Int J Clin Exp Med 2018;11(11):12773-12777
www.ijcem.com /ISSN:1940-5901/IJCEM0080529

Case Report

EV71-infected hand-foot-mouth disease with multiple organ dysfunctions: a case study and literature review

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Received May 29, 2018; Accepted August 4, 2018; Epub November 15, 2018; Published November 30, 2018

Abstract: Hand-foot-mouth disease (HFMD) is a common viral infection that usually affects infants and in some extreme cases can even be life threatening. The following study analyzed a case study of a HFMD patient (2-year-old child) complicated with multiple organ dysfunction. The patient suffered from fever, shiver, limb shaking and atypical rash and later developed pulmonary edema, pulmonary hemorrhage, multiple organ dysfunction, and was positive for blood EV71IgM antibody. After two successive bedside blood purifications and additional active treatments, organ functions were gradually restored. The patient was healed and discharged was done after approximately 3 months of hospitalization. Therefore, this report suggests that the immune injury may be one of the pathologies of severe HFMD. In addition, blood purification offers an effective treatment approach against HFMD.

Keywords: Hand-foot-mouth disease, multiple organ dysfunctions, enterovirus 71, immune damage, blood purification

Introduction

HFMD is caused by viruses that belong to Enterovirus genes and is characterized by sores in the mouth and rashes on the hands and feet. Most patients with HFMD have good prognosis, however in some extreme cases the disease can be accompanied by brainstem encephalitis, meningitis, pulmonary edema, circulatory failure, and even death.

Enterovirus 71 (EV71) infection is considered to be one of the main causes of HFMD. Generally, the clinical manifestations of EV71 infection are diverse (**Table 1**). Few reports have indicated that EV71 can be accompanied with multiple organ dysfunction. The following study analyzed a case study of HFMD patient complicated with multiple organ dysfunction. Furthermore, it reviews the available literature, thus promoting the understanding of the disease.

Case report

A 2-year-old boy of Han nationality, was admitted on August 23, 2016 due to fever (lasting 3 days), oral herpes (lasting 1 day), and abnormal respiratory rhythm (lasting 2 hours), which were accompanied by shiver and limb shaking, but with no cough, running nose, convulsions, diarrhea, or chills. He was immediately treated at a local hospital with Vidarabine and vitamin C injection as well as with mannitol for 3 days. However, the curative effect was unsatisfactory. Two hours before admission to our hospital, he suffered from frequent dual aspiration and long sigh, with a fast heart rate of 200 beats/min, as well as perioral cyanosis. The patient had no history of HFMD and/or drug allergy and was regularly vaccinated. In addition, he was the first child in full-term birth, his parents were healthy, and he had no history of infectious disease and/or family history of hereditary diseases. On physical examination at admission: he had a fever of 39.5 degree Celsius, with a heart rate of 223/min, respiratory rate of 45/min, blood pressure of 104/59 mmHg, blood glucose of 10.4 mmol/L, and transcutaneous oxygen saturation of 82%. He was in light coma, and with complexion cyanosis. A needle-like red rash was found at his left heel. The pupil size of his both eyes was equal, with diameter of 2.0 mm, but the eye reactions to light were slow.

Table 1. The main clinical manifestations of EV71 hand-foot-mouth disease in China (1999-2016)

Date source	Time	EV71 Cases	Clinical manifestations
Guangdong [1]	2012	288	Startled, Myoclonic jerks/tremors, Fatigue/sleepiness, vomiting, anxiety, persistent hyperpyrexia, poor peripheral perfusion
Anhui [2]	2011-2012	220	Myoclonus, ataxia, nystagmus, oculomotor palsies, bulbar palsy, respiratory distress, tachycardia
Guangxi [3]	2014	66	Fever, rash, vomiting, startle response, limb shaking, convulsions, consciousness disorder, tachypnea, tachycardia, elevation of blood pressure, limb coldness
Chongqing [4]	2009-2016	261	Aseptic meningitis, encephalitis, acute flaccid paralysis, pulmonary edema, hemorrhage, cardiopulmonary failure.

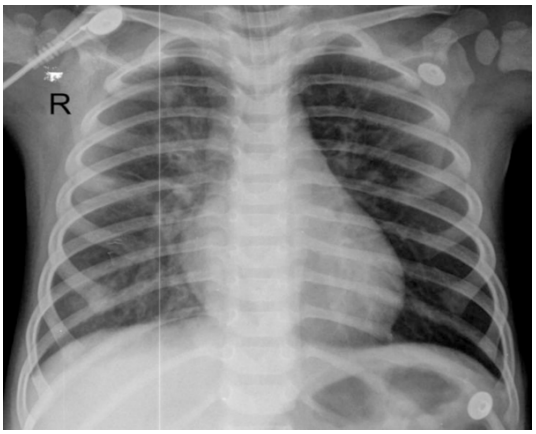

Figure 1. Chest radiography on August 23, 2016 showed a blurred image in the right upper lung and right lower lung. The brightness of the left lung was increased.

His lips were cyanosis, and neck was soft. He had frequent dual aspiration and long sigh. Moist rales in bilateral lungs and low cardiac sound were heard. Her liver was tender and palpable, 2.0 cm below the costal margin in the right midclavicular line. The spleen was impalpable in the left midclavicular line. His muscle strength and limbs' tension were normal. Babinsky, Brudzinski and Kernig's signs were all negative. His limbs were cold to wrists and ankles and the capillary refill time was 5 seconds.

After admission, the patient was immediately given tracheal intubation without trauma, and pink foam and bloody secretions were poured out from the catheter, combined with the chest radiograph which indicated pulmonary edema and pulmonary hemorrhage (**Figure 1**). Laboratory examination showed positive blood EV71IgM antibody and disorder within the environment (**Table 2**). Intracranial pressure was high, but conventional and biochemical examination were normal. Craniocerebral MRI revealed multiple craniocerebral injuries (**Figure 2**). MRI scan of the spine was normal.

The patient was given dehydration therapy with mannitol (5 ml/kg, per time, q4h) combined with albumin (1 g/kg, per timer, q12h) to lower the intracranial pressure, immunoglobulin (1 g/kg, per time, QD) for immune regulation, methylprednisolone sodium succinate injection for anti-inflammation (1 mg/kg, per time, q12h), omeprazole injection (0.8 mg/kg, per time, qd) to protect the digestive tract mucosa, phosphocreatine (1 g/d, qd) to nourish myocardium, and dopamine combined with epinephrine to maintain blood pressure (the pumping speed was adjusted according to the blood pressure, as shown in **Table 2**). On the second day of admission, multiple organ dysfunction was observed and he was additionally given 16 hour of continuous bedside blood purification and was infused with plasma to supplement coagulation factors and red blood cell suspension to correct anemia at the same time.

On the third day of admission, no bloody secretions from the trachea were detected, and the abnormal laboratory indicators decreased. Although, the chest radiography review suggested progressive cardiopulmonary function deterioration (**Figure 3**). On the fifth day of admission, the patient received 18 hour of continuous bedside blood purifications. On the sixth day of admission, the function of the organs gradually recovered and the signs of life gradually stabilized. In the 23st day after-admission, the patient was transferred to Rehabilitation Department for rehabilitation training (exercise therapy for 40 minutes per time, qd, occupational therapy for 40 minutes

Table 2. Monitoring results from one case with hand-foot-mouth disease with multiple organ dysfunctions

Laboratory examination	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 21
Hematological system									
Routine blood test									
WBC (×10^9/L)	21.94	N	11.92	N	10.3	14.78	14.13	N	11.32
Hb (g/L)	106		77		59	86	82		106
PLT (×10^9/L)	596		192		104	95	127		223
N%	70.3		83.2		83.6	84.9	86.7		65.2
L%	24.7		11.4		16.2	10.9	8.7		31.6
Coagulation function									
PT (s)	15.50	25.3	26.3	19.0	18.8	17.0	17.7	15.5	11.8
APTT (s)	34.3	45.4	91.3	24.5	26.1	31.3	34.0	35.1	27.9
Fbg (g/L)	2.77	1.17	1.19	1.15	1.04	1.11	0.99	1.1	2.41
TT (s)	20.10	26.0	106	24.4	23.6	24.0	25.0	30.6	18.2
D-DM (ug/ml)	N	N	N	N	4.3	6.2	10.0	6.0	N
Liver function									
TBIL (umol/L)	10.0	21.0	30.0	19.0	18.0	12.3	29.0	43.0	11.6
BC (umol/L)	1.0	5.0	8.0	2.0	3.0	7.0	5.0	11.0	3.2
BU (umol/L)	9.0	16.0	22.0	17.0	15.0	5.3	24.0	32.0	8.4
ALT (U/L)	32.2	2770.4	6136.4	892.0	892.0	1660.0	1825	1020	29.7
AST (U/L)	96.0	2860.0	4488.0	826.0	677.0	296.0	213.0	131	32.2
※GLU (mmol/L)	3.9-10.4	5.5-7.1	5.8-11.0	8.3-11.1	8.8-10.9	6.7-11.3	6.8-8.9	6.6-7.2	N
Renal function									
Urea nitrogen (mmol/L)	6.9	26.0	14.7	19.6	23.5	29.6	27.4	11.8	5.7
Creatinine (umol/L)	47.0	177.0	124.0	130.0	180.0	198.2	92.0	57.0	49.0
Uric acid (umol/L)	681.0	1191.0	552.0	785.0	965.0	968.0	818.0	271.0	135.0
※Cardiovascular system									
Heart rate (beats/min)	141-223	127-156	127-160	125-156	127-151	102-143	93-121	93-130	N
Blood pressure (mmHg)	51-80/ 78-112	46-68/ 94-115	55-78/ 94-129	60-82/ 112-144	58-82/ 100-128	65-89/ 106-125	58-92/ 90-129	69-90/ 115-130	N
PH	7.14-7.22	7.09-7.25	7.27-7.29	7.29-7.39	7.33-7.35	7.34-7.35	7.32-7.43	7.43-7.49	N
Lactic acid (mmol/L)	1.7-6.8	1.1-2.1	1.2-1.9	1.2-1.5	1.0-1.7	1.3-1.5	1.0-1.2	1.4-1.8	N
Vasoactive agent (ug/kg.min)									
Dopamine	5-10	10	5	3	3	No	No	No	No
Adrenaline myocardial enzyme	0.2-0.9	0.6-0.3	No	No	No	No	No	No	No
LDH (U/L)	290	N	5557.6	550.4	1260.0	N	1088.0	988.0	245.0
CK (U/L)	317		1874.0	1456.0	744.0		625.0	176.0	126.0
CK-MB (U/L)	39		92.0	73.0	51.0		66.0	41.0	18.0
Cardiac function									
BNP (pg/ml)	6696	15674	25468	>30000	21897	19278	10726	5783	79
Digestive system									
Hemorrhagic site	Upper digestive tract	Upper digestive tract	Upper digestive tract	Upper digestive tract	No	No	No	No	No
Hemorrhagic frequency	2 times	1 time	1 time	1 time					
Amount of hemorrhage (ml)	10 ml, 8 ml	15 ml	10 ml	12 ml					

Note: N indicates no measurement made that day. ※referred to the 24 h fluctuation values of corresponding to blood sugar, heart rate, blood pressure, PH, lactic acid and Vasoactive drugs. "No" referred to days which no vasoactive drugs were used, or there was no hemorrhage in the digestive.

per time, qd, low frequency impulse electrotherapy for 20 minutes per time, qd, massage for 30 minutes per time, qd, acupuncture once a day, and wax therapy for 20 minutes per time, qd). On November 18, 2016, he completely recovered and was discharged from the hospital. He was clear minded with normal mental reactions and could stand alone, walk with assistance, say father and mother, had normal muscle strength and tension in upper limbs, normal muscle tension and a muscle strength of IV grade in lower limbs but he could not jump. On December 4, 2016, no abnormality was observed during CT scan check. On June 10,

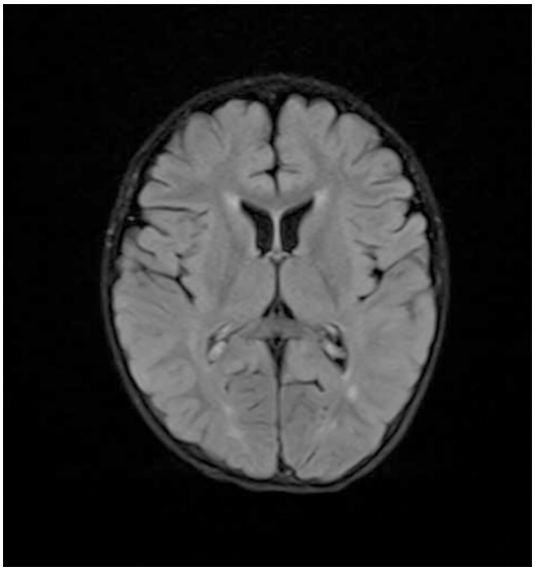

Figure 2. Cranial MRI revealed abnormal signals in the bilateral frontal lobes, left occipital parietal lobe, right temporal lobe, right cerebellar hemisphere, pons and medulla.

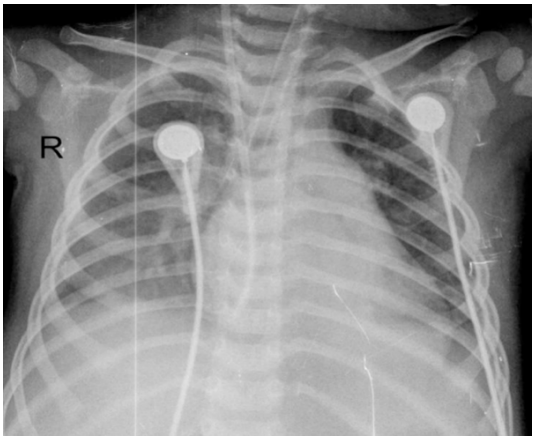

Figure 3. Chest radiography on August 25, 2016 showed a large image in the lower lungs, increased heart shadow and prominent pulmonary artery segment.

2017, the patient could walk alone and say short sentences, but could not run and jump during the follow-up. On December 3, 2017, the exercise and language function of the child were basically the same as those of the children at the same age.

Discussion

Many researchers believe that the sympathetic nerve excitability, caused by virus invasion of brain stem and leading to a release of a large amount of catecholamine, and in turn to larger body circulation pressure and blood redistribution, is the main cause of pulmonary edema and pulmonary hemorrhage in children with HFMD [5]. Sedy et al. have thought that the stimulation of special central nervous system triggering area in the brainstem causes an increase in blood pressure, bradycardia, pulmonary edema and pulmonary hemorrhage, and that severe HFMD is associated with the injury of this area [6]. Furthermore, Zhou et al. have monitored the pulse indication continuous cardiac output (PiCCO) in 5 cases with EV71-induced severe HFMD and speculated that the pulmonary edema was not only caused by neurogenic factors, but also by cardiac factors [7].

In recent years, an increasing number of studies on pathogenesis of EV71 immunization have been reported. In 2012, Gong and his team have found that EV71 infection could promote macrophages to upregulate the expressions of TLR2, TLR7 and TLR8 mRNA, and to release a large number of pro-inflammatory factors such as IL-1, IL-6, IL-8 and TNF- alpha, which suggested that immune damage is involved in the pathogenesis of EV71 [8]. In 2014, Chen et al. have found that the levels of serum IL-6, IL-10, and IL-13 are significantly increased in EV71-infected patients. He hypothesized that systemic inflammatory response may be an important pathogenesis of EV71 infection in patients with HFMD [9]. Moreover, in 2015, Guan et al. confirmed that expression levels of multiple cytokines in the serum of EV71-infected patients with HFMD resident in the Ji'nan area (China) were significantly changed during the development of the disease and were closely related to the severity of the disease [10]. In 2016, Xu et al. have analyzed the IL-8-251A/T gene polymorphism, and confirmed that the level of serum IL-8 in children with severe EV71 infection increases significantly [11], which again confirms the mechanism of immune damage in EV71 infection.

Currently, intravenous injection of immunoglobulin and milrinone is an important treatment method for HFMD [12]. Continuous blood purification can remove inflammatory mediators from the blood, reduce the inflammatory mediator levels in the tissue, improve functions of

major organs, as well as correct internal environment imbalance through filtration, dialysis and adsorption. This approach has been successfully applied to the anti-mediator treatment for multiple organ injuries [13], nevertheless it has been rarely used for the treatment of severe HFMD. In the present study, a case of severe HFMD combined with multiple organ dysfunction was successfully treated by continuous bedside blood purification. Our data suggests that blood purification may a new treatment approach for severe HFMD.

Acknowledgements

This work was partly supported by Department of Pediatrics, Shaoxing Center's Hospital.

Disclosure of conflict of interest

None.

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