Fatal encephalitis accompanied by ARDS in a child with HSV infection

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INTRODUCTION
Herpes simplex virus (HSV) is a ubiquitous human pathogen that causes a range of diseases from mild uncomplicated mucocutaneous infection to life-threatening conditions. HSV-1 is normally associated with orofacial infections, whereas HSV-2 usually causes genital infections and can be transmitted from infected mothers to neonates. Less common manifestations of HSV infection, such as meningitis, encephalitis, and pneumonitis, can occur in both children and adults. After primary infection by HSV, the virus establishes a lifelong latent infection in the neuronal district, resulting in reactivation due to various triggering factors.

CASE REPORT
The patient in this fatal case was a one-year-old girl who was born full-term, developed normally, and had no medical history of asthma or pneumonia and no familial
history of immunodeficiency. She had a 15-year-old sister and a 13-year-old brother, both of whom were healthy.

The patient was admitted to the local hospital due to undergoing more than 20 days of fever, spurting vomit, and convulsions. The symptoms began on 27 April (day 1) with fever (up to 39.8 °C), spurting vomit, and convulsions (4 times), but no cough, runny nose, rash, or diarrhoea presented at that time. Ibuprofen was administered orally, but the patient’s body temperature did not decrease. On 28 April (day 2), the patient’s blood biochemistry results showed a C-reactive protein (CRP) level of <1 mg/L, and the percentage of neutrophil granulocytes was 75.9%. Additionally, the white blood cell (WBC) count in the patient’s cerebrospinal fluid (CSF) was 20×10^6 cells/L. On 1 May (day 5), brain magnetic resonance (MR) scanning revealed swollen gyri in the bilateral parietal lobes. Together, the above-mentioned findings prompted a diagnosis of viral encephalitis. On 3 May (day 7), the patient’s electrocardiogram (ECG) monitoring results were mildly abnormal, with increased δ activities. From 3 May to 5 May, the patient received an intravenous infusion of methyl prednisolone to inhibit inflammatory responses. On 4 May (day 8), the patient’s body temperature decreased to a normal level, but her convulsions reappeared. Sodium valproate and prednisone were then administered orally once daily from 6 May to 12 May. On 10 May (day 14), the patient began suffering from a cough and congestion. On 12 May (day 16), the patient’s body temperature peaked at 39.8 °C, and cephalosporin was intravenously infused. On 18 May (day 22), a high fever (up to 38.9 °C) and reoccurring spurting vomit persisted in the patient, and she was transferred to our hospital’s emergency department. The patient’s CSF was tested, revealing a WBC count of 28×10^6 cells/L, a protein concentration of 1.045 g/L, and a positive Pandy’s reaction. A head CT scan showed encephalatrophy in the bilateral cerebral hemisphere and encephalomalacia with cortical laminar necrosis (Figure 1). Most importantly, both the patient’s blood and CSF were positive for HSV-specific IgM (Herpes Simplex Virus 1/2 IgM ELISA Kit, Virion/Serion, Germany), and no bacteria or fungi were detected in the blood or CSF cultures. Therefore, the patient was definitively diagnosed with a central nervous system (CNS) infection and treated with ceftriaxone and acyclovir. Meanwhile, the patient retained a persistent fever, cough, and wheezing due to the retention of phlegm in her throat. Both lungs exhibited rough breathing sounds, and wheezing and coarse rales could be heard. To promote sputum expulsion, ambroxol was intravenously infused and acetylcysteine was used to humidify the patient’s trachea. Budesonide and ipratropium bromide were administered via atomized inhalation to alleviate the inflammatory response and expand the bronchi. Mannitol and glycerin fructose were administered to reduce intracranial pressure, and the patient was also intravenously infused with immunoglobulin for four days.

On 31 May (day 35), the patient suffered from convulsions on two occasions, but her symptoms were relieved after the administration of midazolam. On 1 June (day 36), the patient’s CSF tested weakly positive for Pandy’s reaction, and her CSF WBC count was 20×10^6 cells/L. On 7 June (day 42), both the patient’s blood and CSF were positive for HSV-specific IgM and HSV-specific IgG. Polymerase chain reaction (PCR) assays to detect viral DNA were performed on 2 June and 7 June; however, the CSF and blood were negative for both HSV-1- and HSV-2-specific DNA. On 13 June, the patient’s CSF tested negative for Pandy’s reaction, and her CSF WBC count had decreased to 12×10^6 cells/L.

On 11 June (day 46), the patient’s lower respiratory symptoms became aggravated, and severe cough and wheezing were prevalent due to the retention of phlegm in her throat. Chest radiographs showed increased

![FIGURE 1 Head CT scans of the patient. (A–B) CT scan images taken of the patient’s head on 21 May (day 25) (A) and 23 May (day 27) (B). Encephalatrophy was seen in the bilateral cerebral hemisphere accompanied by encephalomalacia with cortical laminar necrosis.](image-url)
lung markings with patchy shadows in both lungs, and the patient was diagnosed with bronchopneumonia. Cefepime was intravenously infused, and the patient was administered of more frequent doses of budesonide and ipratropium bromide via atomized inhalation. On 16 June (day 51), the patient’s pulmonary condition deteriorated further, with wheezy phlegm and moist rales unmistakably observable. Chest radiographs showed obvious increases in the densities of both lungs (Figure 2). The patient was then diagnosed with acute respiratory distress syndrome (ARDS) and admitted to the paediatric intensive care unit (PICU) with nasal continuous positive airway pressure (NCPAP) treatment (FiO\textsubscript{2}: 100%, PEEP: 5-cm H\textsubscript{2}O, flow: 12 L/min). The patient’s throat swab was negative for 18 common respiratory viruses, as measured by the Luminex xTAG Respiratory Viral Panel Assay, and no bacteria or fungi were detected in the throat swab culture. On 17 June (day 52), the patient died.

In summary, this report describes a case of ARDS in an HSV-infected paediatric patient. During hospitalization, both the blood and CSF samples collected from the patient were positive for HSV-specific IgM and IgG. The patient was diagnosed with HSV encephalitis, ARDS, encephalomalacia, encephalatrophy, subdural effusion, symptomatic epilepsy, and pneumonia, and she died 52 days after hospital admission.

**DISCUSSION**

Herein, we report the case of a one-year-old girl presenting with viral encephalitis, encephalomalacia, encephalatrophy, subdural effusion, and symptomatic epilepsy that was followed by ARDS and pneumonia during hospitalization. HSV infection most likely played a primary role in the dissemination of inflammatory responses into multiple organs, mainly the brain and lungs, which ultimately caused the patient’s death. No other encephalotropic or respiratory pathogens were detected in the patient’s blood, CSF, or throat swab specimens.

Two distinct types of HSV infection of the CNS are currently recognized: (1) herpes simplex encephalitis of older children and adults, which is the most common cause of sporadic fatal encephalitis and is nearly always caused by HSV-1; and (2) neonatal herpes simplex encephalitis, which occurs during the first month of life and is usually caused by HSV-2.\textsuperscript{4} In the present case, because HSV 1/2 IgM or IgG ELISA kits were used for diagnosis, we cannot definitely assert which HSV subtype was the causative pathogen. HSV-2 typically causes aseptic meningitis and is usually benign.\textsuperscript{4} However, recent studies indicate that a deviation of the prevalent HSV meningitis from HSV-2 to HSV-1 may be underway. Here, because the patient was not a neonate, the fatal encephalitis and pneumonia were more likely to have been caused by HSV-1.

HSV-1 pulmonary infections have recently been reported in critical patients. Such infections were postulated to be due to HSV-1 reactivation in the oropharynx towards the lungs in patients undergoing mechanical ventilation (MV).\textsuperscript{7,9} We further speculate that HSV-1 encephalitis can induce severe complications in the lower respiratory tract of patients not undergoing prolonged MV; however, the

| TABLE 1 | Results from biochemical detection of the patient’s CSF |
|----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Parameters | D2 (04-28) | D25 (05-21) | D28 (05-24) | D36 (06-01) | D44 (06-09) | D48 (06-13) |
|----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| WBC (×10\textsuperscript{6}/L) | 20 | 28 | 38 | 20 | 10 | 12 |
| RBC (×10\textsuperscript{12}/L) | ND | 0 | 0 | 0 | 0 | 0 |
| Protein (mg/L) | ND | 1045 | 553 | 327 | 420 | 321 |
| Chloride (mmol/L) | ND | 124.1 | 129.2 | 124.8 | 124.7 | 118.6 |
| Glucose (mmol/L) | ND | 2.29 | 2.47 | 2.89 | 3.05 | 4.51 |
| Monocytes | ND | 26 | 28 | 17 | 0 | 0 |
| Polymorphonuclear leukocytes | ND | 2 | 10 | 3 | 0 | 0 |
| Pandy’s reaction | ND | Positive | Positive | Weakly positive | Weakly positive | Negative |

CSF, cerebrospinal fluid; WBC, white blood cells; RBC, red blood cells; ND, not done.

**FIGURE 2** Chest radiograph of the patient. Increased density was visible in both lungs on 16 June (day 51).
detailed mechanism underlying this phenomenon remains unclear. Warren et al. speculated that HSV may reach the lower respiratory tract via aspiration from the upper respiratory tract or via reactivation of the virus in the lungs or trachea, depending on the presence of the virus in the superior cervical and vagal ganglia. Interestingly, Astuto et al. reported a similar case of a disseminating HSV-1 infection in which a 44-year-old man presented with seizures followed by an acute respiratory illness with a fatal outcome. In that case, the pulmonary infection preceded the herpes simplex encephalitis, unlike in the present case in which the order of infection was reversed. Therefore, we speculate that severe lower respiratory tract infection and HSV encephalitis are possible triggers for each other during HSV infection.

One limitation of this report is that throughout the hospitalization period only HSV-specific IgM and IgG, but not viral DNA, was measured in both blood and CSF specimens. Rimerio et al reported the detection of infection with various herpesvirus strains in plasma and CSF using nested PCR. Notably, they found that the sensitivity of this method was low for HSV-1 and EBV, and its positive predictive value (PPV) was low for HSV-1 and HSV-2. Thus, low molecular detection sensitivity may be the main reason for the negative HSV DNA results from blood and CSF in our report. The high CRP levels and chest radiographs during the patient’s ARDS period suggest the presence of a pulmonary infection. However, molecular detection of HSV based on the patient’s throat swab was also negative, perhaps because nasopharyngeal aspirates and bronchoalveolar lavage fluid may be more suitable for the detection of pathogens from the lower respiratory tract.

In summary, this report presented the case of an HSV-infected paediatric patient with ARDS. HSV encephalitis may have triggered the severe pneumonia and fatal outcome that followed. We hope that the case reported herein can provide a better understanding of HSV infection in critical patients to aid the management of future similar cases.

**CONFLICT OF INTEREST**

The authors have no potential conflicts of interest.
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