RESEARCH PAPER

Mortality in Children with Severe Hand, Foot and Mouth Disease in Guangxi, China

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Objective: To analyze the clinical features of children with hand foot and mouth disease (HFMD) who died. **Methods**: 331 deaths due to HFMD between 2010 and 2014 were included in this retrospective study; 15 autopsies were performed. **Results**: Most deaths were seen in children aged below 3 y, and with enterovirus 71 infection (91%). The mean (SD) duration of HFMD from onset to death was 3.7(2.9) d. The mean (SD) age of fast progressors (from onset to death less than 4 days) was 17.4 (9.2) mo. Most of them were diagnosed as stage 3 and stage 4 of HFMD. Various pathological changes were observed in brain after autopsy, especially in brain stem and medulla. **Conclusions**: The brain stem encephalitis with the neurotropism of enteroviruses seems to be the main contributor to the death in HFMD.

Keywords: *Complications, Enterovirus, Epidemiology, Mortality.*

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Hand, foot and mouth disease (HFMD) is a highly contagious disease caused by enterovirus (EV) infection [1]. HFMD is usually benign, but severe cases sometimes progress quickly and may cause mortality [2]. Patients may die in a short duration once they progress to pulmonary edema, pulmonary hemorrhage or cardiopulmonary failure [3]. We analyzed the clinical and pathological features from case records of 331 deaths due to severe HFMD in Guangxi province of China.

METHODS

This retrospective study included 331 deaths due to HFMD, which were reported to the Center for Disease Control (CDC) of Guangxi province from 2010 to 2014. The patients' medical history was provided by Guangxi CDC. The diagnostic criteria and clinical stages were based on the guidelines of Ministry of Health for HFMD and the "Clinical Management of EV71". Throat and anal swabs were collected for the detection of enterovirus and coxsackie viruses. The clinical stages were classified as: Stage 1 – vesicular lesions on hand, foot and mouth; Stage 2 – neurological involvement; Stage 3 – early stage of cardiopulmonary failure; Stage 4 – cardiopulmonary failure; and Stage 5 – recovery period [4].

The 331 deaths were distributed in all municipal hospitals in Guangxi province. The clinical data were collected through review of hospital records. The data were collected by three people with a standard data extraction form, and disagreements were resolved by discussion. The form included patients' information such as age, sex, date and time of registry to hospitals, date and time of death, duration from onset to each major complication, duration from each complication to death, clinical features, white blood count (WBC) and blood glucose. Autopsy with the consent of the parents was performed in 15 cases. Based on the duration from onset to death, these cases were classified into slow (equal or more than 4 days) or fast progressors (less than 4 days).

RESULTS

Among 331deaths, 209 were males (M: F=1.71:1). The age ranged from 4 months to 6 years, and 291(87.9%) were aged below 3 years. 3.0%, 27.2%, 28.4% and 41.4% of patients were diagnosed as stage 1, stage 2, stage 3 and stage 4, respectively at the time of registry to the hospitals. The mean (SD) duration from onset of disease to death was 3.7 (2.2) days. The mean (SD) duration from stage 1 to stage 2 was 43.6 (27.2) hours, from stage 2 to stage 3 was 24.6 (16.2) hours, from stage 3 to stage 4 was 3.9 (1.5) hours, and from stage 4 to death was 4 (1.8) hours. The mean (SD) age of fast progressors was 17.4 (9.2) months, and most of them were diagnosed as stage 3 or stage 4 at registry. The neurological and cardiopulmonary symptoms of these cases are summarized in ***Table* I**.

The mean (SD) age of fast progressors was

significantly lower than that of slow progressors [17.4 (9.2) *vs* 26.2 (12.7) mo; *P*<0.01].

301 patients (90.9%) were infected by EV71, nine (2.7%) cases were infected by Coxsackie A16 and two (0.6%) cases were infected by both EV 71 and Coxsackie A 16 viruses. Nineteen (5.7%) cases tested negative for both EV 71 and Coxsackie A 16 virus.

Autopsy in all 15 cases showed similar pathological characteristics. The major pathological changes found in the central nervous system (CNS) were: congestion on the surface of cerebrum, obscured cerebral sulcus, brain stem edema, neuronal necrosis, and neuronophagia and colloid deposition in the brain stem. All lung specimens had pink fluid in alveolar space. Alveolar wall was thickened and widened with interstitial fibrosis, hemangiectasis, and congestion. No obvious infiltration by inflammatory cells was seen in heart.

DISCUSSION

In the present study, we found that most of the deaths in HFMD occurred in younger children (≤3 years). These patients had tachycardia, cyanosis, pale skin, hypertension and dyspnea in stage 3, and pulmonary edema, pulmonary hemorrhage, low blood pressure and bradycardia in stage 4.

Our findings were consistent with previous reports suggesting that EV71 was more likely to cause neurological impairment, which could lead to severe cases [5-7]. Previous studies showed that patients had increased heart rate and hypertension (stage 3) before cardiopulmonary failure (stage 4). These patients may have bradycardia and hypotension leading to cardiopulmonary failure [8]. There was no evidence of viral myocarditis in children in present series, and staining for EV71 antigen was negative in the myocardium and lungs. A previous study also showed that neurogenic pulmonary edema associated with brainstem parenchymal damage, which may be not due to direct virus damage or myocarditis-induced viral damage [9]. However, another study [10] suggested that the invasion of spinal cord and medulla by EV71 contributed to pulmonary edema and other respiratory complications. Kao, *et al*. [11] suggested that pulmonary edema may result from a sympathetic over-activation. The major limitation of this data is its retrospective nature. Moreover, the data were limited to a single province of China. Autopsy was performed in less than 5% of cases, thus limiting the generalizability of the findings.

In conclusion, most cases of HFMD had brainstem encephalitis. Close observation on clinical manifestations such as neurological symptoms is critical to assess the severity and prognosis of the disease. Severe HFMD should be diagnosed earlier before stage 3 and receive proper treatment to reduce the mortality.

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TABLE I SYMPTOMS AND SIGNS BEFORE DEATH IN HAND-FOOT-MOUTH DISEASE (*N*=331)

Symptoms/Signs	*N (%)*	*Symptoms/Signs*	*N (%)*
Nervous system		*Cardiovascular system*	
Lethargy	280 (84.6)	Tachycardia	310 (93.7)
Vomiting	228 (68.9)	Cyanosis	310 (93.7)
Irritability	149 (44.1)	Low blood pressure	164 (69.2)
Limb trembling	127 (38.3)	Hypertension	142 (58.9)
Dysphoria	116 (35.1)	Bradycardia	107 (32.3)
Seizure	103 (31.1)	*Respiratory system*	
Coma	94 (28.4)	Expectoration	265 (80.1)
Eyes stare	65 (19.6)	Dyspnea	263 (79.5)
Neck rigidity	54 (16.3)	Crackles	188 (56.8)
Pale Skin	210 (63.4)		

The HFMD children had multiple symptoms and hence the percentages add up to >100%.

WHAT THIS STUDY ADDS?

- Most deaths due to HFMD occur in children <3 yr of age, and usually due to neurological and cardiac complications.

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