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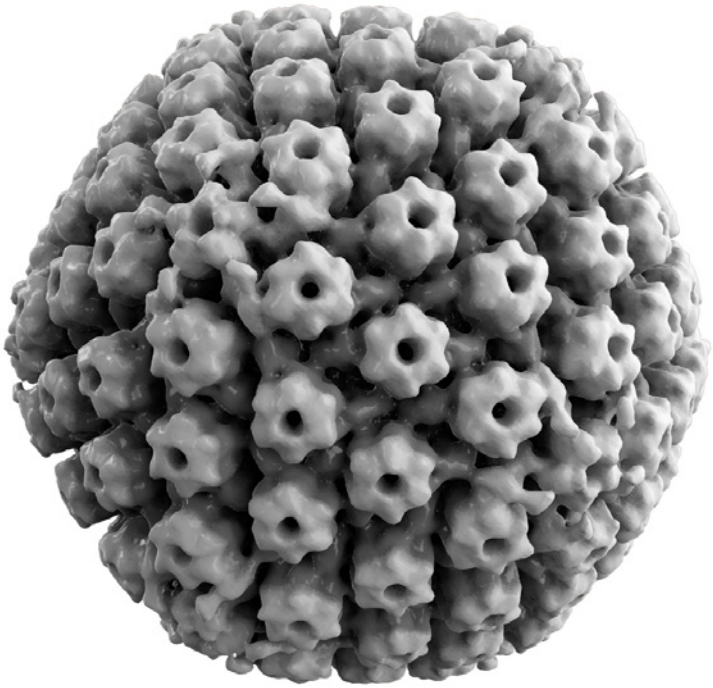
Herpes simplex infection in a newborn



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Title figure:
3D reconstruction of an immature HSV-1 capsid
(source:https://commons.wikimedia.org –
Thomas Splettstoesser (www.scistyle.com))

INTRODUCTION

Disseminated neonatal herpes simplex virus (HSV) infection is the most serious form of neonatal herpes infection and is associated with high mortality and morbidity rates. Early recognition is crucial but can be difficult since clinical presentation often mimics bacterial infection (1).

For poorly understood reasons, large variations in the incidence of neonatal HSV infections have been reported, ranging from 1 case per 2'000 live births in the USA to 5.9 cases per 100'000 live births in Canada. In Switzerland, the incidence is even lower (1.6 cases per 100'000 live births), and more frequently caused by HSV-1 than HSV-2 (2).

We present the case of an 11-day-old baby with favorable outcome after a disseminated HSV-1 infection to highlight the importance to consider HSV infection early in the course of a baby presenting in a septic condition.

This girl was born at 39 3/7 weeks of gestation by normal vaginal delivery with a birth weight of 2990 g (P10 – 25), a body length of 46 cm (< P10) and head circumference of 34 cm (P25 – 50). She was the second child of a healthy 29-year-old woman. Pregnancy had been unremarkable with negative maternal serology results and a negative group B streptococcal swab. The baby adapted well with an Apgar score of 9, 10, 10 at 1, 5, and 10 minutes, respectively, and a normal umbilical artery pH of 7.34. There was no history nor clinical sings of maternal HSV infection.

On day of life (DOL) 9, parents noticed various erythematous spots on the skin of the torso (Fig 1, 2). Otherwise, the girl was in perfect general condition and feeding well. The family and midwife decided to observe the child for now. On DOL 11, the girl developed a distended abdomen. When the parents used a thermometer to stimulate bowel movements, they noted a body temperature of 40°C and therefore brought their daughter to our emergency departement.

On admission, the baby was in a poor general condition, with tachycardia and tachypnea, poor perfusion (recap time of 5 seconds), and an oxygen saturation of 88 % in room air. She was encephalopathic with irritability, lethargy and a tendency for opisthotonus. The anterior fontanel was normal. The abdomen was markedly distended, slightly tender and bowel sounds were absent. There was a bluish discoloration around

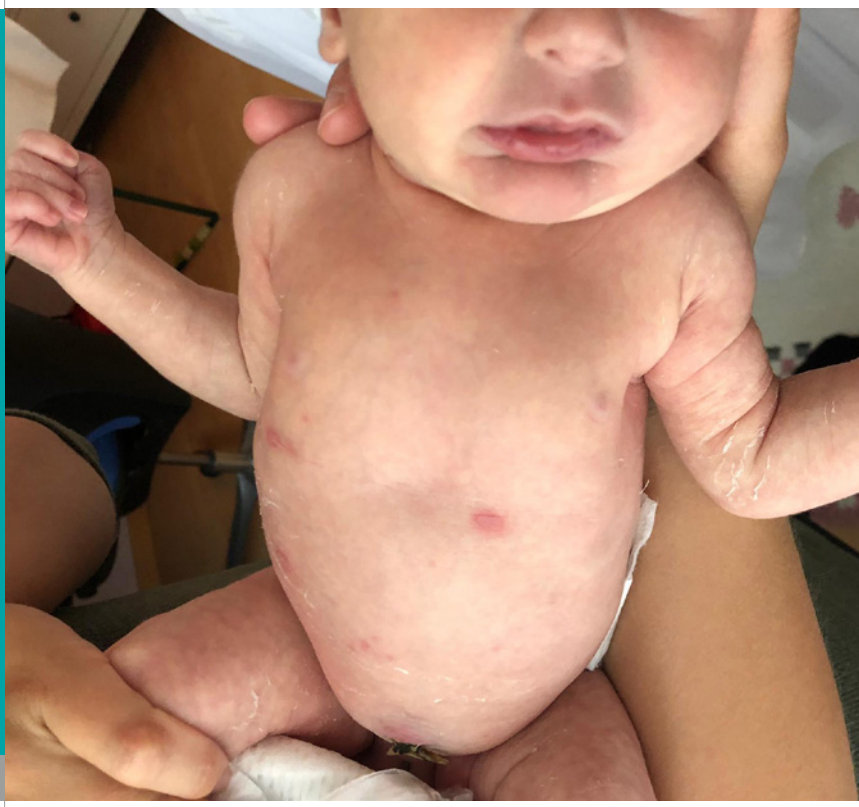

Fig. 1

Skin lesions on the infant's abdomen on DOL 9 (photograph sent to the midwife by the parents).

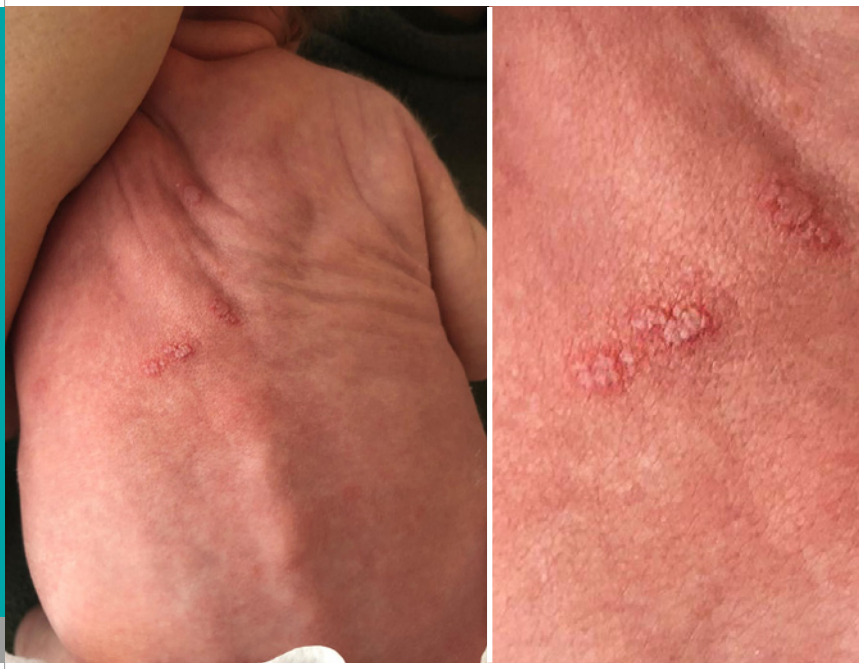

Fig. 2

Skin lesions on the infant's back on DOL 9 (photograph sent to the midwife by the parents on DOL 9): overview (left), close-up view showing grouped vesicles on an erythematous base (right).

the umbilicus. Skin color was pale – greyish with multiple erythematous lesions on the torso; in two areas, these lesions were associated with multiple grouped vesicles on an erythematous base (Fig. 3).

After taking blood cultures, the baby was immediately started on antibiotics (amoxicillin and gentamicin), and, because of the skin lesions, acyclovir was added. Simultaneously, a fluid bolus was given, and the baby was transferred to our ICU. She was started on respiratory support with high flow nasal cannula oxygen (2 l/kg/min, max. FiO_2 0.5). Chest X-ray showed some haziness in the right upper lobe. Her sepsis work-up was completed with a lumbar puncture and a urine culture in the first hour of presentation.

An abdominal X-ray showed no evidence of free air but markedly distended intestinal loops (Fig. 4). Nevertheless, because of the impressive clinical appearance, metronidazole was added to the treatment regime, and enteral nutrition was withheld for 24 hours.

On admission, her leukocyte count was 8.5 G/l, CRP (93 mg/l) and PCT (31.6 ng/l) were both elevated. Despite the poor clinical condition of the baby, blood gas analysis was normal. Cerebrospinal fluid analysis showed a normal white cell count (4/µl), and normal glucose, protein and lactate levels; however, PCR for HSV-1 was positive. Skin lesions were also positive for HSV-1. Liver enzymes were elevated (ASAT

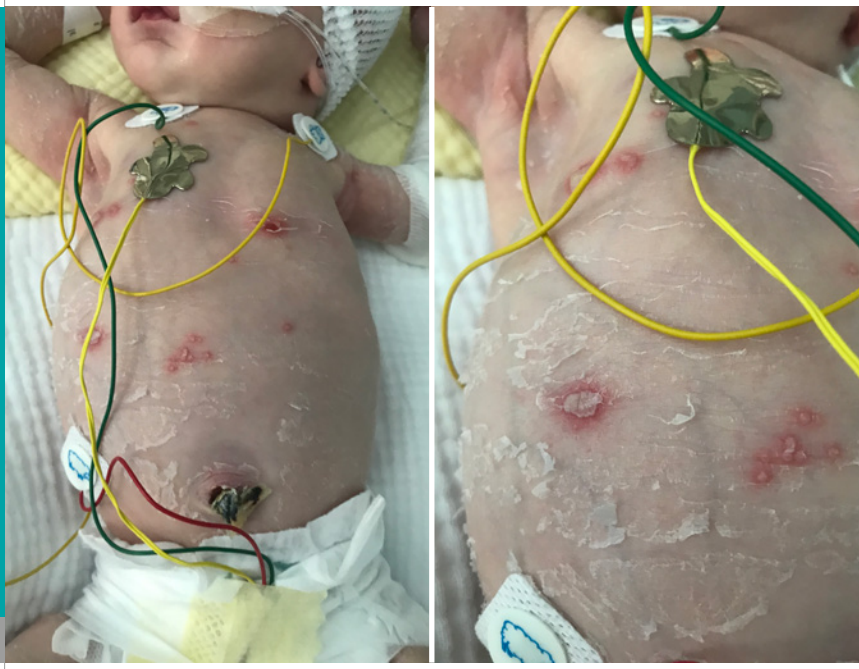

Fig. 3

Skin lesions on admission (DOL 11): note grouped vesicles on an erythematous base, characteristic for HSV lesions.

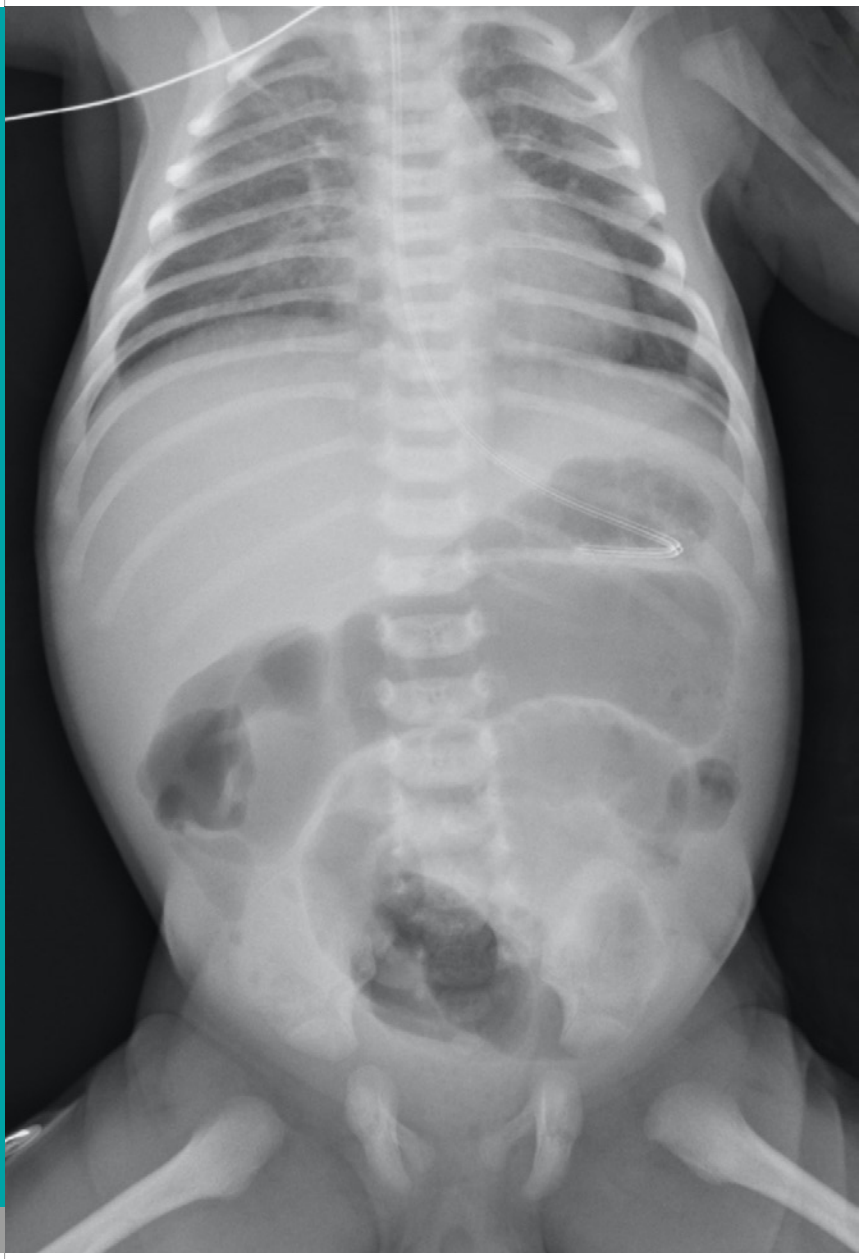

Fig. 4

Babygram on admission showing distended loops of bowel but no evidence of free air.

3529 U/l, ALAT 735 U/l, gGT 136 U/l), but there were no signs of liver failure (normal glucose, lactate and ammonia levels, as well as normal coagulation studies). All bacterial cultures remained negative, and antibiotic treatment was stopped after 48 hours.

A head ultrasound examination was normal. Amplitude integrated EEG (aEEG) was installed for the first 48 hours and showed a normal continuous voltage pattern. A formal EEG showed some low-amplitude background activity with right hemispheric steep waves but no epileptic potentials. The follow-up EEG after one week was completely normal. On cranial MRI on day 4 of treatment, there was no evidence of cerebral involvement, particularly no brain edema or parenchymal lesions.

Within 48 hours, her neurological status improved and she started to feed; only an increased muscle tone of the upper extremities persisted. Respiratory support with supplemental oxygen was required until day 9 of hospitalisation.

To summarize, this baby presented with disseminated HSV-1 infection involving lung, skin, liver and central nervous system. All laboratory values normalised over 10 – 14 days. Treatment with intravenous acyclovir was given for 21 days. HSV-1 PCR on a repeat CSF sample on day 19 of treatment was negative.

DISCUSSION

Most neonatal HSV infections (85 %) are acquired during delivery, although in utero (5 %) and postnatal (10 %) infections from non-genital infections in a parent or other caregiver do occur. The risk of a neonatal transmission was estimated to be 57 % with primary infection compared to 2 % with recurrent genital HSV infections. The perinatal transmission risk of HSV-1 is higher compared to HSV-2; however, HSV-2 infections are associated with more severe presentations and worse outcomes (3, 4). The majority of primary infections in adults is asymptomatic. More than 75 % of neonates with HSV infection are born to a mother with no known history of genital HSV infection, limiting the utility of a negative maternal history (5). In our case, there was neither a family or caregiver history of cold sores, nor a maternal history of a genital HSV infection.

For morbidity and mortality prediction, classification of clinical presentation in the following groups is useful (3, 6):

1) **SEM disease** (skin, eye and mouth) accounts for 45 % of all neonatal HSV manifestations. It may appear benign at the onset of illness but is associated with a high risk of progression to CNS or disseminated disease.
2) **CNS disease** (central nervous system disease) accounts for 30 % of all neonatal HSV manifesta-

tions. Infants present with focal or generalized seizures, lethargy, irritability, and/or poor feeding. Mortality is usually due to devastating brain destruction.

3) **Disseminated herpes infection** is the most severe form and accounts for 25 % of all cases. Presentation is similar to viral sepsis with involvement of multiple organs including CNS, lungs, liver, adrenal glands, skin, eye and mouth. Mortality is 30 % and usually due to liver failure and severe coagulopathy.

In absence of cutaneous vesicles (one third of the cases), diagnosis is challenging because CNS disease and disseminated HSV infection are indistinguishable from other causes of neonatal sepsis. All manifestations usually present around day 10 – 12 of life but may occur at any time during the first six weeks of life. In our case, the first cutaneous manifestations appeared on DOL 9 and progressed to disseminated disease within 48 hours.

Diagnosis of neonatal HSV disease may be confirmed by isolation of virus from skin lesions (if present) or surface cultures (swabs from conjunctivae, nasopharynx, mouth and anus). HSV PCR may also be performed on samples obtained from these swabs. HSV PCR testing is especially useful for cerebrospinal fluid analysis (sensitivity 75 – 100 %, specificity 71 – 100 %) but it is important to consider that the test may be negative in very early stage of disease due to a very

low viral load. CSF typically shows pleocytosis with predominance of mononuclear cells. A positive blood HSV PCR test confirms the diagnosis of HSV infection but cannot be used to determine the type of disease (3, 5).

The Swiss herpes management forum recommends swabs from conjunctivae, nasopharynx, mouth and anus for culture at the age of 24 to 48 hours in a neonate of a mother with proven genital HSV infection or known sub partum viral spreading. In neonates presenting with symptoms suspicious for HSV infection (skin lesions, conjunctivitis, seizures, lethargy, fever of unknown origin), the recommendations include swabs from the lesion(s) (conjunctivae, skin) for culture, CSF HSV PCR, complete blood count, liver enzymes, total and direct bilirubin, ammonia, creatinine, coagulation studies as well as cerebral imaging and/or ophthalmological examination (4 – 6). In our case, CSF examination showed no pleocytosis but HSV-1 PCR was positive. HSV-1 PCR was also positive from the skin lesions. HSV culture and blood HSV PCR were not done.

Standard treatment is acyclovir 20 mg/kg/dose intravenously 8-hourly. This drug works by blocking viral DNA synthesis. The most important side effects of acyclovir are renal dysfunction and neutropenia. Duration of therapy varies depending on disease classification. Infants with SEM should be treated for 14 days. Infants with CNS or disseminated disease

should be treated for a minimum of 21 days. Infants treated for CNS involvement should have a repeat CSF HSV PCR near the end of the treatment course. In case of a persistent positive HSV PCR, treatment should be extended past 21 days until PCR is negative (5).

Oral prophylaxis with acyclovir for 6 months up to 1 year in patients with CNS disease has been reported to improve neurodevelopmental outcome and prevent cutaneous recurrences (7). The Swiss herpes management forum does not give any recommendation on this issue, and most experts agree that the role of suppressive treatment has not yet been clarified. In view of the favorable course in our patient and the potential side effects of acyclovir prophylaxis we decided against it.

The one-year mortality rate for disseminated disease is 30 %. Approximately 80 % of survivors of disseminated neonatal HSV infection have normal neurologic development. The risk of neurodevelopmental abnormalities (developmental delay, hemiparesis, seizures, blindness) is increased among infants with seizures prior or during antiviral therapy. In CNS disease, the one-year mortality rate is lower (5 %), but normal neurodevelopment is observed in only 30 % of patients.

Favorable outcomes depend largely on early initiation of antiviral therapy and treatment delays result in higher mortality rates. In our case, suspicious skin

lesions led to the decision to start empiric acyclovir early on. Given the fact that skin lesions are absent in up to 30 % of neonatal HSV infections it is important to be mindful of possible HSV infection in neonates who present with signs and symptoms of sepsis.

See also: COTM 12/2000:
Congenital herpes simplex type II infection

See also: COTM 02/2007:
Fulminant hepatic failure in a neonate

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