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Clinical features for 89 deaths of hand, foot and mouth disease in Guangxi, China, 2014

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ABSTRACT

Objectives: The aim of this study is to summarize the risk factors of severe Hand, foot and mouth disease (HFMD) and explore the clinical characteristics of pulmonary edema (PE) and non-PE in the deceased patients with HFMD.
Methods: We identified 89 HFMD deaths which were separated into the PE group or non-PE group. Next, patients were divided based on their initial admission to hospitals as stage 1, 2, 3, or 4; at this point, their clinical manifestations were compared.
Results: There were 87 cases in the PE group, and 2 cases in the non-PE group. In the PE group, the difference in median time for patients at different stages from onset to symptoms, showed no significant difference ($p > 0.05$). The etiology was detected as a positive rate for enterovirus 71 (EV71) of 89.19%, which showed a more severe course than other etiologies. The white blood cell (WBC) counts, lymphocyte (LYM) counts and creatine kinase MB (CK-MB) counts of patients admitted in different stages increased significantly with severity ($p < 0.05$).
Conclusions: There may be two clinical subtypes, mostly PE and rarely non-PE, in the deceased patients with HMFD. EV71 and risk factors such as an increased WBC count are associated with a severe course of HMFD.

Introduction

Hand-foot-and-mouth disease (HFMD) is a common childhood infection with small epidemic outbreaks that occur worldwide. HFMD is characterized by fever with mouth ulcers, eruption of vesiculo-papular rash over the hands, soles, and/or buttocks, and sometimes only with mouth disease (herpangina) (Chan et al., 2003). It is caused by a group of enteroviruses, most frequently serotypes EV71 and Coxsackie A16 (CoxA16) (Puenpa et al., 2014; Ji et al., 2012).

In recent years, HFMD has become prevalent in East Asia and Southeast Asia, especially in China, Japan (Fujimoto et al., 2012), Malaysia (Chua and Kasri, 2011), Singapore (Chong et al., 2003), and Korea (Park et al., 2010). In 2008, the disease was listed as a class "C" notifiable disease in China and the morbidity and mortality were first in the 39 notifiable infectious diseases in 2014 (Epidemic situation of legal infectious diseases in China, 2014). While the majority of HFMD cases are mild and self-limiting, severe complications can rapidly develop into progressive encephalitis, the majority of which are accompanied by PE, pulmonary hemorrhage, cardiopulmonary collapse, encephalitis, meningitis, and myocarditis (Chan et al., 2000; Liu et al., 2000). These complications may result in significant morbidity or even mortality. Among the numerous complications, PE is associated with the fasted disease progression, and most of the patients die within 12–18 hours. In 1997, 35 (88%) of 40 Malaysian patients with severe HFMD died from PE (Chan et al., 2000; Shekhar et al., 2005). In 1998, the mortality rate of severe HFMD with concomitant PE or pulmonary hemorrhage was 65 (83%) cases occurring in Taiwan (Ho et al., 1999). Scholars from Malaysia and Taiwan had reported that there were patients with PE and pure brain stem encephalitis among those who died from HFMD. When compared to severe HFMD patients with neurological complications, those patients with PE tended to have a more rapidly developing illness along with a higher death rate (Chan et al., 2000; Chang et al., 1999).

We used retrospective analysis to analyze symptoms on clinical manifestations, laboratory results and urban-rural distribution patterns of the 89 HFMD deaths of the PE and non-PE groups in Guangxi in 2014 in order to summarize the risk factors of severe HFMD and explore the clinical characteristics of PE and non PE in the deceased patients with HFMD.

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Material and methods

Study population and sample collection

This was a retrospective study. We analyzed data from 89 HFMD deaths that occurred in 48 Guangxi hospitals from March 2014 to July 2014.The study was approved by the Ethics Committees of the attending hospitals. In addition, we obtained written informed consent from the guardians of cases.

Grouping and standard

The 89 HFMD deaths were grouped into PE and non-PE groups according to manifestations of PE over the whole course of the disease. Then in each group, patients were divided into stage1 to 4 based on the initial hospital admission situation.

Disease diagnosis and staging were made according to the "HFMD Diagnosis Guidance" (2010 version), which was developed by the Chinese Ministry of Health (HFMD Diagnosis Guidance, 2010), and clinical therapy expert consensus on severe cases infected with EV71 (Clinical therapy expert consensus about EV71 infected severe cases, 2011). PE was determined by dyspnea, polypnea, heart rate acceleration, frothy sputum, and lung diffusion exudation on chest radiography, and (or) pink sputum/bloody sputum in the airway (Ho et al., 1999; Wu et al., 2002).

Clinical data collection

4 sets of disease characteristics were collected and analyzed as follows: 1) Age of onset, gender and urban-rural distribution. 2) Nervous system symptoms, Vital signs (temperature, pulse, respiratory and blood pressure), skin rash and so on. 3) Chest imaging, routine blood examination, C reactive protein (CRP), creatine kinase, CK-MB, immune globulin G (IgG), immune globulin A (IgA), immune globulin M (IgM) and etiological examination. 4) The time of clinical symptoms changes.

Statistical analysis

Measurement data were represented by mean ± standard deviation ($\bar{x} \pm s$). Analysis of variance was adopted to compare the multi-sample means. For data inconsistent with a normal distribution, the rank sum check method was used for data analyses. A result of p value < 0.05 indicated that the difference was statistically significant. SPSS 17.0 software was used for statistical analyses.

Result

General condition of research objects

There were 87 cases in the PE group, and 2 cases in the non-PE group. The average age of the PE group was 22.7 ± 10.1 months (range: 5-51 months), and the male: female ratio was 60:27. In the PE group, due to unfavorable conditions of some hospitals, 13 cases of enterovirus serotype were not examined. Of the remaining 74 cases, the etiology was detected; the positive rate for EV71 was 89.19% (66/74), Coxsackievirus A16(CoxA16) 4.05% (3/74), and other enteroviruses accounted for 6.76% (5/74), When admitted to hospitals, 4 cases were in stage 1, 23 cases were in stage 2, 32 cases were in stage 3, and 28 cases were in stage 4. The non-PE group only had 2 cases, including the case of a 9-month-old male admitted to the hospital in stage 4, and 1 female aged 3 years and 2 months admitted to the hospital in stage 2. Etiological examination was not conducted in either case (Table 1).

The non-PE group

The non-PE group only had 2 cases. The first case of a 9-month-old male in stage 4 developed a fever 4 days before admission to hospital, with a temperature in the range of 39 to 40 °C along with 2 days of vomiting before admission. On the morning of admission, the patient had a convulsion and was in a comatose state. Breath rate was 45 times/min, heart rate was 196 beats/min, blood pressure was 63/42 mmHg, and percutaneous oxygen saturation was 95%. The pupillary light reflex disappeared. Several light red papules could be seen on planta pedes. No moist rales could be heard in the lungs and no frothy sputum poured out during the tracheal intubation. The patient's limbs were cold and showed cyanosis. Mechanical ventilation was begun immediately. After 2.5 hours (h), the heart rate slowed to 110 to 150 beats/min. The electrocardiogram showed paroxysmal atrial fibrillation. After 2.75 h, the heart rate fell to 80 beats/min. Blood pressure and percutaneous oxygen could not be detected; 3.5 h after admission to the hospital, the patient died. The time from onset to death was 99.5 h. According to routine blood examination, the WBC count was 4.94 × 10^9/L, the neutrophil (NEUT) count was 1.88 × 10^9/L, the neutrophil percentage was 38%, the LYM count was 1.78 × 10^9/L, the percentage of lymphocytes was 35.9%, the hemoglobin was 91 g/L, and the blood platelet count was 152 × 10^9/L. The blood glucose was 2.47 mmol/L, the C reactive protein (CRP)was 77.95 mg/L, and the procalcitonin was greater than 200 ng/ml. The creatine kinase was 9491 U/L, the CK-MB was 286.9U/L, the lactic dehydrogenase was 1188 U/L, and the α-hydroxybutyrate dehydrogenase was 638 U/L. The cardiac troponin I (CTnI) was 4.4 μg/L. The IgG was 14.19 g/L, the IgM was 1.025 g/L, and the IgA was 2.365 g/L. The plain chest radiography showed no abnormality on admission.

The second case of a 3-year-old female in stage 2 showed a high fever 2 days before admission, and the hand, foot and mouth mucosa lesions appeared at the same time. The patient vomited on the morning of the day of admission, breathing was 21 times/min on admission, the heart rate was 106 beats/min. After 11.5 h, the patient showed poor spirit, somnolence, heart rate of 210 beats/min, and reduced blood pressure. After 15.5 h, the face and lips of the patient showed cyanosis. No autonomous respiration was detected, and mechanical ventilation by tracheal intubation was started. No frothy sputum poured out. The patient died 16.5 h after admission. The time from onset to heart rate acceleration and blood pressure reduction was 59.5 h; the time from onset to death

Table 1
General condition of research objects (N = 89).

Group	Gender		Age (yr)		Stage				Enterovirus serotype			
	Male	Female	≤3	>3 ≤ 5	1	2	3	4	EV71	CoxA16	Other	Untested
PE (n = 87)	60	27	78	9	4	23	32	28	66	3	5	13
Non-PE (n = 2)	1	1	1	1	0	1	0	1	0	0	0	2