Critically Severe Case of Neonatal Herpes with High Viral Load and Hemophagocytic Syndrome

Hiroki Takehara,[1,2] **Koji Hirohata,**[1,2] **Hiroshi Mutoh,**[1] **Chiharu Irisa,**[1] **Satsuki Kakiuchi,**[1] **Riki Nishimura,**[1] **Akira Oka**[1] **and Naoto Takahashi**[1]

[1]Department of Pediatrics, The University of Tokyo Hospital, Tokyo, Japan
[2]Department of Neonatology, Tokyo Metropolitan Bokutoh Hospital, Tokyo, Japan

Neonatal disseminated herpes simplex virus (HSV) infection is a severe disease with high mortality and morbidity; yet, the pathophysiology remains unclear. Here, we report a male infant with disseminated HSV type 1 (HSV-1) infection, complicated by hemophagocytic lymphohistiocytosis (HLH) and multiple organ failure. The infant, born at 39 weeks of gestation by normal delivery, developed fever (38.5°C) with the high serum C-reactive protein levels on the 1st day of life, and exhibited tachypnea on the 3rd day. On the 5th day of life, the patient received mechanical ventilation and was transferred to our neonatal ICU. Real-time PCR for HSV-1 DNA revealed an extremely high serum concentration (1.0×10^9 copies/μL), and he was diagnosed with HSV-1 infection. Acyclovir (ACV) and corticosteroid pulse therapies with methylprednisolone were started. Continuous hemodiafiltration (CHDF) using cytokine-absorbing hemofilters was also initiated because of renal failure. These therapies, however, failed to control the disease, and the patient died on the 41st day of life. The dose of ACV on CHDF might not be adequate, although we could not measure the serum ACV concentrations. After the patient's death, we measured his serum cytokine concentrations taken four times during the clinical course. Serum concentrations of interleukin (IL)-6, IL-10, IL-1β, and interferon (IFN)-γ were elevated at the time of admission and were remarkably decreased by 10 days after treatment. In particular, the concentrations of IL-1β and IFN-γ were lower than the measurable ranges. It is therefore important to measure serum cytokine concentrations in real time to prevent excessive immune suppression.

Keywords: acyclovir; continuous hemodiafiltration using a cytokine-absorbing hemofilter; cytokines; hemophagocytic lymphohistiocytosis; herpes simplex virus infection

Tohoku J. Exp. Med., 2019 March, **247** (3), 149-152.   © 2019 Tohoku University Medical Press

Introduction

Neonatal disseminated herpes simplex virus (HSV) infection is a severe infectious disease characterized by progressive multi-organ failure. It occasionally involves renal failure (Capretti et al. 2013), and some neonates need continuous renal replacement therapy (Funaki et al. 2015). This disease is sometimes associated with hemophagocytic lymphohistiocytosis (HLH), and anti-cytokine therapy is required (Janka and Schneider 2004; Suzuki et al. 2009; Kojima et al. 2012). We encountered a neonatal patient with disseminated HSV infection with high viral load and HLH. We performed immunosuppressive corticosteroid therapy and continuous hemodiafiltration (CHDF) using a cytokine-absorbing hemofilter with acyclovir, but we could not save the patient. We discuss the treatment to improve outcomes in these patients.

Case Report

The patient was a male newborn infant whose gestational age was 39 weeks and birth weight was 3,785 g. He was born transvaginally without any complications and Apgar scores were 9 and 10 at 1 and 5 min, respectively. The mother was a 26-year-old multigravida and developed fever for 2 days after delivery. On the 1st day of life, the patient developed high fever (38.5°C), and the serum C-reactive protein concentration was elevated at 18.8 mg/L (reference range [rr]; < 0.3 mg/dL). On the 3rd day of life, he developed tachypnea with the elevated serum levels of aspartate aminotransferase (AST) at 156 IU/L (rr, 12-34 IU/L) and lactic dehydrogenase (LDH) at 1,698 IU/L (rr, 115-217 IU/L). On the 5th day of life, he received mechanical ventilation because his respiratory condition worsened, and he was transferred to our neonatal intensive care unit

(NICU).

The patient's clinical course is shown in Fig. 1. On admission to NICU, the serum AST and LDH levels were further increased (979 IU/L and 3,750 IU/L, respectively). The serum alanine aminotransferase (ALT) level was also elevated at 149 IU/L (rr, 5-43 IU/L). We suspected herpes simplex virus (HSV) infection and started intravenous acyclovir (ACV) administration at 20 mg/kg every 8 hours (q8h). HSV type 1 (HSV-1) DNA was detected in the serum and cerebrospinal fluid taken on admission by polymerase chain reaction (1.0×10^9 copies/μL and 1.0×10^2 copies/μL, respectively). The liver and spleen were enlarged. The patient had a low platelet count (92,000/μL) and a low fibrinogen concentration (92 mg/dL; rr, 200-310 mg/dL). We did not investigate bone marrow. The ferritin and soluble interleukin (IL)-2 receptor concentrations were elevated at 113,200 ng/mL (rr, 25-280 ng/mL) and 2,999 U/mL (rr, 220-530 U/mL). We could not investigate natural killer cell function. The patient's conditions fulfilled five out of the eight items for the criteria of neonatal HLH. We thus diagnosed HLH secondary to HSV-1 infection and started corticosteroid pulse therapy with methylprednisolone at 30 mg/kg/day for 3 days. His condition did not improve even with these therapies. On the 8th day of life, he developed renal failure, and we started continuous renal replacement therapy (CRRT) by CHDF using a cytokine-absorbing hemofilter, namely the AN69 surface-treated (AN69ST) membrane hemofilter (SepXiris®, Gambro Industries, Meyzieu). On the 12th day of life, his serum HSV-1 DNA concentration was 7.0×10^6 copies/μL. We considered the possibility of under-treatment because of the expedited elimination of ACV through CHDF. We increased the dose of ACV to 30 mg/kg q8h and added intravenous foscarnet, an anti-viral agent. As shown in Fig. 1, his ferritin concentration did not decrease, and we also commenced lipo-dexamethasone palmitate at 10 mg/m^2/day. We changed the dose of ACV depending on his general condition and serum HSV-1 DNA concentration because we could not measure his serum ACV concentration. Neutropenia and metabolic disturbances as adverse events of ACV and foscarnet were not induced. On the 24th day of life, he developed pneumothorax and his pulmonary condition worsened. On the 36th day of life, the serum HSV-1 DNA concentration still remained at 1.0×10^4
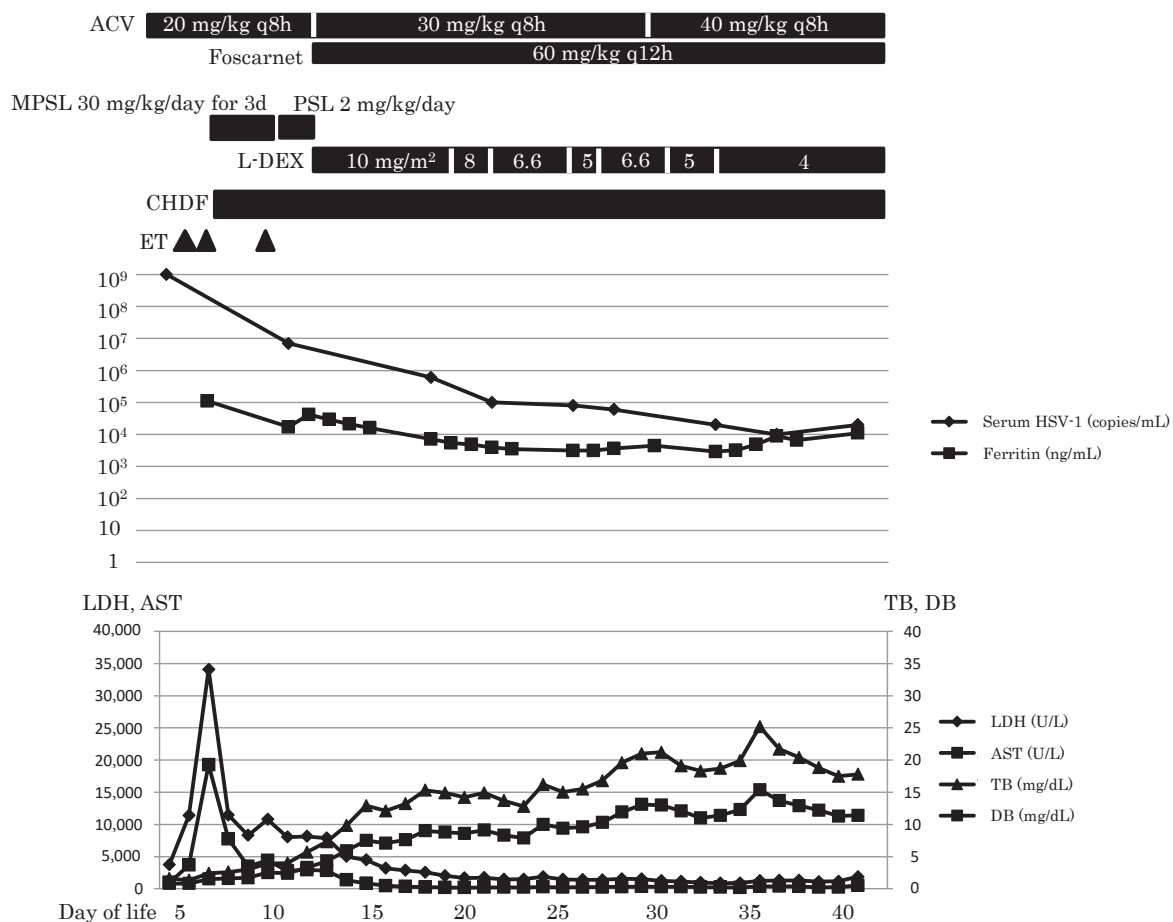

Fig. 1. Clinical course of the patient.
ACV, acyclovir; MPSL, methylprednisolone; PSL, prednisolone; L-DEX, lipo-dexamethasone palmitate; CHDF, continuous hemodiafiltration; ET, exchange transfusion; AST, aspartate aminotransferase; TB, total bilirubin; DB, direct bilirubin; day, day of life.

copies/μL. On the 41st day of life, the patient died of multiple organ failure, and the serum HSV-1 DNA concentration was re-elevated at 2.0×10^4 copies/μL. We did not obtain the parents' consent for autopsy.

After the patient died, we measured his serum cytokine concentrations taken four times during the clinical course. We used the BioPlex beads suspension array (BioRad, Hercules, CA) and Luminex 100 (Mirai Bio, Alameda, CA) system, as described previously (Takahashi et al. 2009). The BioPlex human cytokine 17-plex panel was used. Table 1 lists the serum cytokine concentrations in both our patient and the controls (Suzuki et al. 2013). The serum concentrations of all cytokines examined were elevated. In particular, IL-6 (17,280 pg/mL; rr, 4.3 ± 3.1 pg/mL), interferon (IFN)-γ (1,484 pg/mL; rr, 5.3 ± 5.2 pg/mL), and IL-10 (808 pg/mL; rr, 1.8 ± 2.1 pg/mL) were high at the time of admission on the 5th day of life. The concentrations of the elevated cytokines were rapidly decreased on the 7th day of life (Table 1). On the 15th day of life, almost all cytokines were within normal ranges, but the concentrations of IFN-γ and IL-1β were lower than the measurable ranges. However, IFN-γ and IL-1β were re-elevated on the 40th day of life according to his worsening general condition.

Written informed consent was obtained from the infant's parents.

Discussion

We present a neonatal patient with disseminated HSV-1 infection complicated by HLH and multi-organ failure. His clinical conditions were consistent with neonatal HLH (Suzuki et al. 2009). The clinical manifestations of HLH are caused by hypercytokinemia of various kinds of proinflammatory mediators, such as IL-6, IL-10, and IFN-γ, released from stimulated lymphocytes and histiocytes (Janka and Schneider 2004). The aim of HLH treatment is to suppress hyper inflammation. We reported a case of HSV infection with HLH, in which we could control hypercytokinemia with corticosteroids and cyclosporine (Kojima et al. 2012).

Melvin et al. (2015) showed that no infants with plasma HSV concentrations $\leq 1 \times 10^7$ copies/μL died, and the concentrations of all infants who died were over 1×10^7 copies/μL. Kawada et al. (2004) reported that there were positive correlations between HSV and cytokine concentrations and that immunopathological damage that results from host responses to viral infection leads to organ dysfunction. In our case, the concentration increased after disease onset and was 1.0×10^9 copies/μL just before we started ACV at the time of admission. This was the highest concentration we have reviewed (Melvin et al. 2015). In the present case, the serum HSV-1 DNA concentrations were decreased slowly.

The correct dose of ACV for neonates with HSV infection on CRRT remains unclear. Kimberlin et al. (2001) reported that neonates with normal renal condition were given intravenous ACV at a dose of 15 mg/kg q8h, and the mean ± SD of ACV peak concentration was 18.82 ± 5.22 μg/mL. Funaki et al. (2015) showed that neonates on CRRT received ACV at a dose of 20 mg/kg q8h, and the peak concentration was 18.9 to 24.5 μg/mL. ACV concentrations are consistent between the two studies. ACV is a small molecule and is removed at a constant rate according to the CRRT condition (Funaki et al. 2015). The efficiency of ACV removal should depend on the dialyzer condition. We could not obtain ACV concentrations because the laboratory company in which the concentrations had been measured before stopped the measurement. Probably, the slow reduction of HSV-1 concentration was due to the elimination of ACV through CHDF. To maintain the proper dose of ACV, we have to measure the serum concentration of

Table 1. Concentrations of cytokines in the patient and controls.

	Patient				Negative control group (n = 8)
Gestational age (weeks)	39				
Birthweight (g)	3,785				
Age (days)	5	7	15	40	5
IL-1β	12.15	1.83	OOR <	1.83	2.1 ± 1.9
IL-6	17,280.41	332.53	47.4	606.35	4.3 ± 3.1
IL-8	383.69	144.03	206.55	491.44	20.0 ± 10.4
IL-10	808.21	507.59	10.27	15.88	1.8 ± 2.1
IL-12	25.19	28.59	3.84	26.04	2.6 ± 4.1
IFN-γ	1,484.97	148.29	OOR <	128.82	5.3 ± 5.2
TNF-α	248.80	28.45	4.6	20.54	6.5 ± 5.8

Eight patients free of any infections were enrolled as a negative control group. Informed consent was obtained from the parents.

IL, interleukin; IFN-γ, interferon γ; TNF-α, tumor necrosis factor α; OOR <, out of range below.

ACV in such patients.

We added foscarnet on the 12th day of life due to the possibility of ACV-resistant HSV-1 and started at 60 mg/kg q12h as referenced dose. However, foscarnet is a small molecule as is the case with ACV and might be eliminated at a constant rate through CHDF. It might be better to change the dose of foscarnet according to the dialyzer condition.

Maeba et al. (2015) reported a case of HSV infection successfully treated with a corticosteroid. They used methylprednisolone within 72 hours after the disease onset and suggested that methylprednisolone therapy might be effective for the control of neonatal disseminated HSV infection with HLH. Nagamori et al. (2012) reported a successfully treated case of neonatal disseminated HSV infection with early anti-inflammatory therapy using prednisolone and concluded that anti-inflammatory intervention might only be effective if it is undertaken during the early phase. In our case, 6 days were passed from disease onset before using methylprednisolone. We should consider earlier intervention in these cases.

In the present patient, the serum concentrations of IL-6, IL-10, and IFN-γ were elevated at the time of admission. His serum ferritin and direct bilirubin remained at high concentrations even with aggressive treatment, and we continued administration of lipo-dexamethasone palmitate. After his death, we found that his serum cytokine concentrations had rapidly decreased on the 7th day of life, and on the 15th day of life the concentrations of IFN-γ and IL-1β were lower than the measurable range. We feel that corticosteroid pulse therapy following intravenous lipo-dexamethasone palmitate might decrease the concentrations. Maeba et al. (2015) and Yamada et al. (2008) reported the serum cytokine concentrations during clinical courses of their successfully treated cases, and the concentrations of IFN-γ were within normal range as the diseases were controlled. IFN-γ is a key cytokine in viral infection (Jordan et al. 2004; Janka 2007). In our case, anti-cytokine therapies may be too strong to maintain anti-viral immunity and the concentrations were re-elevated on the 40th day of life. It is necessary to measure serum cytokine concentrations in real time to prevent excessive immune suppression in critically severe cases.

Conflict of Interest

The authors declare no conflict of interest.

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