7. Time to recurrence has long been reported as highly unpredictable (Corey, 1988), which is consistent with the disparity in the age of recurrence in the two cases at hand.

Finding only two cases greatly limits the extrapolation and analyses of long-term outcomes after an initial neonatal HSV infection. Several reasons might be behind this phenomenon, including efficacy of acyclovir treatment, changes in HSV disease prevalence, and the role of stigma in disclosing and treating sexually transmitted infections. These potential reasons for a dearth in the long-term outcomes reported are discussed next.

## Efficacy of the treatment

For the initial treatment of both HSV-1 and HSV-2 in neonates, intravenous administration of the antiviral drug acyclovir is prescribed. This drug has been available for medical use for over three decades and it has showed outstanding efficacy for treating an initial viral infection in neonates, as it not only reduces the days with active infection, but also lowers the odds of recurrence and mortality among newborns (Kimberlin & Whitley, 2007). Previously, HSV infection was treated with vidarabine, and although both vidarabine and acyclovir were effective, vidarabine required high doses, making acyclovir the treatment of choice, not only because it requires a lower dose, but it is also easier to administer. Despite its ability to improve symptoms and reduce the days of active infection, acyclovir is not a cure

In the first case report (Kato et al., 2015), the boy was treated with valaciclovir, a prodrug of acyclovir, as the oral suppressive therapy after the first intravenous treatment with acyclovir. A study showed that both acyclovir and valaciclovir have the same effects when used as oral suppressive therapy (Miserocchi et al., 2007); however, Gupta et al. (2004) report that valacyclovir is better absorbed. Nevertheless, considering

the results of the two case reports in which valacyclovir was used for the suppressive therapy post initial outbreak in the male patient and acyclovir was used as suppressive therapy for the female patient, one might speculate acyclovir is more effective for this purpose because the female patient did not have a recurrence for seven years, while the male patient treated with valacyclovir, had a second outbreak two weeks after the termination of the initial suppressive oral therapy. This is merely speculation as a conclusion cannot be drawn based on two case studies. A well-powered, long-term randomized controlled clinical trial comparing the use of acyclovir versus valacyclovir would be needed to make this conclusion.

It is important to point out that, before acyclovir was discovered to work against the HSV infection, a great percentage of patients with congenital herpes died within their first year of life. Based on the effectiveness of acyclovir in treating an initial HSV infection in neonates, one might infer that there may be a long-term benefit of this drug in terms of decreasing the chance of having an outbreak later in life, as was the case in the female case report. Nevertheless, this too is speculation and would need to be borne out by a long-term clinical trial.

## Change in HSV incidence rate

Before acyclovir treatment was commonplace, for every five pregnant women not infected with HSV-2 there was one pregnant woman with the infection (Whitley et al, 2007). Even though the neonate may acquire the infection from someone with either genital or oral herpes, the most common mechanism reported is vaginal delivery occurring when an active outbreak is present in the mother (James & Kimberlin, 2015).

It is important to point out that, according to the National Center for Health Statistics (NCHS), from 2000 (18.0%) to 2016 (12.1%), the incidence of HSV-2 infection in ages 14-49 has decreased by almost 6% (McQuillan et al., 2018). Whereas the incidence of HSV-1 infection among the same age group and time interval decreased by about 11%, going from 59.4% to 48.1% (McQuillan et al., 2018). The declining incidence may be the result of education about the importance of using protection during sexual activity and knowing the medical history of the sexual partners to avert sexually transmitted infections.

## The role of stigma

It is not a secret that sexually transmitted infections (STIs) are stigmatized worldwide resulting in patients being marginalized and shamed for their sexual history. Researchers believe that, due to potential shame, parents may be reluctant to speak out about their STIs and how they transmitted it to their babies (Melvin et al., 2015). It is possible that mothers omit informing their child about their past medical history due to the possible guilt they may feel. Expectant mothers with HSV infections may fail to tell their healthcare provider about their own medical record, again, for the possible shame they may feel. Because of this, it is presumed that parents would not enroll their children in studies that aim to research the long-term outcomes of this infection in neonates.

The aforementioned implications of efficacy and stigma may explain, at least partially, why there are not enough follow-up studies on children after the initial diagnosis of neonatal HSV.

## Possible transmission to future sexual partners

Viral infections like HSV do not have a cure as the virus continues to reside in the body. Even though babies get treated after initial diagnosis, it is known that the virus stays latent in the dorsal ganglia of the spinal cord, and it has the potential to recur at any time. HSV infection may remain dormant for many years and may never show signs or symptoms of infection in the future. Whether HSV infection acquired as a neonate can be transmitted to a future sexual partner is unknown, so researchers cannot confirm or eradicate the question of possible partner-to-partner transmission of neonatally acquired HSV infection.

## Study limitations

There are several limitations of the investigation undertaken to explore the long-term effects of neonatal HSV infection and treatment. The dearth of research and case reports in the literature presented the greatest limitation to answer the research questions, with only two case reports identified from the databases used for this research. The lack of reports may be due in part to reporting and subject bias. Narrative reviews like this one depend on previous publications, but there is a possibility that clinicians are not reporting recurrences of neonatal herpes infections. This may be due to their busy schedules or their lack of knowledge about the current gap in the literature on long-term outcomes of neonatal HSV infection. It is also possible that asymptomatic HSV infection contracted perinatally may eventually be manifested later in life.

## CONCLUSION

The signs and symptoms of neonatally acquired HSV infection are treatable with antiviral therapy; however, recurrence of symptoms, as has been documented in two published case reports, is possible, with the length of time between the initial and subsequent outbreaks varying between the two cases. Triggers that may cause recurrence are yet to be identified, as is the true frequency with which subsequent outbreaks occur. Based on the documented cases identified for this project, one difference that may account for variability in the length of time from the initial to subsequent outbreak might be related to the choice of drug therapy; however, there is purely speculation that needs to be borne out through additional research. Even though there is not much literature on the inquiry of this project, the fact that long-term sequelae were documented in the two case reports where CNS disease recurred, suggests the need for surveillance, reporting, research, and strategies for prevention. Future studies might include an observational study that systematically reviews and compares all cases of neonates acquiring HSV infection during the perinatal period through adolescence or adulthood. Although this type of study could provide data needed to support the need for further investigation using a more rigorous study design, a drawback to this approach would be the duration of time needed to identify possible patterns or associations. Given enough evidence to support the idea that differences in therapeutic approaches might be related to the duration between initial and subsequent occurrence, a randomized clinical trial comparing treatment approaches would be in order and would provide more concrete evidence to support or refute this hypothesis.

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