



Diagnostic Dilemmas of a Herpes-Like Rash in Healthy Neonates

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“All uncertainty is fruitful ... so long as it is accompanied by the wish to understand.”

— Antonio Machado

Three different full-term neonates at three different initial visits presented with peculiar worrisome vesicular rashes. Each of them was thriving, robust, afebrile, and otherwise healthy. None of the respective infant’s parents had been ill or febrile, nor did they provide a history of cold sores, or a history of genital herpes or lesions ever (information that, with much trepidation, I needed to obtain).

The clinical lesions in each of the neonates made me extremely anxious because each could potentially be a sign of impending disaster — neonatal herpes simplex infection. The mortality alone, if untreated, is 70% to 80% for the disseminated form, and 30% to 40% for the encephalitic form.¹

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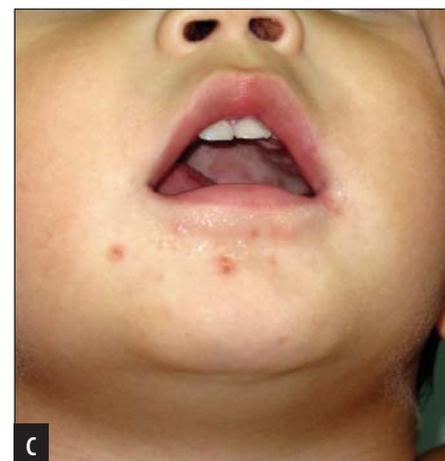


Figure 1. A. Small crop of vesicular lesions on forehead of 2-week-old infant. B. Close-up view of vesicular lesions in photo. C. Crusted herpetic peri-oral lesions in the infant’s 2-year-old sibling. Source: Block SL. Reprinted with permission.

However, about 83% of neonates with skin, eye, and mouth herpes are reported to be initially afebrile.¹ Neonatal herpes is a rare disorder for any general pediatrician to suspect in a neonate within a routine practice. The incidence is about 350 to 1,050 cases annually in the US.¹ Welcome to my world of “zebras” in rural Kentucky.

Given the following three clinical presentations, which of these infants do you suspect had neonatal herpes rash?

CASE 1: A 5-DAY-OLD INFANT WITH PUSTULOVESICULAR LESIONS IN THE DIAPER AREA

The patient was a 5-day-old infant with scattered papulovesicular lesions in the groin area. I explained to the mother that I thought the odds were quite high that her baby had neonatal pustular melanosis, a self-limited benign condition. However, I thought to myself that if I were wrong, the consequences could be devastating. So I requested that the baby return to the office daily for evaluation to assess the infant and the progress of the lesions. I also advised the mother to return immediately with the patient if any signs of illness or fever developed.

CASE 2: A 2-WEEK-OLD INFANT WITH VESICULAR LESIONS ON THE FOREHEAD

The patient was a 2-week-old infant with an incidental consolidated vesicular rash localized to the forehead for 2 days before presentation (see Figures 1A and 1B, page 98). I was highly suspicious that this otherwise healthy child was infected with neonatal herpes of the skin. But the mother was in total denial of this possibility. I felt compelled to convince her that this apparently healthy newborn actually needed a full diagnostic evaluation at the regional tertiary care hospital for

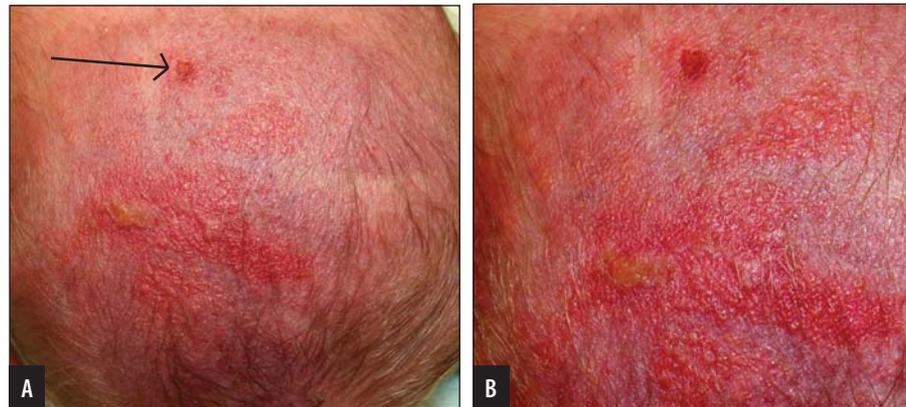


Figure 2. A. Crop of vesicular lesions in a 1-day-old infant. Arrow points to site of earlier fetal monitor. B. Close-up view. Source: Block SL. Reprinted with permission.

potential neonatal herpes. The patient also needed the prompt initiation of intravenous acyclovir. To deflect any moral recriminations, I explained to the mother that her child possibly could be infected with herpes type 1, which is usually acquired from cold sores, not genital lesions.

The patient's 2-year-old brother happened to be in my office at the same visit. He had a history of a fever and sore throat. I noted the sibling's perioral lesions (Figure 1C, see page 98). Thus, I suggested to the mother that he most likely could be the source of her infant's possible infection with type 1 herpes. This reassured me about the accuracy of the infecting agent, but the mother still seemed unconvinced.

CASE 3: A 1-DAY-OLD INFANT WITH VESICULAR LESIONS ON THE SCALP AT BIRTH

The patient was a 1-day-old newborn whom I saw in the nursery; the infant had a large crop of vesicular lesions on the scalp (see Figures 2A and 2B). The nursing staff told me this was the approximate location of the predelivery, in utero scalp monitor. The delay in notifying the pediatrician concerned me. In their defense, none of the staff in our small rural hospital had ever seen or

suspected a critically ill child with neonatal herpes. Still, I was fairly convinced about the diagnosis. Neonatal herpes in the first few days of life (termed “congenital” herpes infection) is extremely rare — or so I thought. But later, after a literature search, I discovered that, in a series of 30 congenital herpes infections cases, an alarming two-thirds of patients demonstrated extensive CNS damage at birth or autopsy.²

My next concern was how to tell the mother about the high likelihood of neonatal herpes, when she was expecting to be presented with a healthy newborn on the first morning of the infant's life. I nervously hemmed and hedged, and explained that this could just as easily be a herpes type 1 nongenital infection as well as a herpes type 2 infection. We just needed to perform all the diagnostic tests and to have the neonatal experts at the tertiary care center offer their opinions as well.

The mother, understandably, was in total denial, and before being transferred, requested the opinion of another doctor at our hospital. I once again explained that this was a diagnosis that must be evaluated thoroughly and immediately in a tertiary care center because of all the dire consequences of delay.



Figure 3. A. Five-day-old infant with vesicular-pustular rash in the groin area. B. Milia rubra rash 2 days later in the same infant. Note also a few petechiae replacing many of the original pustules. Source: Block SL. Reprinted with permission.

DISCUSSION

Case 1: A 5-Day-Old Infant with Pustulovesicular Lesions in the Diaper Area — Not Herpes

Fortunately, by 48 hours, the infant's initial rash markedly dissipated, replaced by what I suspected was an obvious case of milia rubra (see Figures 3A and 3B). Yet, I wondered if I was reading too much into the appearance of this newly evolved version of a very commonly observed neonatal rash; I went with my instinct, and the infant's new rash mostly resolved over the next 2 days.

Case 2: A 2-Week-Old Infant with Vesicular Lesions on the Forehead — Probable Herpes

Before transferring the child, I performed the second most important test: I photographed the child's lesions with a digital camera. In the tertiary care hospital, the child received multiple diagnostic herpes cultures and polymerase chain reaction (PCR) tests performed on the skin (think: lots of scrapings); cerebrospinal fluid, nasopharynx, rectum, eye, mouth, and blood tests were also performed. Both IV antibacterials and IV acyclovir were initiated upon admission. Several days later, all initial tests turned up negative in this infant, which is not uncommon.

The direct fluorescent antibody (DFA) sample for herpes was insufficient. Herpes IgM serologic titers were all also negative. However, by the time the pediatric infectious disease and dermatologist experts were consulted, the lesion was macerated and scabbed over from all the scrapings (it was a good thing I had the invaluable "before" photos). Per protocol, they were unsure whether to continue a full 14-day course of acyclovir or consider a protracted prophylactic 6-month course of oral acyclovir. Because the photographs were convincing in this case, the consultants chose both therapeutic options.

Three weeks later (at 5 weeks old), she was readmitted to the hospital for a recurrence of the identical lesions in the identical forehead spot. Inadvertently, the prophylactic dose of acyclovir she was receiving was only half the recommended dose. Again, the entire thorough herpes workup was negative. However, several days later, the lesions were even growing the fungal pathogen *Trichophyton tonsurans*, thought to be a secondary commensal as a pathogen. This was treated with topical ketoconazole, but she still completed another 14-day course of acyclovir. The appropriate dose of prophylactic oral acyclovir was restarted to finish the full 6-month course.

Case 3: A 1-Day-Old Infant with Vesicular Lesions on the Scalp at Birth — Possible Herpes

Reluctantly, the mother agreed to the transfer. To obtain an optimal laboratory technique for PCR and cultures (think: tertiary care center), I deferred starting acyclovir in this otherwise healthy newborn. After the transfer, getting consent for a lumbar puncture was an ordeal for the neonatologists as well. However, all the cultures and PCR testing for herpes were negative. No other consultations were obtained, and acyclovir was discontinued after about 7 days. No acyclovir prophylaxis was instituted.

The family was not particularly happy with any of our medical skills or diagnostic concerns. Although obtained, no digital photographs of the initial lesions were requested for further review. After a few months, the lesions had not recurred. But our entire office was on notice to immediately seek hospital consultation for any recurrence of vesicular lesions in this child until 6 months of age.

This patient's presentation was the most perplexing because, until then, I had not heard of "congenital herpes," which presented me with the following issues:

- Approximately 60% of neonates with disseminated or CNS disease have skin lesions.³
- Infants with disseminated disease present at a younger age.³
- As seen in Case 2, herpes infection of the skin has been reported to recur one to 12 times in 46% to 80% of neonates in the same original location.¹
- Most importantly, frequent herpes skin recurrences alone also places these infants at a higher risk of CNS sequelae.³

LATEST DEVELOPMENTS IN NEONATAL HERPES MANAGEMENT

Currently, the CDC recommends that all infants with “possible” neonatal herpes be evaluated and treated promptly with IV acyclovir for 14 to 21 days. Two recent placebo-controlled, parallel, randomized, double blind trials in multiple centers across the US studied acyclovir treatment and outcomes in neonatal herpes.⁴ One group had CNS infection, while the other had skin, eye, or mouth infection. Each group received either 21 or 14 days of acyclovir, respectively. Afterward, 6 months of prophylactic oral acyclovir or a placebo was prescribed.

At 1 year, the CNS arm treated with acyclovir had 20-point higher Bayley developmental intelligence scores (88 vs 68) than did the placebo-treated group at 1 year. Yet, at 1 year, no difference in developmental intelligence was observed in the skin, eye, and mouth arm for the acyclovir-treated group. The findings appeared in the October 2011

issue of *The New England Journal of Medicine*. Nonetheless, an accompanying editorial suggested that, “it makes sense to treat all survivors of neonatal HSV with oral acyclovir,” given the limitations of the small sample size, and the risks and benefits of prophylaxis.⁵

So, in the future, would you recommend that both Case 2 and Case 3 of probable/possible skin HSV infection be treated prophylactically with oral acyclovir for 6 months? Consider the potential for occasional acyclovir-induced neutropenia (frequent CBC testing is needed), the moderate costs, and the parental energy needed to adhere to twice-daily dosing. Furthermore, in these trials, none of the untreated babies who developed recurrences of skin HSV went on to develop CNS infection as well.

By contrast, in these trials, acyclovir prophylaxis prevented skin recurrences, which can be both expensive (eg, another hospitalization, as we experienced in Case 2) and frustrating, and can create the potential for CNS sequelae. I personally would opt for prophylaxis for any unproven but highly suspicious cases.

Unfortunately, after a physician suggests a diagnosis such as neonatal herpes, families may seek further routine care for their child from another practitioner, either inside or outside of one’s practice. This is the sometimes unfortunate result of being the messenger who delivers bad news to families who are expecting a healthy baby. Understandably, no parent wants to explain to friends and family a neonatal diagnosis like this. ■

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Addendum

Many thanks to readers, such as Joe Banks, MD, and Hal Quinn, MD, for suggesting the following clarifications in the January article on frenectomy:⁶

- The tongue elevator is available from McKesson (1-800-877-1919) using item #469890 or #469891 depending on the size desired.
- Hurricane spray may be substituted for the Hurricane gel instead, depending on your preference.
- Although three CPT codes for frenectomy are similar, the most precise one is 41115, which is the code for excision of lingual frenum. Codes 40819 and 41010 are codes for excision of labial or buccal frenum and for incision of lingual frenum, respectively.

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