Ref: Ro J Infect Dis. 2022;25(4)
DOI: 10.37897/RJID.2022.4.2

The management of neonatal herpes simplex virus infection in a small for gestational age neonate - Case report

Maria-Andreea Racean[1], Laura Mihaela Suciu[1,2], Cristina Oana Marginean[3,4]

[1]Department of Neonatology, Mures County Clinical Hospital, Targu-Mures, Romania
[2]Department of Neonatology, "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Targu-Mures, Romania
[3]Department of Pediatrics, County Clinical Emergency Hospital, Targu-Mures, Romania
[4]Department of Pediatrics, "George Emil Palade" University of Medicine, Pharmacy, Science and Technology, Targu-Mures, Romania

ABSTRACT

Neonatal herpes simplex virus infections are rare, normally acquired through vertical transmission in the peripartum period, usually manifesting before 14 days of life and being identified on the basis of history, clinical and laboratory evaluation. We present the case of a small for gestational age male infant born at 38 weeks gestational age with neonatal herpes simplex virus infection. The diagnosis was delayed because the attention was focused on an unidentified bacterial infection. In cases where a clinical picture suggestive of infection is described, with laboratory tests that support the diagnosis of infection, but with cultures that do not highlight bacterial or mycological agents, we must not forget about viral agents, specifically among those newborns from intrauterine growth restricted pregnancies. Neonatal HSV infections can be present even in the absence of herpetic vesicles in the newborn and even if the mother is asymptomatic.

Keywords: herpes simplex virus, infection, twin newborn

INTRODUCTION

Herpes simplex virus (HSV) is double-stranded, enveloped DNA virus [1]. Neonatal HSV infections are rare, normally acquired through vertical transmission in the peripartum period, usually manifesting before 14 days of life (DOL) and being identified on the basis of history, clinical and laboratory evaluation [2,3,4]. The major manifestations of neonatal HSV infection are: skin, mucosa and conjunctiva disease; central nervous system (CNS) disease; disseminated disease with multiple organ involvement [2]. HSV is associated with the classic triad of manifestations in skin (aplasia cutis, scarring, erosions), CNS (ventriculomegaly, microcephaly, intracranial calcifications) and eyes (chorioretinitis, atrophy), along with skeletal manifestations and fetal loss [5]. The outcome of neonatal HSV infection depends on the extent of the disease [6].

The diagnosis of neonatal HSV can be difficult, but it should be suspected in any newborn with irritability, lethargy, fever or poor feeding at one week of age [7]. Polymerase chain reaction (PCR) is a powerful diagnostic tool that has enhanced the ability to correctly diagnose neonatal HSV infections and has proven especially beneficial in patients without overt manifestations of HSV disease such as skin vesicles. It also has provided an additional means by which response to therapy can be assessed [8].

Corresponding author:
Maria-Andreea Racean
E-mail: marry_deea@yahoo.com

Article History:
Received: 26 December 2022
Accepted: 30 December 2022

Human HSV infection in neonates can result in devastating outcomes, including significant mortality and morbidity (including sequelae) [9,10]. Early diagnosis of the condition and prompt initiation of acyclovir have been imperative to improve outcomes in infants [11]. Most neonatal HSV infections can be treatable when found early [12]. Effective antiviral treatment is available for HSV infections [13]. Acyclovir is the treatment of choice, but its implementation is often delayed while awaiting test results, such as PCR and serology [14].

Even with the use of high dose of acyclovir, case fatality rates remain high [15]. The gold standard for prevention of neonatal HSV would be the development of a safe and effective vaccine [16].

The aim of this case report was to take into account in the differential diagnosis of neonatal infections, neonatal infection with HSV, even in the absence of skin vesicles. Written informed consent was obtained from the patient's mother, the minor's legal guardian, for the publication of this case report.

CASE REPORT

We present the case of a small for gestational age (SGA) male infant born at 38 weeks GA. He was the first twin of a 26-year-old mother, gesta I para II, who had a pregnancy with affirmative physiological evolution until 32 weeks of GA when one fetus presented intrauterine growth restriction, without obvious signs of fetal distress. The birth was achieved by elective caesarean section for the twin pregnancy, with the second twin located in pelvic presentation. The amniotic fluid was clear. The infant's birth weight was 2280 grams (2nd centile), length 51 cm (65th centile) and cranial perimeter 32 cm (10th centile). His twin sister's birth weight was 2540 grams (10th centile), length 52 cm (89th centile) and cranial perimeter 33 cm (85th centile). His Apgar scores were 9 and 10 at 1 and 5 minutes and his twin sister's Apgar scores were 9 and 10 at 1 and 5 minutes. He was resuscitated in the delivery room by unobstructing the upper respiratory tract and tactile stimulation. The early postpartum adaptation was appropriate, with pink integuments and without signs of respiratory distress.

Clinical findings

On the first clinical examination, the newborn was alert and warm. The temperature was 36.8°C, the heart rate 140 beats per minute, the blood pressure 60/43 mm Hg, the respiratory rate 48 breaths per minute and the oxygen saturation 98% while he was breathing ambient air. The anterior fontanelle was flat and soft. The lungs were clear on auscultation. The abdomen was soft without distention, tenderness, or palpable masses. No hepatomegaly was detected, and the liver had a smooth surface and sharp edge. The male genitalia appeared normal. There were no dysmorphic features and neurologic examination revealed normal primitive reflexes.

Subsequent, the twin newborn was successfully fed orally with small volumes of milk. He started to choke on feeding. Later he was fed by gavage, which he tolerated, but he began to have swallowing disorders, so that he required frequent suction of saliva from the oral cavity. This was the moment when we thought he had an esotracheal fistula and we did a radiological study with an orally administered contrast substance. The large quantity of secretions had an obstructive character leading to medium respiratory effort, with normal oxygen saturations.

Laboratory tests

A sepsis evaluation was performed. The initial C reactive protein level was 38 mg/liter. We collected a blood culture and the treatment with ampicillin and gentamicin was started. The blood culture was negative at 72 hours, but the C reactive protein level remained high (19 mg/liter). After 5 days of antibiotic treatment the infant had leukopenia and the C reactive protein had increased at the level of 32 mg/liter. We stopped the antibiotics, collected another blood culture and initiated treatment with meropenem. We also collected a TORCH (toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus) serology. The second blood culture was negative at 72 hours and the C reactive protein level dropped at 10 mg/liter.

Radiology aspects

A chest x-ray revealed that the lungs were clear. The heart size was normal and the costophrenic angles were well-defined, indicating that there is no pleural effusion. The radiological study of the upper digestive tract revealed: stomach in the shape of a hook, with a cascade at the level of the upper pole; retroantral located pylorus; gastroesophageal reflux; normal initial evacuation of the contrast agent; intestinal loops of normal appearance.

Ultrasound findings

A cranial and abdominal ultrasound was completed at 24 hours of life and they were in normal limits according to the GA. An echocardiogram was performed in the first 72 hours of life and revealed patent ductus arteriosus with restrictive left-right shunt and patent foramen ovale with restrictive left-right shunt.

DISCUSSIONS

Congenital HSV is a rare presentation of neonatal HSV infection [17]. Initially, the respiratory symp-

toms were interpreted in a malformative context, but repeated radiological studies-native and with contrast-ruled out tracheoesophageal fistula. The newborn was fed by gavage initially and frequent aspiration of secretions from the upper airways was performed. Later, he was fed with a bottle and then exclusively naturally. Unlike our case, the 10-day-old neonate, born vaginally presented by White et al was brought to his primary care doctor's office by his mother for fever [12]. The SGA newborns are different from the appropriate for GA (AGA) newborns in terms of their ability to mount an immune response.

Similar to our case, the male neonate described by Bittencourt et al. was born from a mother with no history of genital herpes simplex during pregnancy or at the time of delivery, but differently he presented grouped vesicles [14]. The second case reported by Hon et al. presented feverish and vesicles and also he was born from a mother with no history of vaginal herpes or cold sore [13].

Our twin neonate had positive immunoglobulin (Ig) M and IgG antibodies against HSV. Compared to him, his twin sister had positive IgG antibodies and negative IgM antibodies against HSV. The peculiarity of this case was that only one of the twins developed neonatal infection with HSV. Four out of the five cases described by Pujol et al presented grouped vesicles [3]. In contrast to our case, Pujol et al. presented the case of twin sisters: one of them had skin vesicles and had HSV infection; her twin sister had no symptoms or skin lesions, but had HSV infection [3].

When the results from the TORCH serology came, the antibiotic treatment was stopped and the antiviral treatment with Acyclovir had started. The twin infant benefited from treatment with brain tonics and vitamin B complex at the recommendation of the pediatric neurologist. Like in our case, in the case of the 10-day-old male neonate described by White et al. antibiotic treatment with ampicillin and gentamicin was primarily started and it was discontinued after blood culture was negative [12]. Similar to our case, Kidszun et al. treated the all neonates with HSV infections with Acyclovir [2].

Nonfatal cases were more likely to be missed than fatal cases [15]. The diagnosis was delayed in our case because the attention was focused on an unidentified bacterial infection. Although the criteria for systemic inflammatory syndrome is not established yet in the neonatal period, the evaluation of the inflammatory response, i.e. IL-6, and soluble TNF receptor 1 would add tremendously for in time detection of inflammation associated with HSV infection in this case [18]. The measurement of the mitochondrial aspartate aminotransferase and cytochrome c would also have been beneficial because recently, it has been reported that apoptosis plays a role in the pathophysiology of systemic inflammatory response secondary to HSV infections [18]. Unfortunately, none of this measurements or real time PCR assay for HSV loading quantification were available at the institution where infant was cared for.

The twin newborn was discharged from the maternity unit at the twenty-seventh DOL because he was stable, with an upward growth curve and with blood tests with normal values. He remained with discrete hypotonia in the limbs, more accentuated in the upper limbs. The case will be followed by the pediatric neurologist, cardiologist and ophthalmologist.

CONCLUSIONS

In cases where a clinical picture suggestive of infection is described, with laboratory tests that support the diagnosis of infection, but with cultures that do not highlight bacterial or mycological agents, we must not forget about viral agents, specifically among those newborns from intrauterine growth restricted pregnancies. In these situations, it is necessary to perform TORCH serology to confirm the diagnosis of neonatal HSV infection. Neonatal HSV infections can be present even in the absence of skin vesicles in the newborn and even if the mother is asymptomatic. Neonatal infection with HSV is rare, but it should not be excluded when performing the differential diagnosis of a neonatal infection.

Conflict of interest: none declared
Financial support: none declared

REFERENCES

1. Harris JB, Holmes PA. Neonatal Herpes Simplex Viral Infections and Acyclovir: An Update. *J Pediatr Pharmacol Ther*. 2017;22(2):88-93.
2. Kidszun A, Bruns A, Schreiner D, Tippmann S, Winter J, Pokora RM et al. Characteristics of neonatal herpes simplex virus infections in Germany: results of a 2-year prospective nationwide surveillance study. *Arch Dis Child Fetal Neonatal Ed*. 2022;107:F188-F192.
3. Pujol MJS, Simon AD, Sanguino L, Blanes M, Betlloch I. Herpes Simplex Virus Infection in Neonates Born to Asymptomatic Mothers: A Case Series. *Cureus*. 2022;14(12):e32393.
4. Ramgopal S, Wilson PM, Florin TA. Diagnosis and Management of Neonatal Herpes Simplex Infection in the Emergency Department. *Pediatr Emer Care*. 2020;36(4):196-204
5. Megli CJ, Coyne CB. Infections at the maternal-fetal interface: an overview of pathogenesis and defence. *Microbiology*. 2022;20:67-82.
6. Pinninti SG, Kimberlin DW. Management of neonatal herpes simplex virus infection and exposure. *Arch Dis Child Fetal Neonatal Ed*. 2014;99:F240-F244.

7. Rudnick CM, Hoekzema GS. Neonatal Herpes Simplex Virus Infections. *American Family Physician*. 2002;65(6):1138-1142
8. Kimberlin DW. Neonatal Herpes Simplex Infection. *Clinical Microbiology Reviews*. 2004;17(1):1-13.
9. Allen UD, Robinson JL. Prevention and management of neonatal herpes simplex virus infections. *Paediatr Child Health*. 2014; 19(4):201-206
10. Pascual A, Moessinger A, Gerber S, Meylan P. Neonatal herpes simplex virus infections in Switzerland: results of a 6-year national prospective surveillance study. *Clin Microbiol Infect*. 2011;17:1907-1910.
11. Samies NL, James SH, Kimberlin DW. Neonatal Herpes Simplex Virus Disease Updates and Continued Challenges. *Clin Perinatol*. 2021;48:263-274.
12. White JC, Magee SR. Neonatal Herpes Infection: Case Report and Discussion. *JABFM*. 2011;24(6):758-762.
13. Hon KL, Leung TF, Cheung HM, Chan PKS. Neonatal herpes: what lessons to learn. *Hong Kong Med J*. 2012;18(1):60-62
14. Bittencourt MJS, Drago MG, Nascimento BAM, Freitas LKM, Carvalho AH. Cutaneous neonatal herpes simplex virus infection type 2: a case report. *An Bras Dermatol*. 2016;91(2):216-218
15. Matthias J, Bernard S, Schillinger JA, Hong J, Pearson V, Peterman TA. Estimating Neonatal Herpes Simplex Virus Incidence and Mortality Using Capture-recapture Florida. *Clin Infect Dis*. 2021;73(3):506-512.
16. Poole CL, Kimberlin DW. Antiviral Approaches for the Treatment of Herpes Simplex Virus Infections in Newborn Infants. *Annu Rev Virol.* 2018;5:407-425
17. Purewal R, Costello L, Garlapati S, Mitra S, Mitchell M, Moffett KS. Congenital Herpes Simplex Virus in the Newborn: A Diagnostic Dilemma. *Journal of the Pediatric Infectious Diseases Society*. 2016;5(3):e21-e23.
18. Kawada JI, Kimura H, Ito Y, Ando Y, Kitajima NT, Hayakawa M et al. Evaluation of systemic inflammatory responses in neonates with herpes simplex virus infection. *J Infect Dis*. 2004;190(3):494-498.