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CLINICAL CASE

Neonatal ophthalmia caused by Herpes Simplex Virus type I

Oftalmia neonatal causada por Virus Herpes Simple tipo I

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What do we know about the subject matter of this study?

Neonatal Ophthalmia is a type of conjunctivitis with multiple etiologies. It affects up to 12% of newborns. Its treatment and prognosis depend on its etiology.

What does this study contribute to what is already known?

This work describes the importance of considering Herpes Simplex Virus as a cause of neonatal ophthalmia given the potential associated complications. Timely diagnosis and treatment are key to prognosis.

Abstract

There are different etiologies of neonatal ophthalmia such as viral ones. Among them, the Herpes simplex virus, both type I and II, is particularly relevant due to its potential severity. It is a rare, infrequent entity, but with a high rate of morbidity and mortality without appropriate diagnosis and management. **Objective:** To describe a case of neonatal ophthalmia caused by Herpes Virus type I, its clinical characteristics, and correct diagnosis. **Clinical Case:** 8-days old newborn, with no notable history, presenting edema and erythema of eyelids, accompanied by bilateral ocular discharge. Herpes Virus type I infection was diagnosed by PCR, without evidence of disseminated disease or central nervous system involvement. He received full treatment with intravenous Acyclovir with complete clinical improvement. **Conclusions:** Herpes Simplex Virus should always be considered as a differential diagnosis in all neonatal ophthalmia. Early and timely diagnosis and treatment are of vital importance.

Keywords:
Newborn;
Eye Infection;
Herpes Simplex Virus;
Acyclovir

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Introduction

Neonatal Ophthalmia is a type of conjunctivitis present in the first 28 days of life. It has an incidence of 1.6 - 12% of live newborns. Causes include chemical, bacterial, viral and lacrimal obstruction with differences in clinical presentation, treatment, and prognosis. Transmission can be of three types: vertical when there is premature rupture of the ovular membranes, hematogenous, or during passage through the birth canal, which is the most frequent[1]. The diagnosis is clinical and is based on the presence of conjunctival hyperemia and ocular discharge[2]. Table 1 shows the most frequent etiologies, their clinical characteristics, and treatment.

Prognosis varies depending on the etiologic agent involved[2]. Herpes simplex virus (HSV) infection is caused by both serotypes 1 (HSV-1) and 2 (HSV-2). It is a rare infection but is associated with a high rate of neonatal morbidity and mortality. Disease presentation predicts outcome and is classified into 3 categories: disseminated disease, central nervous system (CNS) disease, and skin, eye, and mouth (SEM) disease[3,4]. Early recognition and early treatment of neonatal HSV disease is not only associated with better outcomes but can also prevent progression to disseminated disease, which has a high mortality despite treatment[5]. SEM disease has the best outcome and very low mortality; however, it has significant morbidity associated with recurrences[4].

The objective of this publication is to describe a case of neonatal HSV-1 ophthalmia, its clinical features, and its diagnostic sequence.

This publication has the informed consent of parents and the approval of the Institutional Ethics Committee.

Clinical Case

21 year old mother, first pregnancy, without morbid history. Early control pregnancy, complicated with threat of preterm delivery at 31 weeks, for which she received full antenatal corticosteroids. She presented hypertension during pregnancy with preeclampsia-eclampsia syndrome and pregnancy cholestasis in third trimester, treated with Ursodeoxycholic acid. -No history of HSV infection, before or during pregnancy. Spontaneous onset of labor, with cesarean section due to unstable fetal status.

Male newborn, birth weight 3000 grams, good adaptation to extrauterine life, discharged at 4 days of life with exclusive breastfeeding. At 8 days of life, consulted in pediatric emergency department due to a 48-hour history of eyelid edema and bilateral ocular secretion. Physical examination revealed significant bilateral eyelid edema that made it impossible to visualize the conjunctiva, redness, local heat, and purulent ocular discharge (Figure 1), without skin lesions. The temperature on admission was 36.7 °C, and physical examination showed no other worthy elements.

He was diagnosed with neonatal ophthalmia and hospitalized. Ocular secretion culture and polymerase chain reaction (PCR) for Chlamydia, Gonococcus, and HSV type 1 and 2 were performed. Treatment was started with intravenous cefotaxime at 100 mg/kg/dose, azithromycin at 20 mg/kg/day, and ophthalmic tobramycin every 6 hours. After 24 hours, the patient tested positive for HSV-1, so treatment was started with acyclovir at 20 mg/kg/dose intravenously every 8 hours, suspending antibiotic treatment. During the evolution, he remained without neurological symptoms and no skin lesions, with clear improvement of ocular secretion and eyelid edema after treatment.

Blood count, liver function, azotemia, and serum creatinine were normal (table 2). Cerebrospinal fluid analysis showed a normal cytochemical study and PCR for HSV, multiplex PCR, and culture were negative. The cerebrospinal fluid study was not repeated. PCR in blood, nasopharynx, and rectum samples was negative for Herpes Virus. At 72 hours, an eye fundus study was performed which showed a bilateral epithelial corneal sore, so topical acyclovir and artificial tears were added to the treatment. He completed 14 days of intravenous acyclovir, with normal fundus study, and without corneal sore. At 22 days of life, he was discharged with suppressive treatment with oral acyclovir at 60mg/kg/day, and outpatient follow with pediatrician and ophthalmologist.

Discussion

Neonatal ophthalmia is a conjunctival infection, usually papillary and acute, that starts during the first 28 days of life. Its prognosis will vary depending on the etiologic agent involved and the early treatment given[5].

There are 3 main etiologies of ophthalmia: bacterial (predominantly *N. gonorrhoeae* and *C. trachomatis*), viral (predominantly adenovirus, HVS-1 and 2), and chemical, and three mechanisms of transmission: intrauterine, peripartum, and postnatal[1,3,6,9]. Our patient presented with a florid picture of conjunctivitis so an extensive etiologic evaluation was performed, and antibiotic treatment was initiated to cover the most frequently involved microorganisms. The clinical features, treatment, and prognosis will vary depending on the etiology (table 1). Finally, after evaluation, HSV-1 ophthalmia was diagnosed.

HSV infection in the newborn is not very prevalent. The overall rate of neonatal HSV, based on seropre-

Table 1. Clinical characteristics and treatment according to etiology. Adapted from bibliographic reference number 9

	Chemical	Bacterial			Viral
Etiological agent	Silver nitrate	*N. Gonorrhoeae*	*C. trachomatis*	Others*	HSV 1 y 2
Onset of symptoms	< 24 hours	2-7 days	5-14 days	5-14 days	6-14 days
Clinical presentation	+ Mild + conjunctival hyperemia	+ serohematic purulent secretion + Eyelid edema and chemosis + conjunctival membranes + Severe keratitis, corneal ulceration and perforation	+ mucopurulent secretion + palpebral edema and chemosis	+ mucopurulent secretion	+ palpebral edema + conjunctival Hiperemia +serohematic/ mucopurulent secretion + sore + acute retinal necrosis + skin or mouth injuries (80%)
Complications	No	Pneumonitis, Otitis, meningitis, sepsis.	Pneumonitis, rhinitis, arthritis, stomatitis	Sepsis	Disease progression to central nervous system or disseminated disease.
Treatment	Self limited	+ Localized: Cefotaxima IV 100mg/kg unique dosis or intramuscular or iv Ceftriaxone 25-50 mg/kg unique dosis (maximun dosis 125 mg) +Sistemic: Iv Cefotaxima 100 mg/kg/day in 2 dosis for 7 days, if meningitis 10-14 days.	azithromycin VO 20 mg/kg/day for 3 days.	+ Gram positiv: ocular Erythromycin 3 times a day for 7 days. + Gram negatives: ocular Tobramicin 3 times a day for 7 days.	Iv Aciclovir 60mg/kg/day in 3 dosis for 14 to 21 days. If corneal afection, topic acyclovir.

**Staphylococcus* spp., *Streptococcus pneumoniae*, *Haemophilus influenzae* no tipable, *Streptococcus mitis*, *Streptococcus* del grupo A y B, *Neisseria cinérea*, *Corynebacterium* spp., *Moraxella catarrhalis*, *Escherichia coli*, *Klebsiella pneumoniae, Pseudomonas aeruginosa*.

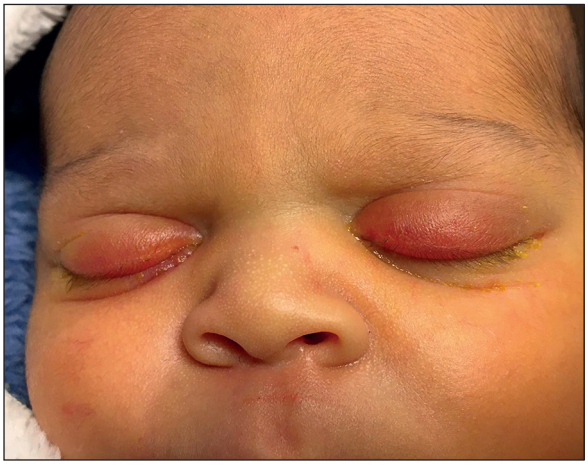

Figure 1. Patient with herpetic ophthalmia at time of hospital admission

Table 2. Summary of assessment tests performed.

Hemogram	Renal function	Hepatic function	Ionogram
Hemoglobin 14.3 g/dL	Creatininemia 0.47 mg/dl	Bilirrubin total 10 mg/dL	Na+ 140mEq/L
hematocrit 42%	Azotemia 0.06 g/L	Direct Bilirrubin 0.52 mg/dL	K+ 4.8 mEq/L
white blood cells 16900		Indirect Bilirrubin 10.1 mg/dL	Cl- 107 mEq/L
Platelets 533000		GOT 32 UI/ml GPT 10 UI/ml FA 206 U/L GGT 61 U/L LDH 881 U/L	Ca2+ 1.1 mmol/L

valence, is estimated to be 10 per 100,000 live births[8]. Mahant et al. reported an incidence of neonatal HSV infection of 4.6 per 10,000 births, noting an increase from 3.4 per 10,000 births in 2009 to 5.3 per 10,000 births in 2015.

Among the risk factors for neonatal herpes, the following are recognized: vaginal delivery (compared with cesarean delivery), invasive procedures at delivery, and HSV-1 infection (versus HSV-2)[1,3]. In our clinical case, no evident risk factors were recognized.

HSV-1 and HSV-2 are enveloped double-stranded DNA viruses[1,3] and humans are their only natural reservoir[7]. The spectrum of disease caused by HSV includes primary and recurrent infections of mucous membranes (e.g., gingivostomatitis, herpes labialis, and genital infections) in the immunocompetent adult, and visceral infections and encephalitis in immunocompromised hosts and neonatal herpes[7].

The different manifestations seem to be related to host characteristics and the age at infection[7]. The incubation period of primary infection ranges from 1 to 28 days. HSV is infectious during asymptomatic shedding and the 5 to 10 days that the mucous membrane lesions take to heal[7]. After primary infection, they establish lifelong latency in the sensory neural ganglia and can cause recurrent disease and asymptomatic episodes of viremia[1,6].

While HSV-2 has historically been the predominant serotype as a cause of genital and neonatal herpes, HSV-1 has clearly increased in incidence and is the most frequently isolated serotype today, as is the case in this patient[1,3]. Most genital infections caused by HSV-1 and 2 in immunocompetent adults are asymptomatic or may present lesions, which due to their location may be difficult to visualize[3,6]. This is consistent with the fact that 60% to 80% of women who have vertically transmitted HSV to their child do not report a history of genital herpes, as in our case[1]. Among women with a history of genital herpes, 75% have at least one recurrence during pregnancy and 14% will have symptoms or prodromal lesions at delivery[1,3].

Post exposure transmission rates increase from 2% in recurrent infections to 60% and 25% in primary and non-primary infections respectively[1,3,4,6], given the lack of transplacental antibodies transfer to the newborn of women with primary infection[1,3]. Considering that most of the patients do not report a history of herpetic infection, it is worth asking whether there is a need for peripartum screening to detect the presence of viremia at that time, similar to what is currently proposed for patients with active lesions and history of herpetic infection, in order to identify more newborns at high risk of developing HSV infection[8].

Neonatal HSV can be acquired *in utero* (congenital presentation) (5%), in the peripartum period (85%), or the postnatal period (10%)[1,3,6,9]. For the latter two acquisition periods, the extent of disease can be classified into the following categories: disease exclusively affecting skin, eyes, and mouth (SEM), central nervous system (CNS) disease, and disseminated disease. Each category may or may not include the other and manifest concomitantly. This classification is predictive of morbidity and mortality[3]. Prevalence rates are 25%, 30%, and 45%, respectively[1,6]. According to this classification, our newborn can be categorized as SEM disease, since only the conjunctivae are affected, and further lesion extension has been ruled out by specific evaluation.

In SEM disease, infection is limited to the skin, eyes, and/or mouth. Symptoms usually present early, at 10-12 days of life and 80% of these patients have a vesicular rash on physical examination, which was not observed in our patient[3,9].

HSV ocular disease can be classified as primary or recurrent and also as blepharitis, conjunctivitis, epithelial keratitis, stromal keratitis, iridocyclitis, or retinitis based on inflamed tissue[7]. Herpes virus conjunctivitis is associated with corneal opacity and visual loss[8] and the clinical presentation can be unilateral or bilateral[10].

The correct diagnosis of herpetic infection is essential, as early initiation of an appropriate treatment significantly reduces morbidity and mortality. The cornerstone of diagnosis is virological detection. Definitive microbiological diagnosis requires virus growth in tissue culture (gold standard) or detection of viral nucleic acid by real-time polymerase chain reaction (RT-PCR), as was the case in our patient, in whom the ocular sample was positive[11].

The diagnostic procedure is not simple, especially because of the stratification, since several samples must be obtained from different parts of the body, such as nasopharynx, jugal mucosa, conjunctival mucosa, rectum, skin lesions if exists, blood, and cerebrospinal fluid (CSF)[12]. Lumbar puncture should be performed in every neonate with suspected herpetic infection, even if isolated skin involvement is presumed[12].

Viremia can exist in any of the three forms of infection (disseminated, CNS, or SEM). Therefore, a positive PCR or blood culture does not classify the type of infection, but it does confirm it.

Central nervous system involvement is confirmed by positive PCR in CSF. This has a sensitivity of over 95% and a specificity of 100%[2]. CSF analysis shows predominantly mononuclear pleocytosis and moderate protein- and hypoglycorrhachia[13].

Serological diagnostic methods have a limited role in the diagnosis of neonatal HSV infection due to the transplacental passage of maternal immunoglobulins, which is why they are not indicated in the diagnosis[2].

If only skin or conjunctival samples are positive, a

diagnosis of SEM HSV infection is confirmed, as in this case of herpetic conjunctivitis.

With a positive diagnosis, the lesion extension of the virus should always be evaluated by blood count, neuroimaging, and renal, liver, and enzymatic function. There was no involvement of other parenchyma or inflammatory response in this case, and all results were within normal parameters.

Herpetic infections involving the eyes should be complemented with an eye fundus study in search of keratitis, uveitis, and corneal sore. In the case presented, corneal sore was observed, and it was resolved 14 days after treatment. Treatment of HSV includes life support measures as for any infectious process in the newborn, management of potential complications, and antiviral treatment. In this case, given the clinical stability, the child was admitted to the Intermediate Care Unit, where he received strict surveillance and continuous monitoring of his evolution and treatment. Clinical suspicion is sufficient to initiate treatment and should not wait for the confirmatory result since early treatment improves the morbidity and mortality associated with the disease by reducing mortality from 80% to 30% in disseminated disease and from 50% to 5% in forms with CNS involvement[2]. It also prevents progression to disseminated disease or neurological involvement of SEM disease[2].

The drug of choice in all types of neonatal herpes is acyclovir[2,7,11,14]. This drug is a nucleoside analog that selectively inhibits HSV replication[14]. The recommended dose is 20 mg/kg/dose every eight hours intravenously. The duration of treatment is 14 days for SEM disease and 21 days for disseminated forms and CNS involvement[2,7,11,14]. In the latter cases, treatment can be extended if the cerebrospinal fluid test continues to be positive.

A control lumbar puncture should be performed in these patients after 21 days. If it continues to be positive, treatment is extended for one week and the puncture is repeated. This is done successively until a negative result is obtained[7]. Persistence of positive HSV PCR in CSF beyond 21 days is associated with a worse neurological prognosis[3,6].

In SEM-type disease, where there is involvement of the ocular conjunctiva, topical treatment should be performed in addition to intravenous treatment using acyclovir 3%, administered every 6 to 8 hours[10,15].

In all clinical forms, after treatment of acute disease, suppressive treatment with acyclovir at 300 mg/m2/dose orally every eight hours is recommended for at least six months[2,7,11,13,14]. There is evidence to affirm that suppressive therapy considerably improves neurodevelopment in these children and, in SEM disease, cutaneous recurrences are reduced[2,3,3,7,16]. Control with blood count at 2 and 4 weeks and monthly is necessary, given the risk of reversible neutropenia which is dose-dependent[2,3].

Conclusions

Despite its low incidence in neonates, HSV is in the category of the most potentially serious viruses, with possible devastating neurological effects. Neonatal ophthalmia is a common infectious disease in the perinatal period and has an excellent prognosis if well treated. It is essential to always include HSV PCR in the diagnostic algorithm for this type of infection.

Early and timely initiation of antiviral treatment is not only associated with better outcomes but also prevents progression to severe disease, which has high morbidity and mortality.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the parents (tutors) of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

References

1. James S, Kimberlin D. Neonatal Herpes Simplex Virus Infection. Clin Perinatol. 2015;42(1):47-59.
2. Vila J, Frick M, Suy A, et al. Infección Neonatal Por Virus Herpes Simplex. Unitat de Patologia Infecciosa i Immunodeficiències de Pediatria. Hospital Universitari Vall d'Hebron, Barcelona 2015;1-24. [online] Available at <https://www.upiip.com/sites/upiip.com/files/HERPES%20NN_0.pdf> [Accessed 31 October 2020]
3. Pinninti S, Kimberlin D. Neonatal herpes simplex virus infections. Semin Perinatol. 2018;42(3):168-75.
4. Mahant S, Hall M, Schondelmeyer A, et al. Neonatal Herpes Simplex Virus Infection Among Medicaid-Enrolled Children: 2009-2015. Pediatrics. 2019;143(4):e20183233.
5. Martín-Begué N, Frick MA, Alarcón S, et al. Conjuntivitis neonatal. Acta Estrabológica. 2017;XLVI(2):159-64.
6. Wang A, Wohrley J, Rosebush J. Herpes Simplex Virus in the Neonate. Ann Pediatr. 2017;46(2):e42-e46.
7. Liesegang T. Herpes Simplex Virus Epidemiology and Ocular Importance. Cornea, 2001; 20(1):1-13.
8. Kimberlin D, Baley J. Guidance on Management of Asymptomatic Neonates Born to Women With Active Genital Herpes Lesions. Pediatrics. 2013;131(2):e635-e646.
9. Matos R, Pires J, Cortesão D. Management of Neonatal Herpes Simplex Infection: A Rare Case of Blepharoconjunctivitis and Concurrent Epithelial and Stromal Keratitis. Ocul Immunol Inflamm. 2018;26:625-7.
10. Weisenthal R, Daly M, de Freitas D, et al. External Disease And Cornea. Infectious Diseases of the External Eye: Basic Concepts and Viral Infections. San Francisco: American Academy of Ophthalmology. 2019;9:246-73. <https://www.aao.org/course/herpes-simplex-virus-diagnosis-management-copy. [Accessed 31 October 2020].
11. Gleason C, Juul S. Avery. Infecciones víricas del feto y del recién nacido Enfermedades del recién nacido. 10 ª ed. Barcelona: Elsevier 2019;482-91.
12. Kabani N, Kimberlin D. Neonatal Herpes Simplex Virus Infection. NeoReviews. 2018;19(2):e89-e96.
13. Baquero F, Prieto L, Ramos J, et al. Guía de la Sociedad Española de Infectología Pediátrica sobre prevención, diagnóstico y tratamiento de la infección neonatal por virus herpes simplex. An Pediatr (Barc). 2018;89(1):64.e1-64.e10.
14. Cloherty J, Eichenwald E, Hansen A, et al. Infecciones víricas. Manual De Neonatología. 8 ª Ed. Barcelona: Wolters Kluwer 2017;622-8.
15. Muñoz E, Morillo B. Infecciones Por Virus Herpes Simple. Grupo de patología infecciosa. AEP Asociación Española de Pediatría [online] 2017;1-33. Available at: <https://www.aepap.org/grupos/grupo-de-patologia-infecciosa/biblioteca/infecciones- por-virus-herpes-simple-gpi-2017> [Accessed 31 October 2020].
16. Kimberlin D, Whitley R, Wan W, et al. Oral Acyclovir Suppression and Neurodevelopment after Neonatal Herpes. N Engl J Med. 2011;365(14):1284-92.