SHORT COMMUNICATION

Clinical characteristics of hand, foot and mouth disease in Daklak Province, Vietnam and associated factors of severe cases

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Abstract The Hand, Foot and Mouth Disease (HFMD) outbreaks occurred throughout Daklak province, Vietnam in 2011. This study reviewed all 744 medical records of HFMD patients admitted to Daklak Hospital in 2011 to describe the clinical characteristics of HFMD patients and determined factors associated with severe illness. Among 744 patients, 63 (8.5%) cases were severe. Most (695, 93.4%) of the cases were 3 years old or younger, and 464 (62.4%) were boys. The number of cases peaked between August and November. Most (726, 97.6%) recovered, 17 severe cases (2.3%) were transferred to higher level hospitals, and one death. Symptoms at admission included fever (93.5% had a fever ≥ 38.5 °C), blisters (99.1%), myoclonus (58.5%), and leukocytosis ($> 11,300/\text{mm}^3$: 38.8%). Viral cultures were performed for 61 of 63 severe cases, of which 26.2% were positive for Enteroviruses. Multivariable analysis found that oral ulcers (Odds Ratio (OR) 3.74; 95% Confidence Interval (CI) 2.13–6.58), myoclonus (OR 44.75; 95% CI 6.04–331.66) and high white blood cell count (OR 1.08; 95% CI 1.01–1.16 per $1000/\text{mm}^3$ increase) were significantly associated with severe illness. HFMD mainly occurs in children younger than 3 years old and rainy season. Oral ulcers, myoclonus, and leukocytosis should be closely monitored to promptly detect severe cases of HFMD.

Keywords Hand, foot and mouth disease · HFMD · Clinical · Enterovirus 71 · Associated factors

Hand, foot and mouth disease (HFMD) is a common infectious disease among children caused by more than 20 different enteroviruses, mainly genotype of *Enterovirus A*. In Vietnam, the first HFMD outbreak was reported in 2003 in Ho Chi Minh City and data has demonstrated an increase in cases of HFMD in the Daklak Province, which is located in the Central Highlands region of Vietnam and has a tropical climate with two seasons: rainy and dry season.

HFMD usually affects children under 5 years of age and is generally mild and self-limited, but can be life-threatening [11]. Clinical characteristics include febrile illness with papulovesicular rash on palms and soles, with or without vesicles/ulcers in the mouth. The rash may occasionally be maculopapular without vesicular lesion, and may also involve the buttocks, knees or elbows [1, 13]. Risk factors that contribute to severe forms of illness are high fever, history of lethargy, age, vomiting, myoclonus and raised total leukocyte count [2, 3, 7, 9, 10, 14]. However, studies in Vietnam investigating the epidemiology and clinical features of HFMD, as well as factors related to severe cases of HFMD are limited [4, 5, 12]. This study described the epidemiology, clinical and laboratory features of HFMD in General Hospital, Daklak Province. We also identified risk factors associated with severe cases for use towards early intervention.

This study reviewed all 744 cases of HFMD admitted to the General Hospital of Daklak Province in 2011. HFMD cases were defined according to Vietnam MOH guidelines. At the time of admission, patients were classified into five grades of illness split between mild and severe disease

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according to clinical management guidelines produced by the Vietnam MOH.

A standardized form was used to abstract data from medical records. Information collected included demographics, medical history, days between onset and hospital admission, and signs/symptoms present upon hospital admission and during the course of disease. Laboratory tests included white blood cell and platelet counts. All severe cases underwent throat swabs for virus isolation and subtype testing.

Descriptive analyses were used to describe the epidemiology, clinical and laboratory characteristics of cases. Associations between severity of illness and demographic, clinical and laboratory characteristics were examined using logistic regression analyses. The variables investigated included age, gender, days between onset and hospital admission, fever ≥ 38.5 °C, blisters, oral ulcers, diarrhea, vomiting, myoclonus, pulse $> 150/\text{min}$, unstable blood pressure, dyspnea/tachypnea, seizure, at least one neurologic sign (agitation/irritability, lethargy, limb weakness or coma) and white blood cell count.

All analyses were performed using R program version 3.0.1 for Windows and $p < 0.05$ was considered statistically significant.

The study was performed with the approval of Ethics Committee of General Hospital of Daklak Province, Vietnam. Patient information was anonymized and encoded prior to analysis.

Of the 744 patients of HFMD included in this study, 681 (91.5%) were classified as mild cases (1, 2a grades) and 63 (8.5%) as severe cases (grade of 2b, 3 and 4). Most of the patients, including both mild and severe cases, recovered without complication (726, 97.4%), 17 severe cases (2.3%) were transferred to higher level hospitals, and one severe case ended in death (0.3%). The mean duration of treatment was 6.6 ± 3.3 days. The number of cases peaked from August through November. There were more males than females (464; 62.3%/280; 37.6%) and the median age was 20 months (range: 1–120). Most of the cases (93.4%) were 3 years old or younger.

The median number of days between onset and hospital admission was 2 days (interquartile range: 2–3 days).

Common symptoms of the patients at the admission time were: fever (93.5% cases had a fever ≥ 38.5 °C), blister (99.1%), myoclonus (58.5%) with 195 cases at grade 2a and 61 cases at grade 2b, and oral ulcers (21.1%). Other symptoms were gastrointestinal symptoms (vomiting: 11.2% and diarrhea: 10.4%), seizure (2.7%), and at least one neurologic sign such as agitation/irritability, lethargy or limb weakness (7.9%). Three severe cases had a pulse rate over 150 beats/min, however, none of the mild cases had a pulse rate over 150 beats/min. No case had unstable blood pressure or dyspnea at admission.

In the laboratory assay of all 744 cases, 455 cases (61.2%) exhibited leukocyte levels above the mean ($> 11,300/\text{mm}^3$). As per Vietnam MOH treatment protocol, viral cultures were only performed in severe cases, of which 96.8% (61 out of 63 cases) of patients were available. Of those, enteroviruses were identified in 16 samples (26.2%), with 10 samples (16.4%) positive for enterovirus 71.

Univariable analysis showed that myoclonus (Odds Ratio (OR) and 95% Confidence Interval (CI): 52.14; 7.12–381.98), oral ulcers (OR: 3.87; 2.20–6.80), diarrhea (OR: 1.94; 1.03–3.65) and increased white blood cell count (OR: 1.10; 1.04–1.17 per 1000/ mm^3 increase) were independently associated with severe HFMD. Multivariable logistic regression showed that myoclonus (OR: 44.75; 6.04–331.66), oral ulcers (OR: 3.74; 2.13–6.58), and increased white blood cell count (OR: 1.08; 1.01–1.16 per 1000/ mm^3 increase) were significantly associated with the outcome severe HFMD (Table 1).

HFMD is an emerging public health problem in Vietnam. The disease threatens the health of children, and causes loss and financial burdens to both families and the country. Consistent with previous studies of this disease in Vietnam and other countries [1, 2, 8, 14], findings of this study showed that HFMD patients were mostly boys (62.3%) and children under 3 years of age (93.4%). The number of cases admitted to Daklak hospital peaked during rainy season (from August through November), which was similar to other provinces in Vietnam [12]. Other studies have also shown a seasonal distribution of HFMD, but exact reasons for this distribution are not well understood. In the rainy season, it is necessary to intensify routine surveillance and set up sentinel surveillance for early warnings for the public.

Studies have reported a wide variety of clinical manifestations of HFMD [4, 8, 11]. This study showed that although cases with clinical signs of HFMD presented with varying symptoms, common symptoms were fever, blisters, oral ulcers and myoclonus. Myoclonus occurred in more than half (58.5%) of patients diagnosed with HFMD based on Vietnam MOH guidelines. Infrequent symptoms were diarrhea, vomiting, and neurologic signs. The clinical features of this outbreak are generally similar to those reported in previous studies in Vietnam and other countries [4, 5, 8, 12].

According to Vietnam MOH guidelines on diagnosis and treatment of HFMD, clinical samples (throat swabs or rectal swabs) for viral cultures are only collected for severe cases. In this study, viral cultures from throat swabs were performed for 96.8% of severe patients (61 out of 63 cases). Of those, 16 cases (26.2%) were positive for enteroviruses with 10 samples positive for enterovirus 71.

Table 1 Adjusted relationship between clinical, laboratory, and demographic characteristics and severity of illness (OR, 95% CI)

Characteristics	OR (95% CI)	
	Univariate analysis	Multivariable analysis
Gender (male vs. female)	1.39 (0.78–2.50)	1.47 (0.78–2.80)
Age (year) per a year increase	0.80 (0.60–1.08)	0.91 (0.62–1.33)
Days between onset and hospital admission (≥ 2 days and > 2 day)	0.76 (0.44–1.30)	0.88 (0.48–1.61)
Fever ≥ 38.5 °C	N/a	N/a
Blisters	0.27 (0.04–1.68)	0.68 (0.08–5.70)
Oral ulcers	3.87 (2.20–6.80)	3.74 (2.13–6.58)
Diarrhea	1.94 (1.03–3.65)	1.88 (0.90–3.91)
Vomit	1.05 (0.47–2.34)	0.69 (0.28–1.71)
Myoclonus	52.14 (7.12–381.98)	44.75 (6.04–331.66)
White blood cell counts (per 1000/mm ³ increased)	1.10 (1.04–1.17)	1.08 (1.01–1.16)

Other studies have also shown that enterovirus is the main etiological agent of HFMD in Vietnam [5, 12].

The disease is usually mild and self-limiting [1, 13]; however, some cases develop severe clinical manifestations and it is considered a potentially life-threatening disease [2, 11, 14]. In 2011, there were 113,121 cases of reported infection and 170 deaths linked to HFMD in Vietnam. Furthermore, in Taiwan, from April to July 1998, approximately 90,000 reports of HFMD cases were made based on passive surveillance from sentinel physicians; among these 320 children were hospitalized with severe forms of HFMD and 55 children died. This study found that the symptoms associated with severe cases of HFMD at the time of admission included oral ulcers, myoclonus and raised white blood cell count. Additionally, other studies have investigated clinical features and laboratory abnormalities associated with severe and fatal HFMD cases. Young age is associated with increased risk of severe disease in some [3, 11]. A study in Taiwan demonstrated that myoclonic jerk was independently associated with more severe disease [9] while others have found that the presence of at least two of the following: peak temperature of 38.5 °C or more, fever for 3 days or longer, a history of lethargy and raised white blood cell [6], can predict severe outcomes. A study of 169 HFMD deaths in Vietnam in 2011 showed that 75% cases had white blood cell count $> 16,000/\text{mm}^3$. However, a meta-analysis found no significant association between severe HFMD and peak body temperature ≥ 38.5 °C, oral rash or increased leukocyte count [3]. Importantly, some signs may appear after the time of admission, generally in fulminant state, thus could not be used in analysis for clinically meaningful predictors of complications and death.

This study ascertained all cases of HFMD in Daklak hospital in 2011 and used data from medical records to

present a picture of HFMD in one province in the Central Highlands region of Vietnam. However, data was retrospectively collected and did not include some important information such as attendance at a child care center, cerebrospinal fluid pleocytosis on hospital admission, high temperature and lethargy, cause of the death case or reasons for transfer to higher level hospitals. Furthermore, the number of deaths was very small and therefore not suitable for a thorough analysis of risk factors for mortality from HFMD. HFMD remains an important public health problem in Vietnam which mainly effects children younger than 3 years of age. In conjunction with signs/symptoms recommended by MOH guidelines, oral ulcers, myoclonus, and leukocytosis should be closely monitored for early detection of severe cases of HFMD in order to appropriately and promptly treatment.

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