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ORIGINAL INVESTIGATION

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Fatal outcome of herpes simplex virus type 1-induced necrotic hepatitis in a neonate

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Abstract In neonates, herpes simplex virus (HSV) infections can lead to severe diseases associated with high mortality. We report a 6-day-old girl who developed clinical signs of fulminant hepatic failure accompanied by infectious-toxic shock and disseminated coagulopathy secondary to HSV type 1 (HSV-1) infection. The diagnosis was performed postmortem by demonstration of HSV-1 DNA in liver tissue as well as by retrospective detection of HSV-specific antibodies.

Keywords HSV-1 infection · Neonatal herpes · Polymerase chain reaction · Sepsis

Introduction

Herpes simplex virus (HSV) is regarded as a common viral pathogen which produces a wide variety of diseases. After primary infection during childhood with or without clinical signs, the virus establishes latent infection in the local sensory ganglia and can be reactivated frequently [19]. There are two closely related viral types: the HSV type 1 (HSV-1) and the HSV type 2 (HSV-2). In Germany, the prevalence of HSV-1 antibodies reaches high levels of more than 80% in adults, whereas nearly 15% of the adult population possess antibodies to HSV-2 [27, 18]. Clinical manifestations of HSV infections range from mucosal blisters, usually caused by HSV-1 (herpes labialis), to ulcerating vesicular lesions most commonly due to HSV-2 (herpes genitalis). However, Buxbaum et al. [2] showed that HSV-1 could be detected in one-fourth of cases in genital herpes. Additionally, HSV infections may result in keratoconjunctivitis, eczema herpeticum, herpes encephalitis, and generalized disseminated diseases in neonates as well as immunocompromised patients [19].

Neonatal HSV infections may occur transplacentally, intrapartum, and postpartum. Most HSV-infected neonates acquire the infection in the intrapartum period via viral shedding in the female genital tract [7]. In the neonates, 70–85% of HSV infections are type 2 and the remainder type 1 [20]. Clinical manifestations are divided into three major categories: (i) localized infections including skin, eye, and mouth, (ii) involvement of the central nervous system (CNS), and (iii) disseminated diseases [13]. Despite the availability of antiviral drugs for the treatment of neonatal HSV infections, the outcome remains poor, particularly for babies with disseminated multi-organ infection or CNS disease [25]. The present case report highlights potential trouble in the diagnosis of neonatal herpes virus infection and underlines the need for early diagnostic and therapeutic measures.

Case report

A female neonate was born at term with a birth weight of 2,865 g. She was discharged from the maternity ward without any clinical conspicuousness. The pregnancy was normal except signs of bleeding and imminent abortion during the third month. At the time of delivery, the mother presented with fever followed by a rubella-like exanthem. A virological diagnosis was not performed.

Clinical findings and management

At the age of 6 days, the neonate was admitted to a local community hospital because of icterus and poor feeding.

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In addition, the baby showed a fine-papular exanthem of the trunk. Neither lympadenopathy nor hepatomegaly was diagnosed clinically. Since there was a 1,000-fold increase of transaminases, the neonate was transferred to an intensive neonatal care unit of a district hospital on day 9. On admission, the baby was still in good all-round health but with the laboratory signs of hepatic failure. Clinical examination yielded mild icterus and enlargement of the liver by 4 cm with a relatively hard margin. There was no particular smell and the neurological status was normal. Complete blood count revealed 18.3×10^9 white blood cells/l, hematocrit 36%, platelet count 69.0×10^9/l, and a differential of 11% band forms, 37% segmented neutrophils, 42% lymphocytes, and 4% monocytes. Extended screening of neonates including amino- and organoacidopathy did not show any pathological findings and a chest radiograph revealed no abnormalities. Ultrasound of the liver demonstrated a homogeneous parenchyma, but, at the upper liver pole, there was visible a clear sickle-shaped collection of free fluid. Further ultrasound examinations of skull, kidneys, adrenal glands, and pancreas yielded no pathologic changes.

The initial management included the administration of polyclonal human immunoglobulin at a dosage of 2 g/kg of body weight, substitution of coagulation factors, low-dose heparinization, compensation of electrolytes, and drip-feeding with highly concentrated glucose solution.

In the following days her state of health deteriorated dramatically. The infant developed hyponatremia, hyperhydration, oliguria with concentrated urine, and hypernatriuria, interpreted as Schwartz–Bartter syndrome. The therapy consisted of fluid restriction and the administration of diuretics and sodium chloride. Furthermore, cardiac and respiratory insufficiency required the administration of catecholamines and artificial ventilation. Nevertheless, the neonate died on day 13 due to an uncontrollable pulmonary hemorrhage.

Autopsy

The neonate had a moderate icterus of the skin and sclerae as well as a weak fine-papular exanthem of the trunk. There was an extremely serious necrotizing hepatitis with nearly complete destruction of the organ and disseminated small necrotic foci were found in both adrenal glands. The neonate presented the characteristic picture of an infectious-toxic shock associated with disseminated intravascular coagulopathy (DIC). Typical shock-induced changes were evident in lungs, liver, kidneys, adrenal glands, and pancreas.

Histology

A liver biopsy obtained postmortem confirmed the severe necrotizing hepatitis with confluent mass necrosis (Fig. 1a). Autoptic histological findings were as follows: the liver showed a most serious necrotizing hepatitis with large confluent coagulation necroses, DIC combined with hyaline thrombi and rarely single-enlarged hepatocytes containing intranuclear inclusion bodies (Fig. 1b). In the adrenal glands, multiple small necrotic foci (Fig. 1c), DIC with hyaline thrombi, and acute blood stasis were demonstrated. The spleen revealed atrophy, toxic alteration of the follicles, and hyperemia of the red pulp. The cervical, mediastinal, peripancreatic, and paraaortal lymph nodes showed toxic alteration as well as atrophy of follicles. Shock-dependent changes characterized by hyaline thrombi, hyperemia, and focal intraalveolar hemorrhages were seen in the lungs. There were also signs of a shock kidney with typical hyaline thrombi, hyperemia, and remarkable degenerative changes of tubuli. The thymus showed toxic alteration. In the brain, edema and disseminated degeneration of ganglionic cells combined with blood stasis were demonstrated. The pancreas contained hyaline thrombi in the capillary vessels. The heart, glandula submandibularis, glandula parotis, intestine, urinary bladder, and genital organs revealed no pathologic findings.

Laboratory findings

No pathogen could be found in bacteriological studies including blood cultures. Serological investigations, which were performed in different local laboratories using enzyme-immunoassay (EIA), yielded seronegativity for Leptospira, *Toxoplasma gondii*, parainfluenza virus, and cytomegalovirus. Furthermore using EIA, no IgM, but IgG class antibodies could be detected against adenovirus, rubella virus, parvovirus B19, varicella-zoster virus, Epstein–Barr virus, and human herpesvirus 6 suggesting transplacentally transmitted maternal antibodies. Using complement fixation reaction, no antibodies could be revealed against coxsackie virus, echo virus, and poliomyelitis virus. IgG and IgM class antibodies against HSV-1 on day 9 were reported as negative (EIA). By contrast, the serum specimen obtained on the eighth day of life in the local community hospital had shown a weak EIA-reactivity of HSV-specific IgM, whereas no reactivity was seen for HSV-IgG as well as for HSV-2-IgG- and IgM.

At autopsy, liver tissue was obtained for detection of viral pathogens and sent to our institute. DNA was isolated by the QIAamp® DNA Mini Kit (Qiagen, Hilden, Germany). HSV-1 DNA could be demonstrated using polymerase chain reaction (PCR) technique as described previously [21, 23]. In comparison, no DNA from HSV-2, varicella-zoster virus, cytomegalovirus, or human herpes virus 6 was amplified.

Available sera of the female neonate and her mother were analyzed retrospectively in our institute for HSV-specific antibodies. The results suggested primary HSV-1 infection in mother and child and PCR findings

confirmed the same (Table 1). Using indirect fluorescence antibody test (IFAT) [21], there was a clear evidence for HSV-specific IgM in both the neonate and her mother on days 9 and 11 after delivery. In a type-specific IgG EIA (R-Biopharm AG, Darmstadt, Germany), only HSV-2-specific IgG class antibodies were detected at this time, whereas HSV-1 IgG was negative. In a second maternal serum sample obtained on the day 41 after delivery, a seroconversion of HSV-1-specific IgG as well as persisting IgM were diagnosed.

Table 1 HSV-specific serological findings in the neonate and her mother

	IFAT	EIA (type-specific)
Neonate		
Serum I (day 9)	IgG: 1:160	HSV-1 IgG: negative
	IgM: 1:160	HSV-2 IgG: positive
Mother		
Serum I (day 11)	IgG: 1:640	HSV-1 IgG: negative
	IgM: 1:40	HSV-2 IgG: positive
Serum II (day 41)	IgG: 1:640	HSV-1 IgG: positive
	IgM: 1:80	HSV-2 IgG: positive

Values given within parenthesis indicate the days after delivery
HSV herpes simplex virus, *HSV-1* HSV type 1, *HSV-2* HSV type 2, *EIA* enzyme-immunoassay, *IFAT* indirect fluorescence antibody test

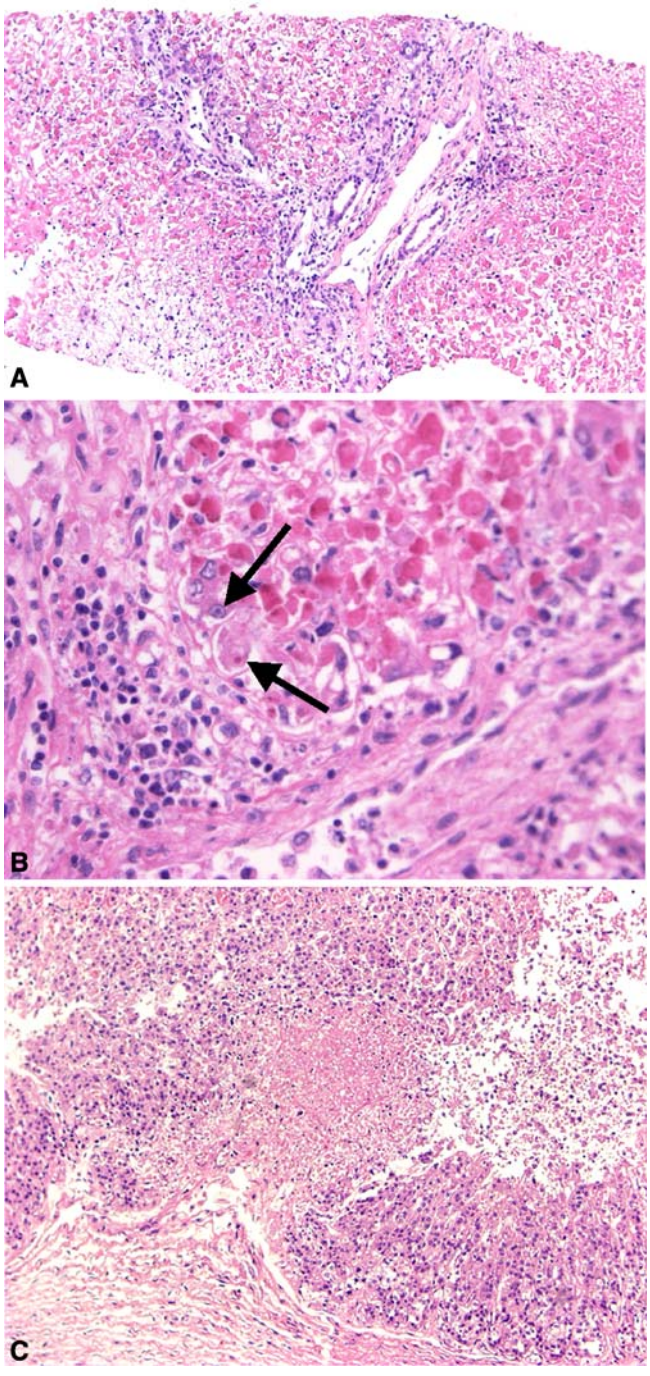

Fig. 1 Histology a Liver cylinder, biopsy specimen: extensive damage of the parenchyma and inflammatory infiltration of portal fields. Hematoxylin-eosin. Original magnification 100×. **b** Liver: necrotizing hepatitis. Around the edges of the necrosis partly necrotic hepatocytes with intranuclear inclusion bodies (*arrows*). Hematoxylin-eosin. Original magnification 400×. **c** Adrenal gland: focal necrosis. Hematoxylin-eosin. Original magnification 100×

Discussion

Neonatal herpes is a rare disorder affecting newborn infants, but it belongs to the most severe infections acquired during the perinatal period. Therefore, neonatal HSV infection should be considered in the differential diagnosis of each acutely unwell neonate [6]. At the onset, the disease is often difficult to distinguish from bacterial sepsis, and the maternal infection may be completely asymptomatic [10]. The majority of neonatal herpes is caused by HSV-2, since the passage through an infected birth canal is the most probable route of transmission [7]. In our case, HSV-1 infection was not diagnosed when the infant was alive. The pathologist was the first who thought of neonatal herpes and sent autoptic liver tissue to the virological institute of our university. Thus, HSV-1 was identified as the causative agent of the disease. This and the lethal outcome due to acute hepatic failure with DIC justify this case report.

One-third of neonatal herpes leads to disseminated infection with or without involvement of CNS [3]. Comparable to our findings, several studies have demonstrated that generalized HSV infections can present with the major symptom of liver failure [1, 8, 9, 15]. The extended histological investigations in our case demonstrate the irreversible damage of this organ. Furthermore, this case confirms that DIC, if occurs, has to be considered as a poor prognostic sign [26]. Although the majority of cases of HSV infection in the newborn are due to HSV-2 [20], our patient had HSV-1 infection. However, HSV-1 is responsible for more severe cases than HSV-2 [20].

Because HSV infection can mimic other neonatal diseases, laboratory diagnosis is indispensable. Since

diagnosis has to be rapid and reliable, PCR technology has been revolutionized the detection of HSV in neonatal herpes [11]. Thus, detection of HSV DNA in cerebrospinal fluid, serum/plasma, or peripheral blood mononuclear cells [4, 12, 14] indicates that PCR allows a highly sensitive and specific diagnosis. Unfortunately, in our case, the diagnosis was only performed postmortem. The examination of blood using PCR was omitted. However, the detection of HSV-1 in the blood could have allowed an earlier diagnosis and could have led to a decision to begin antiviral treatment.

Although serological methods have traditionally been widely used for the diagnosis of HSV infections, the presented case demonstrates that the determination of antibodies does, in principle, not allow an early diagnosis of neonatal HSV infections. Additionally, the diagnosis was made more difficult since there were reported deviating results from different laboratories. In most cases, serological studies are only convenient for retrospective diagnosis. However, detection of type-specific antibodies revealed that the mother of the neonate had the rare antibody constellation: HSV-1 seronegative and HSV-2 seropositive. In a seroprevalence study, Rabenau et al. [18] demonstrated that there is no serological evidence for in vivo cross-immunity—i.e., protective effect—between HSV-1 and HSV-2. Thus, HSV-1 primary infection in the late pregnancy could result in perinatal transmission of the virus to the infant before seroconversion was completed. Therefore, our case report underlines the special value of HSV type-specific serological testing for the management of pregnant women [22].

There is clear evidence that intravenous administration of high-dose aciclovir at 20 mg/kg of body weight every 8 h for 21 days significantly reduces mortality for babies with either encephalitis or disseminated disease [25]. Antiviral treatment must be introduced before an irreversible damage of liver tissue is present [1]. In the reported neonate, aciclovir was not given because all diagnostic measures failed to identify the causative agent. An empiric treatment with aciclovir has been recommended in neonates with (i) typical HSV lesions of the skin, eyes, or mouth, (ii) encephalitis or sepsis with negative bacterial cultures, and (iii) the combination of hepatitis and pneumonitis [16]. As shown by Pilorget et al. [17], early administration of aciclovir may favor complete recovery of neonatal HSV hepatitis. There are little experiences in the literature about successful management of neonates with HSV-induced liver failure by other measures such as liver transplantation [5, 24].

In conclusion, the fatal outcome of the reported case with fulminant hepatitis due to neonatal HSV infection emphasizes the need for early diagnosis of this potentially treatable viral infection. With the use of available laboratory methods and the resulting administration of aciclovir, the death of this neonate could have been possibly avoided.

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