Sys Rev Pharm 2020; 1(1):7-13 *Original Research*
A multifaceted review journal in the field of pharmacy
E-ISSN 0976-2779 P-ISSN 0975-8453

Factors related to severe hand, foot, and mouth disease among Vietnamese children patients

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Article History: *Submitted: 12.08.2019* *Revised: 28.10.2019* *Accepted: 25.11.2019*

ABSTRACT

Background: Hand, foot, and mouth disease (HFMD) is mostly benign, with patients recovering within a week. However, if the disease is caused by enterovirus A71 (EV-A71), it can cause major epidemics or outbreaks and can cause rapid death in children, and especially in young children. The aim of this study was to determine the association of clinical, laboratory characteristics, and viral infections with severe HFMD in children.

Materials and methods: This case-control study was conducted on 280 pediatric patients diagnosed with HFMD admitted to The Children Hospital 1 and Tien Giang General Central Hospital. The study used a convenience method.

Results: Clinical symptoms associated with severe HFMD included vomiting, high fever >39ºC, rapid breathing, convulsions, rapid pulse >130 beats per minute, flounder, lethargy, drowsiness/coma, myoclonus/stumbling, apnea, and hiccup breathing. Laboratory features associated with severe HFMD included platelet count >400,000 cells/mm^3 and blood glucose >180 mg/dL. The EV-A71 strain was associated with severe cases. The independent factors associated with severe HFMD were identified through the multivariate logistic regression model and including the carrier's gender, high fever >39ºC, rapid pulse >130 beats/minute, platelet count >400,000/mm^3, blood glucose >180 mg/dL, and EV-A71 infection.

Conclusion: Implications are indicated for clinical and laboratory characteristics and viral types with severe hand, foot, and mouth disease in children.

KEYWORDS: clinical, hand, foot, mouth, subclinical, laboratory, Vietnam.

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DOI : 10.5530/srp.2020.1.02

INTRODUCTION

Hand, foot, and mouth disease (HFMD) is an infectious disease that spreads from person to person, mostly to children under 5 years old; over 80% of infected children are under 3 years old. This disease can spread very quickly from child to child through two ways: stool-to-mouth and by respiration. HFMD is mostly benign and self-healing within one week. However, if the disease is caused by enterovirus A71 (EV-A71), it can create large epidemics or circulations and can kill children quickly, especially young children. HFMD can lead to dangerous complications, such as encephalitis, meningitis, myocarditis, or acute pulmonary edema due to nerve involvement. These complications often lead to high mortality rates and progress very quickly, within 24 hours.

In Vietnam, many children with HFMD have been recorded in the past few years, including children with HFMD who have neurological, respiratory, and circulatory complications. In 2011, an HFMD outbreak occurred in 63 provinces and cities nationwide, with 87,500 cases and 147 deaths, according to published data. This was the highest mortality rate for HFMD ever recorded in Vietnam. At present, not been many general studies have been conducted on the epidemiology or clinical and subclinical aspects of HFMD with severe complications (level 2b, 3, 4); however, predicting the warning factors leading to severe HFMD is very important. Therefore, this study was conducted to determine the relationship between the clinical and subclinical symptoms, viral type, and severe HFMD in children.

MATERIALS AND METHODS

The study was designed as an unmatched case-control study and used a convenience sampling method. All cases were pediatric patients diagnosed with HFMD and hospitalized at The Children Hospital 1 and Tien Giang General Central Hospital. The children were diagnosed as having HFMD if they had a RT-PCR test result that identified the presence of enterovirus. Patients were selected for the study only with the consent of a legal guardian. Children who had other diseases, such as liver failure, kidney failure, and nephrotic syndrome, prior to the onset of hand, foot, and mouth disease were excluded from the study.

According to the sample size, the formula compares two ratios. The number of samples in the case group was 140, and the control/case ratio selected was 1/1. In this study, a case subject was a child diagnosed with severe HFMD (level 2b, 3, or 4). A control subject was a child diagnosed with less severe HFMD (level 1 or 2a). The classification of disease was based on both clinical and subclinical criteria, according to the guidelines of Vietnam Ministry of Health in 2012.[1]

Statistical analysis

Data were analyzed with SPSS Software version 18.0. The univariate relationship was determined by the Chi-square and Fisher's exact test. The study determined the independent association between severe HFMD and related factors by multivariate logistic regression analysis. The degree of association was estimated with an odds ratio (OR) and a confidence interval of 95% of the OR. A p-value of less than 0.05 ($p<0.05$) was considered statistically significant.

Ethical considerations

This study was approved by the Scientific Research Committee of The Children Hospital 1 and Tien Giang General Central Hospital. The collected data were only used in this study and were not for any other purpose. Participation was voluntary and anonymous. The child's guardian was asked to sign an informed consent form prior to enrollment.

RESULTS

Prior to admission to the hospital, the patients showed clinical symptoms associated with severe HFMD, such as sore throat, vomiting, high fever >39°C, rapid breathing, and convulsions. The most typical sign was rapid breathing; children with this sign had a 9.55 times higher risk of severe HFMD than children without rapid breathing. By contrast, the risk of severe HFMD in the group with sore throat symptoms was lower than in the group without these symptoms (OR=0.5, 95% CI: 0.3-0.84). The relationship between the clinical characteristics before hospitalization and severe HFMD is shown in Table 1.

Table 1. Relationship between the clinical characteristics before hospitalization and severe HFMD

Symptoms and signs	Severe HFMD (n=140)	Mild HFMD (n=140)	*p value*	OR (95%CI)
Sore throat				
Yes	83 (59.3)	104 (74.3)	0.008*	0.50 (0.30 – 0.84)
No	57 (40.7)	36 (25.7)		1
Vomiting				
Yes	54 (38.6)	36 (25.7)	0.021*	1.81 (1.09 – 3.02)
No	86 (61.4)	104 (74.3)		1
Diarrhea				
Yes	19 (13.6)	19 (13.6)	0.999	1.00 (0.50 – 1.98)
No	121 (86.4)	121 (86.4)		1
High fever (>39°C)				
Yes	8 (5.7)	1 (0.7)	0.036¢	8.42 (1.04 – 68.28)
No	132 (94.3)	139 (99.3)		1
Fussing and crying				
Yes	99 (70.7)	105 (75.0)	0.420	0.80 (0.47 – 1.36)
No	41 (29.3)	35 (25.0)		1
Oral ulcers				
Yes	126 (90.0)	124 (88.6)	0.699	1.16 (0.54 – 2.48)
No	14 (10.0)	16 (11.4)		1
Rash				
Yes	133 (95.0)	136 (97.1)	0.541¢	0.56 (0.16 – 1.95)
No	7 (5.0)	4 (2.9)		1
Blister				
Yes	132 (94.3)	137 (97.9)	0.217¢	0.36 (0.09 – 1.39)
No	8 (5.7)	3 (2.1)		1
Rapid breathing				
Yes	9 (6.4)	1 (0.7)	0.019*,¢	9.55 (1.19 - 76.42)
No	131 (93.6)	139 (99.3)		1
Abnormal breathing				
Yes	7 (5.0)	1 (0.7)	0.066¢	7.32 (0.89 – 60.26)
No	133 (95.0)	139 (99.3)		1
Convulsions				
Yes	17 (12.1)	2 (1.4)	< 0.001*,¢	9.54 (2.16 – 42.11)
No	123 (87.9)	138 (98.6)		1
Cyanosis				
Yes	7 (5.0)	2 (1.4)	0.173¢	3.63 (0.74 – 17.80)
No	133 (95.0)	138 (98.6)		1
Meningeal signs				
Yes	0	3 (2.1)	0.247¢	//
No	140 (100)	137 (97.9)		
Acute flaccid paralysis				
Yes	0	0	//	//
No	140 (100)	140 (100)		
Cognitive disorders				

Symptoms and signs	Severe HFMD (n=140)	Mild HFMD (n=140)	*p value*	OR (95%CI)
Yes	3 (2.1)	1 (0.7)	0.622[¢]	3.04 (0.31 – 29.62)
No	137 (97.9)	139 (99.3)		1

[¢]Fisher's exact test, [*]p<0.05
Values are the number (percentage) of patients

After the patients were admitted to the hospital, they were evaluated for clinical symptoms related to severe HFMD status, such as rapid pulse >130 beats per minute, flounder, lethargy, rapid breathing, drowsiness, coma, myoclonus, stumbling, apnea, and hiccup breathing. The detailed analysis is shown in Table 2.

Table 2. Relationship between the clinical characteristics after hospitalization and severe HFMD

Symptoms and signs	Severe HFMD (n=140)	Mild HFMD (n=140)	*p value*	OR (95%CI)
Rapid pulse >130 beats per minute				
Yes	93 (66.4)	4 (2.9)	<0.001[*,¢]	67.28 (23.44 – 193.09)
No	47 (33.6)	136 (97.1)		1
CRT > 2 seconds				
Yes	2 (1.4)	0	0.498[¢]	//
No	138 (98.6)	140 (100)		
Low blood pressure / low pulse pressure				
Yes	0	1 (0.7)	0.999[¢]	//
No	140 (100)	139 (99.3)		
SpO_2 < 92%				
Yes	6 (4.3)	1 (0.7)	0.120[¢]	6.22 (0.74 – 52.39)
No	134 (95.7)	139 (99.3)		1
Cognitive disorders (GCS <10)				
Yes	8 (5.7)	2 (1.4)	0.103[¢]	4.18 (0.87 – 20.06)
No	132 (94.3)	138 (98.6)		1
Limb Weakness/paralyzation				
Yes	1 (0.7)	1 (0.7)	0.999[¢]	1.00 (0.06 – 16.15)
No	139 (99.3)	139 (99.3)		1
Swallowing choke, changing voice				
Yes	3 (2.1)	0	0.247[*,¢]	//
No	137 (97.9)	140 (100)		
Flounder				
Yes	53 (37.9)	3 (2.1)	<0.001[*,¢]	27.82 (8.43 – 91.79)
No	87 (62.1)	137 (97.9)		1
Startle				
Yes	119 (85.0)	125 (89.3)	0.284	0.68 (0.33 – 1.38)
No	21 (15.0)	15 (10.7)		1
Lethargy				
Yes	29 (20.7)	0	<0.001[*,¢]	4.18 (0.87 – 20.06)
No	111 (79.3)	140 (100)		1
Rapid breathing				
Yes	7 (5.0)	0	0.014[*,¢]	5.22 (0.74 – 52.39)
No	133 (95.0)	140 (100)		1
Drowsiness, coma				
Yes	9 (6.4)	1 (0.7)	0.019[*,¢]	9.55 (1.19 - 76.42)
No	131 (93.6)	139 (99.3)		1
Myoclonus, stumbling				
Yes	32 (22.9)	7 (5)	<0.001[*]	5.63 (2.39 – 13.25)
No	108 (77.1)	133 (95)		1
Cyanosis				
Yes	4 (2.9)	0	0.122[¢]	//

Symptoms and signs	Severe HFMD (n=140)	Mild HFMD (n=140)	*p value*	OR (95%CI)
No	136 (97.1)	140 (100)		
Apnea, hiccup breathing				
Yes	9 (6.4)	1 (0.7)	0.019*,¢	9.55 (1.19 – 76.42)
No	131 (93.6)	139 (99.3)		1

¢Fisher's exact test, *p<0.05
Values are the number (percentage) of patients

Subclinical factors related to severe HFMD status included platelet count > 400,000/mm^3, blood glucose > 180mg%, and detection of enterovirus A71 (EV-A71). In particular, children infected with EV-A71 were 5.29 times more likely to contract severe HFMD than were children infected with other enteroviruses.

Table 3. Relationship between subclinical characteristics and severe HFMD

Laboratory examinations	Severe HFMD (n=140)	Mild HFMD (n=140)	p value	OR (95%CI)
Leukocyte count >16,000/mm^3				
Yes	16 (11.4)	16 (11.4)	0.999	1.00 (0.48 – 2.09)
No	124 (88.6)	124 (88.6)		1
Platelet count >400,000/mm^3				
Yes	16 (11.4)	7 (5.0)	0.050	2,45 (0.98 – 6.16)
No	124 (88.6)	133 (95.0)		1
Blood glucose >180mg%				
Yes	29 (20.7)	5 (3.6)	0.046*	1.02 (1.01 – 1.23)
No	111 (79.3)	135 (96.4)		1
CRP > 10mg/l				
Yes	8 (5.7)	2 (1.4)	0.103¢	4,18 (0.87 – 20.06)
No	132 (94.3)	138 (98.6)		1
SPECIMENS DITECT VIRUS				
Stool sample				
Enteroviruses-positive	105 (75.0)	118 (84.3)	0.054	0.56 (0.31 – 1.01)
Enteroviruses-negative	35 (25.0)	22 (15.7)		1
Virus strains				
EV-A71	132 (94.3)	106 (75.7)	<0.001*	5,29 (2.35 – 11.91)
Others Enterovirus	8 (5.7)	34 (24.3)		1

¢Fisher exact test, *p<0.05
Values are the number (percentage) of patients

The multivariate logistic regression model is shown in Table 4. Rapid pulse had the most important role in predicting severe cases. The risk of severe HFMD was 86.3 times higher in children with a rapid pulse than in the other children. A high fever over 39^{o}C was the second most important risk factor, with OR = 13.6.

Table 4. Multivariate logistic regression analysis of factors associated with severe HFMD (n=280)

Characteristics	OR (95%CI)	Adjusted OR (95%CI)	*p value*
Care's gender (M)	4.18 (0.87 - 20.06)	9.51 (1.50 - 60.25)	0.017
High fever >39^{o}C	8.42 (1.04 - 68.28)	23.92 (2.33 - 245.20)	0.007
Rapid pulse >130 beat/minute	67.28 (23.4 - 193.1)	86.34 (26.0 - 278.4)	<0.001
Flounder	27.82 (8.43 - 91.79)	6.40 (1.47 - 27.80)	0.013
Platelet count > 400,000/mm^3	2.45 (0.98 - 6.16)	1.01 (1.01 - 1.01)	0.007
Blood glucose > 180mg%	1.02 (1.01 - 1.23)	1.02 (1.01 - 1.04)	0.029
EV-A71	5.29 (2.35 - 11.9)	4.55 (1.92 - 10.0)	0.001

DISCUSSION

Clinical symptoms associated with severe hand, foot, and mouth disease

The clinical features were analyzed and many features that were recorded before and after hospitalization were associated with severe HFMD. A sore throat symptom was detected as an early warning factor for HFMD cases, but the risk of severity in children with sore throat was lower than in the non-symptomatic cases (OR=0.5, 95%CI 0.30-0.84). Two studies by Zhang[12] and Owatanapanich[9] showed that children with blisters or ulcers on the skin and mucous membranes of the mouth, lips, and limbs had a lower risk of getting the disease. However, Zhang[12] found that blisters or ulcers on the hips and chest were more common in severe cases.[15] Disease manifestations in the mouth and limb areas can be very uncomfortable for children and are easily detected; therefore, these manifestations are considered early warning factors for cases. Children whose symptoms are discovered early are more likely to have earlier access to medical treatment. The manifestation of ulcers in the hip and chest areas is a warning sign for severity.

In the present study, children with vomiting had an associated risk of severe HFMD (OR=1.81, 95% CI: 1.09–3.02). The studies of Zhang [12] and Fang [5] also showed similar results. Therefore, a vomiting symptom was a predictor of severe HFMD. An association was also noted between fever >39ºC and severity, as children with high fever were 23.9 times more likely to develop severe HFMD than were children without this symptom. These findings were similar to those reported by Nguyen[7] and Thai.[11] Nguyen showed that patients with high fever ≥38.5ºC were 2.72 times more likely to develop severe disease than were patients with mild fever or no fever.[7] In Thai also showed that prolonged fever ≥38.5ºC or high fever >39ºC were associated with severe HFMD in children (OR=7).[11] However, the odds ratio in the present study was much higher than the ORs reported in other studies. This difference may reflect different thresholds for identifying fever, as a higher fever threshold was chosen in the present study to improve the estimates of incidence of severe illness. A dose-response relationship was clearly evident, as the incidence of severe HFMD increased with the severity of the fever.

Respiratory symptoms were manifested as rapid breathing. This symptom was noted at the time of presentation and after hospitalization and was associated with the body's resistance response during the course of the virus infection. Children with this symptom were 7.32 times more likely to develop severe HFMD than were children without this symptom. Other studies have also reported that cases of pneumonia, pulmonary edema, and dyspnea were also associated with severe HFMD.[8,9,12] Apnea and hiccup breathing recorded during hospitalization was strongly associated with severe HFMD (OR=9.55). In general, respiratory complications are less commonly detected in HFMD patients; however, studies have shown a prevalence of respiratory complications in the seriously diseased group; these are dangerous complications related to important functions of the body and need to be monitored and treated promptly.

A rapid pulse >130 beats per minute recorded after hospitalization showed a strong association with severe HFMD. The incidence of this symptom was up to 66.4% in severe HFMD cases, while it was only 2.9% in mild HFMD cases. The risk of severe HFMD in rapid pulse cases was 67.3 times higher than the risk in the mild HFMD. Other studies that followed patients with severe conditions showed a very high rate of signs of rapid pulse in up to 96% of the cases.[3] The average pulse at admission was up to 144 beats/minute.[4] Do[4] also found a strong association between rapid pulse cases and severe or fatal HFMD.[4] Therefore, monitoring the child's heartbeat and pulse is very important in assessing the condition of HFMD.

A univariate association was also detected between convulsion or myoclonus/stumbling and severe HFMD. Previous studies in patients with severe HFMD also showed that a rate of central nervous system complications of 71%, with a myoclonus rate of 66% and startle of 50%.[4] Do found that severe cases commonly showed neurological manifestations, with 32% to 34% myoclonus, 24% to 37% stumbling, and 11% cross-eyes.[4] Che showed that up to 77% of severe cases had muscle tremor and 30% had flounder.[3] An association was also reported between neurological symptoms, including languidness, drowsiness, startle, convulsions, and muscle tremor, and severe HFMD.[5,9,11,12] When children show convulsions as well as other neurological symptoms, the disease has become severe and the children are usually in a high fever period, so early detection and timely intervention are important to avoid a worsened condition.

Subclinical symptoms and virus type associated with severe hand, foot and mouth disease

The correlation test indicated an association between an increased severity of HFMD and a platelet count >400,000/mm^3 in blood. Nguyen KT. [7] and Nguyen MT. [8] also showed similar results at the same platelet threshold. At a platelet threshold >300,000/mm^3, Bui also showed this trend.[2] The increase in platelet count is probably due to the important function of platelets in the body's response to infections, especially viruses. However, a recent cohort study in Guangdong (a province of China) by Zhang found that the average platelet count was lower in severe cases than in mild cases.[12] All the analytical results indicate that platelet count should be considered further in the prognosis of severe HFMD.

The findings of the present study indicate an association between blood glucose and severe HFMD (OR=1.01), in agreement with many other studies.[5,7,9,10] Research by Nguyen also suggested this association with OR = 2,9.[7] Another study in China also showed that the prevalence of blood glucose of 126 mg% or more was statistically significant in the case of severe HFMD when compared to moderate or mild HFMD.[10] Research by Nguyen MT also showed that blood glucose >180 mg% was associated with deaths or sequelae.[8] Increased blood glucose in patients with severe disease was due to of

inflammatory mechanisms that led to increased catecholamine secretion, caused by autonomic nervous system disorders, Increased blood glucose levels were directly proportional to the course of the disease. These results showed that increases in blood glucose will contribute to the prognosis of clinical disease progression.

The findings of the present study also revealed the important role of EV-A71 in prognosis of severe HFMD, in agreement with earlier results by Chen.[5] Although previous studies found that most cases of EV-A71 infection were asymptomatic and self-healing, this strain of virus causes serious neurological complications, including aseptic meningitis, ataxia, cerebral palsy, polio-like paralysis, Guillain-Barré syndrome, acute encephalitis, and acute/hemorrhagic pulmonary edema with high mortality.[6] Therefore, when isolating the virus strain in HFMD, special attention should be paid to children infected with EV-A71.

No association was detected between leukocyte count >16,000 cells/mm^3 and severe HFMD, in agreement with the research by Bui.[2] This lack of an association can be explained by the nature of the disease as a viral infection, as a characteristic of these viral infections is no increase in leukocytes. However, Pan showed that an increase leukocytes >17,000 cells/mm^3 was a sign of severe prognosis.[10] Zhang study also found a higher average number of leukocytes in the serious cases.[12] Studies in Vietnam have also shown cases of leukocytosis associated with severe HFMD. Thai also noted that the risk of severe HFMD in cases with leukocytes >15,000 cells/mm^3 was 4.8 times higher than that of the mild cases.[11] Nguyen MT. noted an association between leukocytes >16,000 cells/mm^3 and death.[8] Nguyen KT also showed that the risk of developing severe HFMD was 1.5 times higher in the group with leukocytes >16,000 cells/mm^3 than in those with mild HFMD.[7]

Factors independently associated with severe hand, foot, and mouth disease

Multivariate logistic regression analysis revealed factors that were independently associated with severe HFMD, similar to the signs of transition mentioned in the guidelines of the Ministry of Health in 2012. These included rapid pulse >130 beats/minute, high fever >39ºC, and flounder.[1] These three signs show the popularity and importance of predicting severe HFMD.

The results presented here also show some important sub-clinical features that have not been used as signs of transition monitoring in the guidelines of the Ministry of Health in 2012;[1] these include leukocytosis >400,000/mm^3, blood glucose >180mg/dl, and EV-A71. These are characteristics that showed an association with severe HFMD when considered in the multivariate logistic regression analysis model.

The EV-A71 strain has been evaluated in association with severe cases, complications, and deaths in numerous previous studies, as well as in the guidelines of the Ministry of Health. The present study has also demonstrated that the risk of severe HFMD was 4.55 times higher in the group infected with EV-A71 than in the group infected with other enteroviruses.

CONCLUSION

Clinical symptoms associated with severe HFMD include vomiting, high fever >39ºC, rapid breathing, convulsion, rapid pulse >130 beats/minute, flounder, lethargy, drowsiness/coma, myoclonus/stumbling, and apnea/hiccup breathing. Subclinical symptoms associated with severe HFMD include platelet count >400,000/mm^3 and blood glucose >180mg/dL. EV-A71 infection is also associated with serious illness. Factors independently associated with severe HFMD identified through the multivariate logistic regression analysis model included the carer's gender (Male), high fever >39ºC, rapid pulse >130 beats/minute, flounder, platelet count >400,000/mm^3, blood glucose >180mg/dL, and EV-A71 infection.

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