

Clinical Features and Management Outcomes of Severe Hand, Foot and Mouth Disease

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Key Words

Hand, foot and mouth disease · Enterovirus 71 · Mechanical ventilation · Mortality

Abstract

Objective: This study was designed to describe the clinical features and management outcomes of severe hand, foot and mouth disease (HFMD). **Subjects and Methods:** Data on 147 severe HFMD patients during an outbreak in 2009 were analyzed. **Results:** Most patients were under 3 years of age; 102 (69.4%) were boys. All had skin rashes and fever of $\geq 38^{\circ}\text{C}$. All ($n = 147$, 100%) showed signs of central nervous system involvement, such as lethargy ($n = 124$, 84.4%), myoclonic jerks ($n = 76$, 51.7%), or drowsiness ($n = 34$, 23.1%). Respiratory symptoms were mainly tachypnea ($n = 112$, 76.2%) or bradypnea ($n = 21$, 14.3%). Common cardiovascular symptoms included tachycardia ($n = 134$, 91.2%) and hypertension ($n = 23$, 15.5%). Chest X-ray showed increased markings in 76 (51.7%) or consolidation in 44 (29.9%). Hyperglycemia and elevated blood lactic acid levels were found in 127 (86.4%) and 130 (88.4%), respectively. Positive enterovirus EV71-PCR was found in 113 (76.9%). All patients were treated with mechanical ventilation for 61.2 ± 12.8 h (range, 40–96 h), as well

as mannitol, dexamethasone, gamma globulin and ribavirin. Dopamine, dobutamine or amrinone was administered in 58.5, 51.0 and 21.8%, respectively. Three patients (2%) died during hospitalization. All others had a full recovery and were discharged after 14.2 ± 1.6 days (range, 12–17 days). **Conclusion:** Central nervous and cardiorespiratory systems were involved in the patients with severe HFMD. Fasting blood glucose and lactic acid levels increased in the majority of patients. Mechanical ventilation and supportive pharmacotherapy were associated with a good clinical outcome in these patients.

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Introduction

Hand, foot and mouth disease (HFMD) is a communicable disease that mainly affects children. It is frequently associated with enterovirus EV71 and its main clinical features include rashes in hand, foot, or mouth, aseptic meningitis, poliomyelitis-like acute flaccid paralysis, brainstem encephalitis, and other severe systemic disorders, such as pulmonary edema and cardiorespiratory collapse [1]. Large outbreaks of HFMD were first re-

ported in Malaysia and Taiwan between 1997 and 1998 [2–4], and regular epidemics have since been reported in countries across the Asia-Pacific region, in particular in China [5]. Cases of HFMD have also been identified in some European countries and in some of the epidemics coxsackieviruses A6 and A10 were also involved [6, 7]. The HFMD is considered a self-limiting illness and most children who present with aseptic meningitis generally have good outcomes [1]. However, a small proportion can rapidly develop neurological and systemic complications that can be fatal [5, 8]. In this report, we describe the clinical characteristics and management outcomes of patients with severe HFMD from an inland community in China.

Subjects and Methods

Patient Selection

This study was approved by the Institution Review Board of Liaocheng People's Hospital. As this was a retrospective analysis of de-identified patient data, no written informed consent was required. Liaocheng People's Hospital is a 2,600-bed tertiary teaching hospital in west Shandong Province, providing services to approximately 5.6 million people, mostly residing in rural and regional centers or townships. The hospital is the only designated referral center for HFMD in the region, and all identified HFMD cases are required to be hospitalized and managed by a specially equipped pediatrics unit in the hospital. Between January and June 2009, 15,823 patients with a clinical diagnosis of HFMD were admitted to the hospital for treatment. Of the 15,823 patients, 147 (0.9%) were severely ill, requiring mechanical ventilation. The clinical characteristics and the outcomes of the 147 patients were subsequently analyzed.

The initial diagnosis of HFMD was based on the criteria in the Prevention and Control Guidelines for HFMD, and Diagnosis and Treatment Guidelines for human enterovirus EV71, published by the Chinese Ministry of Health in 2008 [9, 10]. Mild HFMD was defined as the presence of fever and vesicular lesions on palms, feet and mouth. Patients' clinical manifestations such as fever, rashes on the hands, foot and mouth, and other symptoms such as lethargy or myoclonic jerks were often the first signs of HFMD. Subsequent virological tests were performed by examining throat and rectal swabs for positive enterovirus EV71 nucleic acid. Severe HFMD was defined as any one of the following findings in a patient: (a) symptoms of central nervous system involvement, such as lethargy, myoclonic jerks, drowsiness, unconsciousness, muscle spasm or rigidity, acute flaccid paralysis, or cerebellar ataxia; (b) respiratory dysfunction, such as tachypnea, bradypnea, or irregular respiration rhythm, and reduction in oxygen saturation levels, and (c) cardiovascular dysfunction, such as hypertension or hypotension, tachycardia or bradycardia, cold extremities, or piebald skin.

The age-specific definitions of respiratory and cardiovascular dysfunction were based on deviations from the normal vital signs that are readily available in the public domain [11].

Mechanical Ventilation

The indications for initiating mechanical ventilations for these patients with HFMD were central nervous system involvement, increased blood level of lactic acid, hyperglycemia or hypoglycemia. In addition, patients must have signs of cardiovascular dysfunction or respiratory dysfunction.

All patients were sedated by intravenous infusion of midazolam (0.1–0.2 mg/kg per hour). The respiration rate was set at 26–30/min, and positive end-expiratory pressure was set at 8–14 cm H₂O. Arterial oxygen saturation rate was constantly monitored and the ventilation parameters were adjusted according to the oxygen saturation results.

Indications for withdrawing mechanical ventilation were all of the following: (a) when the ventilation was changed to continuous positive airway pressure mode, patient's spontaneous respiration rate was maintained between 20 and 30 breaths/min, achieving spontaneous breathing tidal volume of 6–8 ml/kg; (b) normal and stable blood pressure and heart rate with warm extremities and no piebald skin; significant improvement in chest X-ray; normalization of blood sugar and lactic acid levels (<2.2 mmol/l), and (c) absence of myoclonic jerks after cessation of intravenous midazolam.

Other Supportive Treatment

To reduce the increased intracranial pressure, mannitol was intravenously administered (0.5–1.0 g/kg) every 4–6 h, together with intravenous dexamethasone (0.5 mg/kg) once daily. Gamma globulin was also intravenously administered (2 g/kg, over 2–3 days) to all patients. Ribavirin (10 mg/kg per day) was used as an antiviral therapy. Other treatment included amrinone [0.25–0.4 µg/(kg·min) i.v.] or dobutamine for ventricular dysfunction, and dopamine for hypotension. In addition, an ice bag was applied to the head of each patient to reduce brain temperature, and full parenteral nutrition was provided to all patients before they were able to take oral food or fluid.

Data Collection

Patients' demographic data, clinical symptoms, major complications and results of laboratory tests, such as white blood cell count, blood sugar and lactic acid, chest X-ray and viral pathology were collected. The data on mechanical ventilation such as duration of the ventilation, complications of the ventilation and the outcomes of the treatment were also registered.

Statistical Analysis

This is largely a descriptive study. Data are presented as means ± SD or percentages. No statistical analysis was performed.

Results

General Findings

The general characteristics of the patients are shown in table 1. The majority (n = 125, 85%) of the patients were under 3 years old, and 102 (69.4%) were boys. Skin rashes were present in all patients. The most common locations of skin rashes were hands, feet and oral mucosa (fig. 1). However, in more than half of the patients (n = 78, 53.1%)



Color version available online

Fig. 1. Skin rash on hands and feet and mouth ulcers (arrows) of HFMD.

rashes were also found in the hip areas. All patients had a fever of $>38^{\circ}\text{C}$, and more than half ($n = 80$, 54.4%) had high fever of 39°C or above. The main symptom of the central nervous system was lethargy, and 6 patients were unconscious at the time of admission. The majority of the patients had a rapid respiration rate ($n = 112$, 76.2%) and tachycardia ($n = 134$, 91.2%), but 21 (14.3%) had slow and shallow respiration. Twenty patients (13.9%) showed piebald skin, a sign of poor peripheral circulation.

As shown in table 2, increases in white blood cell count occurred in 44 (30%) of the patients and leukopenia was found in 6 (4.1%). The majority ($n = 127$, 86.4%) of the patients had hyperglycemia but hypoglycemia was also found in 5 (3.4%). In 130 (88.4%) of the patients the plasma lactic acid level was increased at admission.

Chest X-Ray and Virology Examination

The X-ray findings are shown in table 2. Increased markings were found in more than half ($n = 76$, 51.7%) of patients, and consolidations in both lungs were identified in nearly a third ($n = 44$, 29.9%). Positive virology tests were found in 113 (76.9%) of the patients (table 2).

Mechanical Ventilation and Pharmacological Therapies

The mean interval between onset of fever to the beginning of ventilation was 3.1 ± 1.0 days (range, 1–4). The mean duration of mechanical ventilation was 61.2 ± 12.8 h (range 40–96). The medications used are listed in table 3. Mannitol, dexamethasone, gamma globulin and ribavirin were administered to all patients. Amrinone was used in 32 (21.8%) of patients and dopamine, dobutamine were used in more than half (51.0–100%) of the patients.

Table 1. General characteristics of the 147 patients

Indices	Values
Age, months	19.5 ± 8.3 (3 months to 5 years)
Age <3 years	125 (85.0%)
Male	102 (69.4%)
Fever	147 (100%)
$\geq 39^{\circ}\text{C}$	80 (54.4%)
$38\text{--}38.9^{\circ}\text{C}$	67 (45.6%)
Skin rashes	147 (100%)
Hands	147 (100%)
Feet	109 (74.1%)
Oral	119 (80.1%)
Hips	78 (53.1%)
Central nervous system	
Lethargy	124 (84.4%)
Myoclonic jerks	76 (51.7%)
Drowsiness	34 (23.1%)
Unconsciousness	6 (4.1%)
Respiratory system	
Tachypnea	112 (76.2%)
Bradypnea	21 (14.3%)
Irregular respiration	14 (9.5%)
Cardiovascular system	
Tachycardia	134 (91.2%)
Bradycardia	13 (8.8%)
Hypertension	23 (15.5%)
Hypotension	5 (3.4%)
Others	
Cold extremities	147 (100%)
Piebald skin	20 (13.6%)

Outcomes

Of the 147 patients, 3 (2.0%) died during the hospitalization due to progressive pulmonary edema and respiratory dysfunction. The other 144 patients recovered fully and were discharged from the hospital. The mean hospi-

Table 2. Laboratory examination results

Indices	Admission (n = 147)	Discharge (n = 144)
White blood cell count		
>15 × 10 ⁹ /l	44 (30.0%)	3 (2.1%)
<4 × 10 ⁹ /l	6 (4.1%)	0 (0%)
Fasting blood sugar		
6.1–9 mmol/l	54 (36.7%)	1 (0.7%)
>9 mmol/l	73 (49.7%)	2 (1.4%)
Hypoglycemic	5 (3.4%)	0 (0%)
Normal range	15 (10.2%)	144 (100.0%)
Plasma lactic acid	0.5–2.2 mmol/l	
Increased	130 (88.4%)	0 (0%)
Chest X-ray		
Normal	27 (18.4%)	141 (97.9%)
Consolidation	44 (29.9%)	0 (0%)
Increased markings	76 (51.7%)	3 (2.1%)
Virology study	113 (76.9%)	3 (2.1%)
Throat swab positive EV-71	51 (34.7%)	1 (0.7%)
Rectal swab positive EV-71	62 (42.2%)	2 (1.4%)

Table 3. Use of medications

Medication	Patients	Duration of treatment, days	Daily dose
Mannitol	147 (100%)	5–7	2–6 g/kg
Dexamethasone	147 (100%)	3–5	0.3–0.5 mg/kg
Gamma globulin	147 (100%)	2	1 g/kg
Ribavirin	147 (100%)	10–14	10 mg/kg
Amrinone	32 (21.8%)	2–3	0.5 mg/kg
Dobutamine	75 (51.0%)	2–3	7–14 mg/kg
Dopamine	86 (58.5%)	2–3	7–14 mg/kg

tal stay was 14.2 ± 1.6 days (range, 12–17). Body temperature, blood pressure, heart rate and respiration were within normal range before the discharge. None of the patients had skin rashes at the end of the treatment. Fasting blood sugar levels, blood lactic acid levels, chest X-ray and virology tests were normal in the majority of the patients before discharge (table 2).

Discussion

The major findings of the present study included central nervous system symptoms, skin rashes and a fever of ≥38°C. Lethargy and myoclonic jerks were the most

common signs of central nervous system involvement. Other symptoms were increased markings or consolidation on chest X-ray, and hyperglycemia and elevated blood lactic acid levels. These symptoms had been reported in other studies [5, 8, 12, 13]. Myoclonic jerks in children with HFMD are considered an early indicator of neurological involvement, particularly in the brainstem [14]. Brainstem encephalitis-associated neurogenic pulmonary edema can develop very rapidly in children, and acute cardiorespiratory failure and shock may soon follow [1]. The acute-phase mortality rate in patients with signs of cardiopulmonary failure can be as high as 33% [15]. Even if neurogenic pulmonary edema is managed successfully in the pediatric intensive care unit, patients may be left with significant debilitating morbidity [16].

Management of these patients in an intensive care unit with mechanical ventilation is critically important. In our hospital, after lessons learned from several large-scale outbreaks in previous years, we developed a set of criteria to help clinicians decide when to commence mechanical ventilation before detecting significant pulmonary edema. These criteria include signs of central nervous system involvement, such as lethargy, myoclonic jerks or drowsiness, unstable hemodynamics (tachycardia, hyper- or hypotension, cold extremities or piebald skins), or changes in normal respiratory rate or rhythm. In addition, there must be elevation of blood lactic acid levels or abnormal fasting blood sugar tests, as these changes may suggest poor peripheral perfusion or more severe disease status. Using these criteria, mechanical ventilation was applied to all 147 patients for an average of 61.2 h. This approach and other supportive pharmacotherapies are associated with a full recovery in the majority of patients with little complications from the mechanical ventilation or HFMD.

All our patients were treated with intravenous gamma globulin to immunomodulate the inflammatory process and provide some anti-inflammatory action. The actual efficacy of this immunoglobulin treatment, however, is uncertain and further randomized clinical trials are required [1]. Ribavirin was also used in all patients as an antiviral drug, as a previous study showed that it reduces viral replication and mortality after enterovirus EV71 infection [17]. Dobutamine was used in 75 (51%) of the patients for the treatment of ventricular dysfunction. In a smaller proportion of patients (32, 21.8%), amrinone, a cyclic nucleotide phosphodiesterase inhibitor, was used in the treatment of congestive heart failure. Although the effect of amrinone in treating heart failure following HFMD has not been prospectively studied, a retrospec-

tive analysis of a similar drug, milrinone, showed that in children with EV71-induced pulmonary edema milrinone treatment was associated with a reduced tachycardia and lower mortality [18].

The long-term outcomes of our patients are not clear; a longitudinal study will be necessary. Other studies have shown that approximately 1 in 5 patients with severe neurological disease have complications, such as focal limb weakness and atrophy [1]. Cerebellar disorders, such as cranial neuropathies, myoclonus, tremor, and ataxia, may develop in about 10% of patients after moderately severe brainstem encephalitis [1]. In the 144 surviving patients in the present study, neurological examination done before hospital discharge did not show abnormalities.

Conclusion

The majority of patients with severe HFMD from this inland Chinese community were less than 3 years old and nearly 70% were boys. All patients had high fever and skin rashes, and more than 80% had elevated fasting blood sugar and lactic acid levels. Mechanical ventilation and supportive pharmacological management in a designated intensive care unit were associated with a good clinical outcome, resulting in full recovery in most of the patients.

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