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EPIDEMIOLOGICAL, CLINICAL AND LABORATORY CHARACTERISTICS OF HAND, FOOT AND MOUTH DISEASE IN CHILDREN AT PHU THO OBSTETRICS AND PEDIATRICS HOSPITAL

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ABSTRACT

Background: Hand, foot and mouth disease is contagious illness transmitted from person to person, often leading to outbreaks, caused by enteric viruses. **Objective**: Describing some epidemiological, clinical, and laboratory characteristics of hand, foot and mouth disease in children. **Methods:** Cross-sectional descriptive study, with 207 children diagnosed with hand, foot, and mouth disease at Phu Tho Obstetrics and Pediatrics Hospital, from September 2022 to May 2023. **Results:** The average age was 22 ± 13 months, the highest group was 12-23 months with 53.1%. The male/female ratio was 1.3/1. The majority of infected children had contact with a source of infection in the 7 days before getting sick, accounting for 65.7%, went to kindergarten, accounting for 55.1%, and lived in rural areas accounting for 57%. Children without malnutrition have the highest disease incidence from January to March and malnourished children have the highest incidence from October to December ($p < 0.05$). High fever ≥ 39 degrees is related to children < 3 years old and have a positive Enterovirus 71 rapid test. The proportion of children with severe severity accounts for 15%. Increased C-reactive protein is common in patients with malnutrition and severe patients. **Conclusions:** Hand, foot, and mouth disease is common in children aged 12-23 months, those who come into contact with infectious sources and go to kindergarten have a higher incidence of the disease. High fever is associated with children < 3 years old and with a positive Enterovirus 71 rapid test.

Keywords: Hand, foot and mouth disease; Children; Epidemiological; Clinical.

INTRODUCTION

Hand, foot and mouth disease (HFMD) is contagious illness transmitted from person to person, often leading to outbreaks, caused by enteric viruses. This disease can occur at all ages but is most common in children under 5 years old, especially those under 3 years old. The two main groups of agents causing the disease that are commonly encountered are: Coxsackie virus A16 (CV-A16) and Enterovirus 71 (EV71). In 2009, there was a HFMD outbreak in China with 1.155.525 reported cases, 13.810 severe cases, and 353 deaths. Subsequent outbreaks have been reported in other countries as well. In Vietnam, the first HFMD case was reported in 2003 and in the following years the disease has been reported in all major provinces and cities across the country. Data from the Ministry of Health indicates an increasing trend in the number of case in recent years, with the peak being in 2011 when Vietnam recorded 113.121 HFMD cases and 170 deaths[1].

The characteristics of HFMD in children vary significantly by geographic region, both within countries and worldwide. A study on the characteristics of HFMD in children at Saint Paul Hospital in Hanoi (2020 – 2021)[2] showed that it was more common in males than females, mouth ulcers and skin rashes were observed in all pediatric patients, with a high proportion (70%) experiencing moderate to severe disease (Grade 2b – 4) and positive PCR test for EV71 was 28.8%. All the while, another study in Tien Giang (2015 – 2019), the positive PCR rate of severe disease at 0.3%[3]; in China (2016 – 2018), the positive PCR rate for EV71 was 8.9%, and for CV-A16 was 5.2%, with an overall rate of severe disease of 16.4% and for the EV71 – positive group was 47.7%[4]. So, what are the differences in the characteristics of HFME in children in Phu Tho province? Therefore, we conducted this study with the aim of "Describing some epidemiological, clinical, and laboratory characteristics of hand, foot and mouth disease in children treated at Phu Tho Obstetric and Pediatric Hospital in 2022 – 2023".

METHODS

Participants, time and location of study: 207 children with HFMD were treated inpatients at Phu Tho Obstetrics and

Pediatrics Hospital from September 2022 to May 2023, meeting the criteria.

Inclusion criteria:

The clinical diagnosis of HFMD was made according to the definition provided by the Ministry of Health[5], based on:

- Epidemiological factors: based on age, season, and disease prevalence in the region.

- Clinical symptoms: typical blistering on the mouth, palms, soles, knees, and buttocks, with or without fever.

Patients aged 15 and lower were tested rapid EV71 testing.

The family of child agreed to participate in the study.

Exclusion criteria: Children with pre-existing dermatological conditions, liver diseases, or blood cotting disorders before contracting HFMD.

Methods

Study design: Cross-sectional descriptive study.

Sample size: Applying the sample size formula for estimating the proportion:

$$n = Z^2_{(1-\alpha/2)} \frac{p(1-p)}{d^2}$$

In which:

n: the required sample size for the study.

$Z^2_{(1-\alpha/2)}$ is the confidence level taken at the threshold $\alpha = 0.05$. We have $Z^2_{(1-\alpha/2)} = 1.96$

p = 0.892; the proportion of mouth ulcers in HFMD patients in the study by Do Quang Thanh, 2022[6].

d: absolute precision requires, in this study, taking d = 0,05.

According to this formula, the minimum required sample size is: N = 148,03.

Sampling techniques in research: Convenient sampling, selecting all eligible patients to include in the study.

Our study collected 207 patients, meeting the sample size formula above.

Research variables, indicator:

Epidemiological characteristics: Age in months (< 12, 12-23, 24-35, 36-47, 48-59, ≥ 60 months), gender, place of residence (urban, rural area), exclusive breastfeeding status for the first 6 months, malnutrition – including mild malnutrition, stunting, and wasting, attendance at daycare before the onset of disease, exposure to a source of infection in the 7 days before falling ill, month of illness, and educational level of the primary caregiver (completed high school, less than high school)[2].

Clinical characteristics: date of illness onset, systemic symptoms (mouth ulcers, skin rashes, fever), neurological symptoms (startling during examination or while asleep, seizures), high fever ≥ 39^o C, disease severity (mild: Grade 1-2a, severe: Grade 2b-4)[5].

Laboratory characteristics: EV71 viral infection hemotological parameters (white blood cell count, platelet count), biochemical parameters (GOT, GPT, C-reactive protein).

Data collection methods: The research team directly collected data through interviews, patient examinations, and extraction from patient medical records using the research, medical record template that was developed. The EV71 virus was tested using the SD BIOLINE rapid test to detect IgM antibodies against EV71 in serum/plasma at the testing center of Phu Tho Obstertric and Pediatric Hospital, with results available from 15 to 20 minutes. Data collection for the research was condcuted from September 2022 to May 2023.

Data analysis: Using SPSS 22.0 software, calculate the frequency and percentage (%) (for qualitative variables); mean, and standard deviation (for quantitative variables). Comparing two proportions using the Chi-square test, statistical significance is considered when $p < 0.05$.

Research ethics: The research was conducted with the approval of the Ethics Council of the University of Medicine - Thai Nguyen University and Phu Tho Obstetric and Pediatric Hospital.

RESULTS

A study of 207 childrenwith HFMD identified the following common characteristics:

Table 1. Characteristics of children with HFMD

Characteristics (n=207)		n	%
Ages (months)	< 12	7	3.3
	12 - 23	110	53.1
	24 - 35	43	20.8
	36 - 47	28	13.5
	48 - 59	12	6.0
	≥ 60	7	3.3
	Mean (min - max)	22 ± 13 (3 - 79)	
Gender	Male	117	56.5
	Female	90	43.5
male-to-female ratio		1.3/1	

The average age of the 207 children with (HFMD) is 22 ± 13 months, Most children with hand, foot, and mouth disease are between the ages of 12-23 months accounting for 53.1% of cases. The number of male patients was higher than females, with a male-to-female ratio was 1.3/1 (Table 1).

Table 2. Epidemiological characteristics of HFMD (n=207)

Characteristics		n	%
Date of illnes onste	Days 1 – 2	124	59.6
	Day 3 onwards	83	40.1
Place of residence	Urban	89	43
	Rural	118	57
Educational background of the caregiver	Below 12^{th} grade	68	32.9
	Graduated from 12^{th} grade	139	67.1
Contact with a source of infection within the last 7 days	Yes	136	65.7
	No	71	34.3
Attendance at kindgarden	Yes	114	55.1
	No	93	44.9
Exclusive breastfeeding for the first 6 months	Yes	126	60.9
	No	81	39.1

The group of children who had contact with a source of infection within 7 days before becoming ill accounted for 65.7%, while the group of children attending daycare accounted for 55.1%. The percentage of children living in rural areas is higher than in urban areas, with rates of 57% and 43% respectively (Table 2).

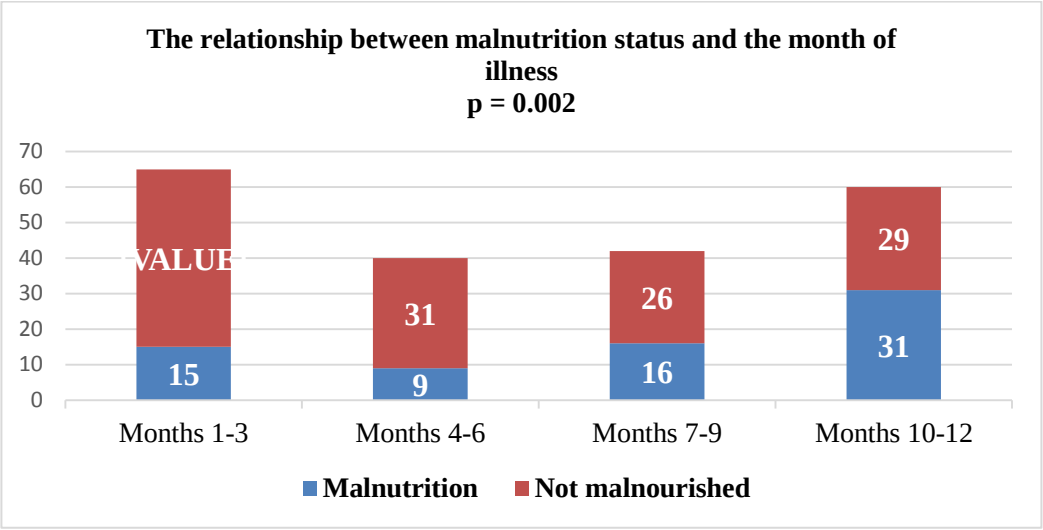

Figure 1. Characteristics of the month of illness with nutritional status

Figure 1 showed that children without malnutrition have the highest illness rate in the months of January to March, while malnourished children have the highest disease incidence in the months of October to December, with a statistically significant difference at $p < 0.05$.

Table 3. Some clinical characteristics in children with HFMD

Contents		Clinical characteristrics (n=207)									
		Mouth ulcer (n = 192)		**Blister (n = 128)**		**Fever ≥ 39 độ (n = 124)**		**Sleep startle (n = 121)**		**Seizure (n = 14)**	
		n	%	n	%	n	%	n	%	n	%
Age	< 3 (n = 181)	166	91.7	109	60.2	113	62.4	110	60.8	13	7.2
	≥ 3 (n = 26)	26	100	19	73.1	11	42.3	11	42.3	1	3.8
p		>0.05		>0.05		**<0.05**		>0.05		>0.05	

Admission date	1-2 (n = 124)	114	91.9	80	64.5	75	60.5	66	53.2	7	5.6
	≥ 3 (n = 83)	78	94	48	57.8	49	59	55	66.3	7	8.4
p		>0.05		>0.05		>0.05		>0.05		>0.05	
Malnutrition	Yes (n = 71)	69	97.2	45	63.4	41	57.7	35	49.3	4	5.6
	No (n = 136)	123	90.4	83	61	83	61	86	63.2	10	7.4
p		>0.05		>0.05		>0.05		>0.05		>0.05	
Rapid EV71 testing	Positive (n = 40)	38	95	15	37.5	31	77.5	12	30	9	22.5
	Negative (n = 167)	154	92.2	113	67.7	93	55.7	74	44.3	5	3
p		>0.05		**<0.05**		**<0.05**		>0.05		**<0.05**	

Symptoms of fever ≥ 39° C are commonly seen in the group of children under 3 years old and those with a positive rapid EV71 test result. Seizure symptoms are also frequently observed in the group with a positive rapid EV71 test result (Table 3).

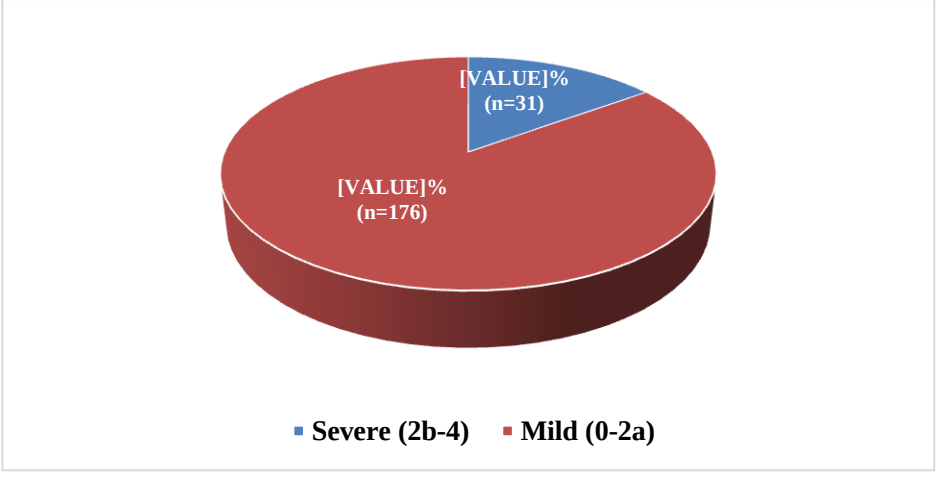

Figure 2. The severity level of HFMD

Figure 2 showed that in the study, the proportion of children with a severe degree of disease was 15%, while those with a mild degree accounted for 85%.

Table 4. Clinical characteristics in children with HFMD

Contents		Clinical characteristics (n=207)									
		Positive rapid EV71 testing: (n = 40)		**Increased white blood cells (n = 127)**		**Increased platelet (n = 9)**		**Increased blood sugar (n = 22)**		**Increased CRP (n = 106)**	
		n	%	n	%	n	%	n	%	n	%
Age	< 3 (n = 181)	38	21	114	63	9	5	18	9.9	94	51.9
	≥ 3 (n = 26)	2	7.7	13	50	0	0	4	15.4	12	46.2
p		>0.05		>0.05		>0.05		>0.05		>0.05	
Malnutrition	Yes (n = 71)	21	29.6	46	64.8	4	5.6	9	12.7	44	62
	No (n = 136)	19	14	81	59.6	5	3.7	13	9.6	62	45.6
p		**<0.05**		>0.05		>0.05		>0.05		**<0.05**	
Severity	Severe (n = 31)	22	71	23	74.2	3	9.7	13	41.9	21	67.7
	Mild (n = 176)	18	10.2	104	59.1	6	3.4	9	5.1	85	48.3
p		**<0.05**		>0.05		>0.05		**<0.05**		**<0.05**	

Elevated CRP levels are commonly found in patients with malnutrition and a severe degree of the disease. Increased blood sugar levels were observed in 41.9% of patients in the severe group compared to 5.1% in the mild group. Positive EV71 test result is associated with patients who have malnutrition and a severe degree of the disease, and this difference is statistically significant at $p < 0.05$ (Table 4).

DISCUSSION

Epidemiological characteristics of HFMD

Regarding individual-related factors, our results indicate that most cases of the disease occur in children under 5 years old, especially in the 1-3 age group, with the lowest incidence in those under 1 year old and over 5 years old. The male-to-female ratio is higher in males, at 1.3 times. These findings are consistent with some

authors such as Phousamay S., where the age group most affected was 1-3 years old (72.5%)[2], and Thai Quang Hung, with the highest incidence in children aged 1-3 years at 73.3%, and a male-to-female ratio was 2/1[7]. The varying incidence of HFMD among age groups can be attributed to maternal antibodies acquired during pregnancy and breastfeeding for the first 6 months. After the initial 6 months, these protective factors start to decline, leading to an increased susceptibility to the disease. According to a study on the prevalence of EV71 antibodies in serum in Singapore, it showed that 44.0% of infants received maternal antibodies against EV71 at birth, but this percentage rapidly decreased, with only 0.8% of children aged 1-23 months having antibodies. From 2 to 5 years old, these antibodies increased by an average of 12% each year. In samples from children over 5 years old, the antibody rate stabilized at nearly 50%[8].

Regarding epidemiological factors, we observed a higher disease incidence rate in rural areas, among children who had direct contact with a source of infection in the past 7 days, and among children attending daycare. The study by Nguyen Đắc Thăng over a 5-year period also showed that more children in rural areas were affected by the disease than in urban areas[3]. HFMD is an infectious disease that can be transmitted from person to person through direct contact with saliva, throat discharge, fluid from blisters, or feces of an infected person, as well as through sharing personal items. Children attending daycare often share toys, meals, and interact with each other. Since young children may not be aware of disease prevention practices, they are susceptible to viral transmission from other children, sometimes even during the asymptomatic incubation period. The incubation period for HFMD typically ranges from 3-7 days[5], so children who have been identified as having had contact with a source of infection in the 7 days before falling ill are at higher risk of contracting the disease compared to other children.

Children with malnutrition are at an increased risk of infection, including severe infections with various microorganisms, including HFMD. HFMD tends to be more prevalent during certain periods, typically from October to December and from January to March when weather conditions are changing. In our

study, we found that the majority of children with SDD were observed during the period from October to December. Other studies have also demonstrated that children who are not exclusively breastfed for the first 6 months experience reduced immunity and are at a 2.03 times higher risk of contracting diseases compared to those who are exclusively breastfed during this crucial period[7].

Clinical characteristics of HFMD

Most of the children in our study exhibited skin and mucosal lesions similar to water blisters in locations such as the buttocks, palms of the hands, soles of the feet, body, and mouth ulcers. These symptoms did not show significant differences among age groups, nutritional status, or the timing from onset to hospital admission. In our study, fever ≥ 39 degrees Celsius was frequently observed in children under 3 years old, particularly in those with a positive rapid EV71 test result, and seizure symptoms were also common in the group with a positive EV71 test result. This is consistent with the findings of other studies. For example, Phousamay S. reported 100% skin lesions and 82.5% mouth ulcers and Vi Ngọc Linh found 54.2% skin lesions in HFMD cases[2,9]. Fever is a commonly encountered symptom in HFMD cases, especially with a high fever (≥ 39 degrees Celsius). In our study, 59.9% of cases had a high fever, while Phousamay S. reported 100% and Vi Ngọc Linh reported 70.8% with high fever. Fever and skin lesions can coexist, but sometimes only one of these symptoms is present, which can complicate diagnosis, especially if a patient presents with fever alone. High fever (≥ 39 degrees Celsius) and seizures were more common in children under 3 years old. Young children have less developed temperature-regulating mechanisms and immature nervous systems, which make them more susceptible to seizure symptoms, including both sleep startle and examination-induced startle.

The rate of severe cases in our study was only 31/207 children, the majority of HFMD patients exhibited mild disease, which means they had only skin and mucosal lesions and/or fever. However, there were still a few cases that had severe disease progression with potentially dangerous complications involving the nervous system, cardiovascular system, and respiratory

system. The severe disease rate (Grade 2b-4) in our study was 15%, lower than that reported by Phousamay S. (70%)[2] and Wang J. (16.4%)[4], but higher than the rate reported by Nguyen Đac Thang (0.03%)[3]. This difference, in our opinion, is partly related to the quality of care and treatment provided by caregivers, and partly due to sample size. Phousamay S. conducted their study with a small sample of just over 80 HFMD cases in 2020-2021, while Wang J.'s study (2016-2018) included 4,760 children, and Nguyen Đac Thang's study (2015-2019) involved 1,114 children. The variation in sample sizes and study periods can lead to differences in reported disease severity rates. Raising awareness among the public about disease prevention and treatment plays a crucial role in reducing the incidence of HFMD, as well as the rates of severe cases and fatalities, especially for infectious diseases.

Laboratory characteristics of HFMD

In Vietnam, two important pathogens that cause HFMD are the CV-A16 and EV71 viruses[5,10]. Currently, there are several testing techniques used to detect the presence of HFMD, including rapid tests and PCR tests. Rapid tests help identify the presence of IgM antibodies in the body, providing quick and cost-effective results. These tests are widely available in many healthcare facilities, but they have limitations, including low positive predictive value and a high rate of false-positive results. However, according to various reports, the positive test rate for HFMD-causing viruses is not extremely high. For instance, Vi Ngọc Linh's EV71 study reported a 5.8% positive rate using rapid testing[9], Phousamay S. found a 28.8% positive rate using PCR[2], Wang J. reported an 8.9% positive rate for EV71 and a 5.2% positive rate for CV-A16 using PCR[4]. Within the scope of this study and considering the conditions of the research facility, we conducted rapid testing for EV71, and the positive rate was 19.3%. Diagnosing HFMD still primarily relies on clinical cases with typical skin and mucosal lesions and/or fever symptoms. In our study, we observed that a positive EV71 test result was associated with patients who had malnutrition and a severe disease degree, with statistical significance at $p < 0.05$. EV71 is known as the primary agent responsible for severe cases and fatalities in HFMD[7,10].

Regarding other laboratory tests, in our study, elevated white blood cell counts exceeding 10 G/L was observed in 127 patients, accounting for 61.4% of cases. In the early stage of the disease, an increase in white blood cells is associated with the body's immune response, creating a defense mechanism to combat the HFMD virus. Elevated platelet counts and increased blood glucose levels were observed in a low percentage of cases in our study, at 4.3% and 10.6%, respectively. The proportion of patients with CRP levels exceeding 10 mg/L was 106/207 patients, accounting for 51.2%. These results indicate that CRP levels increased in most children in the severe disease category and among those with malnutrition, as seen in various patient groups. In the study conducted by Do Quang Thanh (2020), children with elevated blood glucose levels were 1.02 times more likely (95% confidence interval: 1.01 - 1.23) to have severe HFMD compared to those without elevated blood glucose levels. Children with elevated platelet counts were 2.45 times more likely (95% confidence interval: 0.98 - 6.16) to have severe HFMD compared to those without elevated platelet counts. However, there was no significant difference observed in CRP levels between these two groups[6].

CONCLUSION

In our study, HFMD was predominantly observed in children aged 12-23 months, constituting 53.1% of cases. The average age of the study was 22 ± 13 months. The majority of affected children had contact with a source of infection within 7 days before falling ill, accounting for 65.7%. Approximately 55.1% of the children attended daycare, and 57% resided in rural areas. Among children without malnutrition, the highest incidence of HFMD occurred from January to March, while children with malnutrition had the highest incidence from October to December. Fever symptoms of $\geq 39^{o}C$ were more common in children under 3 years old and in those with a positive rapid EV71 test result. Severe cases accounted for 15% of all cases. Elevated CRP levels were frequently observed in patients with malnutrition and severe disease degrees. Elevated blood glucose levels were present in 41.9% of severe cases compared to 5.1% in mild cases.

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