CASE REPORT

A rare infectious cause of severe neonatal skin lesions

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SUMMARY

We present a case of a preterm infant of 28 weeks' gestation with unique cutaneous lesions characteristic of a congenital herpes simplex virus (HSV) type 1 infection. The infant was prematurely delivered due to intractable labour. The mother had no history or clinical signs of genital infection before or during pregnancy. The infant's skin lesions were described as rough white-yellow plaques; a skin biopsy demonstrated calcified plaques and absent epidermis. HSV type 1 was later determined using PCR on the infant's skin biopsy and cerebral spinal fluid as well as the mother's vaginal swab and the placenta. Calcifications have already been described by Allee *et al*, alongside a diagnosis of HSV type 2. As is well known, the morbidity and mortality of congenital herpes infections are very high.

BACKGROUND

Neonatal herpes simplex virus (HSV) infection is rare, with incidence ranging from 1/1400 to 1/30 000 deliveries in the USA.^{1 2} Poeran *et al*³ reported that incidence in the Netherlands may be 10 times lower than in the USA. Only 5% of infections occur through intrauterine transmission, classified as congenital HSV infection.^{2 4} Of these, only 10% are due to HSV type 1.⁵ The most common clinical manifestations are cutaneous lesions, half of which are vesicobullous or ulcerations/erosions.² We describe a unique cutaneous presentation of a congenital HSV type 1 infection in a preterm infant.

CASE PRESENTATION

A preterm male infant was born at the gestational age of 28 weeks by caesarean section performed due to preterm labour and breech position. The baby's mother was gravida 3 para 2, both previous infants having been born spontaneously at term, and was admitted to our hospital in preterm labour 3 days before delivery. She was treated with tocolytics (atosiban and nifedipine) and received 2×12 mg intramuscular betamethasone to promote fetal lung maturation. Besides the bacterial vaginosis present on admission, the mother had no history of genital infection. At previous prenatal care visits, no signs of infection were detected, nor was a HSV serology test performed.

Apgar scores were 1, 3 and 5 after 1, 5 and 10 min, respectively. Birth weight (890 g, SDS -0.9) and birth length (35 cm, SDS -1.1) were both normal. Head circumference, however, indicated microcephaly (23 cm, SDS -2.1). Because of severe respiratory distress after birth, the infant was

intubated for surfactant administration and ventilation. Besides respiratory distress, physical examination revealed prominent skin lesions on the thorax, back and limbs, consisting of rough white-yellow plaques. Furthermore, remarkable general erythroderma was reported with increased bleeding tendency of the skin. Finally, a linear laceration was located at the right fossa, possibly due to traction on the vulnerable skin at time of birth (figures 1 and 2).

In addition to skin lesions, physical examination also revealed a cardiac murmur, a cloudy cornea and a bloated abdomen.

INVESTIGATIONS

The mother's perinatal serum IgG tested negative for HIV, toxoplasma, rubella, cytomegalovirus, hepatitis C and HSV. She was immune to hepatitis B.

Initial laboratory evaluation of the infant revealed thrombocytopenia (24×10^9 platelets/L), a haemoglobin level of 13.8 g/L and a pronounced neutropaenia of 0.5×10^9 /L. Bacterial and fungal cultures taken from blood and skin remained negative. A total body X-ray showed respiratory distress syndrome grade 3–4 and hyperdense metaphyses of femur and humerus, indicating metaphysitis (figure 3). Cranial ultrasound images demonstrated immature brain parenchyma and slightly asymmetric lateral ventricles with no signs of bleeding. A heart murmur was diagnosed as a patent ductus arteriosus, using cardiac ultrasound. Abdominal ultrasound revealed bilateral calcifications of the adrenal glands and hepatomegaly. A skin biopsy demonstrated calcified plaques and absent epidermis. The calcifications prompted a call for PCR HSV, which was positive on a swab of the affected skin after DNA amplification. The diagnosis of congenital HSV infection was thus established. A lumbar

Figure 1 Severe erythrodermia with yellow-white patchy skin lesions in a preterm neonate with congenital HSV type-1 infection.

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Figure 2 Erythrodermia at the abdominal site with linear laceration at the right fossa.

puncture was performed in order to test for encephalitis. A cell count in cerebrospinal fluid (CSF) revealed 4000 white blood cells/mm³ and 585 000 red blood cells/mm³; PCR tested positive for HSV type 1.

DIFFERENTIAL DIAGNOSIS

Initially, congenital syphilis or congenital candida infection was suspected but syphilis serology in the infant and the mother proved negative for *Treponema pallidum*. Moreover, no pathogens could be detected in blood and skin cultures.

TREATMENT

Broad spectrum antibiotics (penicillin and amikacin) and antifungal therapy (fluconazole) were begun empirically. At day 2, the PCR of the skin biopsy became positive for HSV; treatment with high-dose intravenous acyclovir was added to the therapy.

Figure 3 X-ray demonstrating hyperdense metaphyses of femur and humerus.

OUTCOME AND FOLLOW-UP

Despite antiviral and intensive supportive treatment, the patient died 5 days after birth, due to cardiorespiratory arrest preceded by persistent metabolic acidosis and hypovolaemia in spite of massive fluid administration and inotropic therapy, secondary to extremely high insensible water loss and capillary leak syndrome. Permission for an autopsy was refused by the mother.

Histological examination of the placenta demonstrated acute chorioamnionitis, acute vasculitis, and acute and chronic funisitis. An additional PCR test for HSV type 1 was performed on placental tissue and returned a positive result. A second maternal blood sample, taken 2 weeks after the birth in order to diagnose seroconversion, revealed a positive IgG for HSV. However, HSV-IgM antibodies remained negative. The mother's vaginal swab, taken after the birth, demonstrated HSV type 1 after DNA amplification.

DISCUSSION

Mother to child transmission risk

Transmission of HSV from mother to infant can occur in utero (congenital infection), in the perinatal period or in the post-natal period, with vertical transmission rates of 5%, 85% and 10%, respectively.^{6 7} An infection that includes symptoms at birth or within 48 h of rupture of the membranes is classified as a congenital or intrauterine infection and can occur via two different pathways.⁴ The first of these involves maternal viraemia with a primary HSV infection and placental transmission during pregnancy; this is the most common means of vertical transmission. The second pathway involves an ascending infection; it is usually seen in mothers with active HSV and prolonged rupture of the membranes but can also occur with intact membranes.⁶ This is most likely the mode of transmission in our case.

Maternal risk factors

As in our case, approximately 70% of all newborns infected with HSV are born to mothers with no clinical history of infection.^{6 8} Only 75% of women with genital HSV infections acquired during pregnancy have symptoms indicative of such an infection.⁶ Pregnant women with a disseminated disease before 20 weeks of gestation have the highest risk of intrauterine transmission.⁹ Because of proven seroconversion, we can conclude the mother of our patient had an asymptomatic primary genital HSV-1 infection, with amniotic membrane rupture as an additional risk factor.

Clinical morbidity and mortality

Congenital HSV infection is associated with abortion, premature birth and intrauterine growth restriction.¹⁰ A congenital HSV infection usually presents as a disseminated disease with a triad of cutaneous manifestations, eye findings and neurological involvement.^{4 6} In general, the extent of the disease has the highest influence on mortality and morbidity, and neonates with limited disease have higher survival rates than neonates with central nervous system (CNS) involvement or disseminated disease.¹¹

Skin lesions

Several skin lesions have been reported in congenital HSV infections, including vesicles, pustules, erythema, bullae, hypopigmentation, polycyclic patches and erosions.^{2 12 13} In our case, yellow plaques were present. Biopsy determined calcifications

and the absence of epidermis. Intrauterine epidermal necrosis and calcifications of the epidermis in premature infants have been described by Allee *et al*¹⁴ and Ruiz-Maldonado *et al*.¹⁵ The cause of this necrosis and calcification was unknown in the case of Ruiz-Maldonado, but Allee *et al* diagnosed HSV type 2 infection. Our case, however, was diagnosed as a congenital HSV type 1 infection.

Non-cutaneous lesions

Brain lesions such as microcephaly, hydranencephaly, encephalomalacia and intracranial calcifications are common in intrauterine HSV infections.^{6 16} Only microcephaly was present in our case.

Visceral manifestations, such as adrenal calcifications and hepatomegaly, are frequently reported in congenital HSV infection; both were present in our patient.² Johansson *et al*⁵ reported lower limb hypoplasia due to intrauterine infection with HSV type 2 in a preterm infant. Ocular involvement is common with chorioretinitis, retinal detachment, optic atrophy and persistent fetal ocular vasculature.^{6 17} In our case, clinical diagnosis of ocular involvement was performed only because of a cloudy cornea. Anderson *et al*¹⁸ described hydrops fetalis in an unusual presentation of intrauterine HSV infection. The case presented demonstrates unique cutaneous presentation of a congenital HSV type 1 infection associated with visceral abnormalities (hepatomegaly and adrenal calcifications) and clinical ocular involvement.

Diagnosis

To isolate HSV in an infant with possible congenital HSV, recent guidelines advise that viral cultures be taken from surface sites, such as skin lesions, eye, conjunctivae, mouth, anus or oropharyngeal secretions.¹⁹ The direct immunofluorescent antibody technique can be performed only on cutaneous lesions, to guarantee reliability.¹ In identifying CNS involvement, lumbar puncture is essential. Viral cultures on CSF are insufficiently sensitive. In HSV encephalitis, a culture is positive in only 50% of cases. While PCR has a high sensitivity and specificity, false negative PCR results can occur due to low viral load or the sensitivity of the test.²⁰ In some cases, serial PCR testing is necessary.¹ The performance of PCR test for HSV in blood is high for disseminated infection while sensitivity is low for localised neonatal HSV infection.^{20 21}

Serological testing is not recommended due to the lack of sensitivity and specificity of the available tests.^{1 22} In order to diagnose CNS involvement, an EEG can be performed. Even very early in CNS involvement, when CT and MRI of the brain are still normal, EEG already can show focal and multifocal periodic epileptiform changes. After some days, CT and MRI show parenchymal brain oedema, haemorrhage and destructive lesions. An X-ray of the thorax can identify bilateral diffuse pneumonia. Abdominal ultrasound can demonstrate ascites and hepatomegaly.

Treatment

High-dose therapy with 60 mg/kg/day acyclovir for 3 weeks is recommended.¹ In perinatal HSV infection, there is some evidence that oral antiviral suppressive therapy with acyclovir following intravenous treatment improves long-term outcomes, but this was not studied with congenital HSV. Current recommendations are to treat with oral acyclovir for 6 months.²⁰ In vitro studies have shown that HSV type 2 is less susceptible to acyclovir than HSV type 1 is.²³

Learning points

- In the event of unknown extensive skin lesions at birth, it is important to consider congenital herpes simplex virus (HSV) infection.
- Intrauterine HSV infection, especially type 1, is rare.
- Congenital HSV can occur even in asymptomatic mothers with negative HSV serology.
- Immediate treatment with high-dose acyclovir intravenous is known to improve morbidity and mortality.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Enright AM, Prober CG. Neonatal herpes infection: diagnosis, treatment and prevention. *Semin Neonatol* 2002;7:283–91.
- 2 Marquez L, Levy ML, Munoz FM, *et al*. A report of three cases and review of intrauterine herpes simplex virus infection. *Pediatr Infect Dis J* 2011;30:153–7.
- 3 Poeran J, Wildschut H, Gaytant M, *et al*. The incidence of neonatal herpes in The Netherlands. *J Clin Virol* 2008;42:321–5.
- 4 Caviness AC. Neonatal herpes simplex virus infection. *Clinical Pediatric Emergency Medicine*. 2013;14:135–45.
- 5 Johansson AB, Rassart A, Blum D, *et al*. Lower-limb hypoplasia due to intrauterine infection with herpes simplex virus type 2: possible confusion with intrauterine varicella-zoster syndrome. *Clin Infect Dis* 2004;38:e57–62.
- 6 Kimberlin DW. Neonatal herpes simplex infection. *Clin Microbiol Rev* 2004;17:1–13.
- 7 Kropp RY, Wong T, Cormier L, *et al*. Neonatal herpes simplex virus infections in Canada: results of a 3-year national prospective study. *Pediatrics* 2006;117:1955–62.
- 8 O'Riordan DP, Golden WC, Aucott SW. Herpes simplex virus infections in preterm infants. *Pediatrics* 2006;118:e1612–20.
- 9 Anzivino E, Fioriti D, Mischitelli M, *et al*. Herpes simplex virus infection in pregnancy and in neonate: status of art of epidemiology, diagnosis, therapy and prevention. *Viral J* 2009;6:40.
- 10 Avgil M, Ornoy A. Herpes simplex virus and Epstein-Barr virus infections in pregnancy: consequences of neonatal or intrauterine infection. *Reprod Toxicol* 2006;21:436–45.
- 11 Lopez-Medina E, Cantey JB, Sánchez PJ. The mortality of neonatal herpes simplex virus infection. *J Pediatr* 2015;166:1529–32.e1.
- 12 Yasmeen A, Ibhanebeh SE. Severe congenital herpes simplex virus infection. *Arch Dis Child Fetal Neonatal Ed* 2014;99:F157.
- 13 Koch LH, Fisher RG, Chen C, *et al*. Congenital herpes simplex virus infection: two unique cutaneous presentations associated with probable intrauterine transmission. *J Am Acad Dermatol* 2009;60:312–15.
- 14 Allee JE, Saria EA, Rosenblum D, *et al*. Intrauterine epidermal necrosis. *J Cutan Pathol* 2001;28:383–6.
- 15 Ruiz-Maldonado R, Durán-McKinster C, Carrasco-Daza D, *et al*. Intrauterine epidermal necrosis: report of three cases. *J Am Acad Dermatol* 1998;38(5 Pt 1):712–15.
- 16 Duin LK, Willekes C, Baldewijns MM, *et al*. Major brain lesions by intrauterine herpes simplex virus infection: MRI contribution. *Prenat Diagn* 2007;27:81–4.
- 17 Corey RP, Flynn JT. Maternal intrauterine herpes simplex virus infection leading to persistent fetal vasculature. *Arch Ophthalmol* 2000;118:837–40.
- 18 Anderson MS, Abzug MJ. Hydrops fetalis: an unusual presentation of intrauterine herpes simplex virus infection. *Pediatr Infect Dis J* 1999;18:837–9.
- 19 Pickering LK, Baker CJ, Kimberlin DW, *et al*. *Red book report of the committee on infectious diseases*. 29th edn. Elk Grove Village, IL: American Academy of Pediatrics, 2012.
- 20 Pinninti SG, Kimberlin DW. Management of neonatal herpes simplex virus infection and exposure. *Arch Dis Child Fetal Neonatal Ed* 2014;99:F240–4.
- 21 Kimberlin D, Cloud G, Lakeman F, Jacobs R, *et al*. Serum Polymerase Chain Reaction (PCR) may not diagnose neonatal Herpes simplex virus (HSV) disease. *42nd Annual meeting of Infectious Disease Society of America*; Boston, Massachusetts, 2004.
- 22 Jacobs RF. Neonatal herpes simplex virus infections. *Semin Perinatol* 1998;22:64–71.
- 23 Whitley R, Arvin A, Prober C, *et al*. Predictors of morbidity and mortality in neonates with herpes simplex virus infections. The National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. *N Engl J Med* 1991;324:450–4.

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