

Hand, Foot, and Mouth Disease in Children: Clinical Characteristics of an Outbreak in Novi Sad, Serbia

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ABSTRACT Hand, foot, and mouth disease (HFMD) is a relatively common mild viral infection that usually affects young children, mainly occurring during the late spring, early summer, and fall months. It is most commonly caused by members of the human enterovirus (HEV) genus. Recently, HFMD has received renewed attention because of evidence that this disease could have clinical, epidemiological, and etiological characteristics different from those initially associated with it. HFMD may be associated with neurologic or cardiopulmonary complications and can, rarely, lead to death. Our study was a retrospective analysis on 83 children (<18 years of age) who were clinically diagnosed with HFMD at the Department of Dermatology of the Institute for Child and Youth Health Care of Vojvodina, in a single, tertiary-care university hospital in Novi Sad, Vojvodina province, Serbia, for the time period from January 2016 to December 2017. During the study period, HFMD was diagnosed in 83 children. Our results suggest that the outbreak of HFMD occurred in younger children (average age 3.10 years), who seem to be the most susceptible age group for HFMD infection. Taking into account that the diagnosis of HFMD is usually clinical, we believe that it is important for health professionals to be well-informed about the clinical features and the course of the disease. Good personal hygiene and the implementation of a surveillance system can help stop the spread of the disease and prevent outbreaks.

KEY WORDS: hand, foot and mouth disease, clinical characteristics, outbreaks, Serbia

INTRODUCTION

Hand, foot, and mouth disease (HFMD) is a relatively common mild viral infection that usually affects young children, mainly occurring during the late spring, early summer, and fall months. It is most commonly caused by members of the human enterovirus (HEV) genus, including coxsackievirus A16 (CV-A16), enterovirus 71 (EV-71), and recently CV-A6 and CV-A10 viruses. HFMD is characterized by vesicular lesions, mostly on the hands, feet and mouth, that spontaneously resolve in a few days. Recently, HFMD has received renewed attention because of evidence that this disease could have clinical, epidemiological,

and etiological characteristics different from those initially associated with it. HFMD may be associated with neurologic or cardiopulmonary complications and can, rarely, lead to death (1). Although disease flares are sporadic in the majority of cases, epidemics may also occur. Several outbreaks of HFMD have been documented in Asia, particularly in the Western Pacific Region (1-4). Outbreaks of HFMD have been reported in India, Europe, and America as well (1,5-8). An outbreak of HFMD has been reported in a child care center in Croatia, as well (9). There have not been any published reports on an outbreak of HFMD in Serbia until now.

PATIENTS AND METHODS

Our study was a retrospective analysis on 83 children (<18 years of age) who were clinically diagnosed with HFMD at the Department of Dermatology of the Institute for Child and Youth Health Care of Vojvodina, in a single, tertiary-care university hospital in Novi Sad, Vojvodina province, Serbia, for the time period from January 2016 to December 2017. The study was approved by the Institutional Ethical Committee of the Institute.

All patients were clinically diagnosed by a dermatologist (authors SP and AR), based on typical clinical findings of HFMD. Patients with typical signs and symptoms of the disease, including vesicular and/or maculopapular rash on the hands, feet and/or the oral mucosa, face, extremities, trunk, diaper area, or buttocks, as derived from the medical and electronic health records of the patients, were diagnosed with HFMD. Eight (10.84%) children with onychomadesis were diagnosed with precedent HFMD based on the history of typical eruption, as provided by the parents or medical records; these children were also included in the study. Laboratory tests (C-reactive protein (CRP) and/or blood count) were performed in 25 (30.12%) children with constitutional symptoms. Testing of immunoglobulin M and G titers for coxsackie B virus, Epstein-Barr virus, cytomegalovirus, parvovirus B 19, herpes simplex virus, and adenovirus were performed in only 2 (2.41%) hospitalized patients.

T-test and chi-square test were used on statistical analysis; $P < 0.05$ was considered statistically significant. Analysis was performed using Microsoft Excel 2010 and SPSS 21 statistical software.

RESULTS

During the study period, HFMD was diagnosed in 83 children. During 2016, 68 children presented with symptomatology consistent with HFMD. The first case of HFMD was diagnosed in March of 2016. The peak of the HFMD outbreak was reached in the summer of 2016, in the period from June to September (56/68; 82.35%), with its highest peak of cases in the month of June 2016 ($n=22$), then August ($n=14$), July ($n=10$), and September ($n=10$). From January 2017 to December 2017, HFMD was detected in 15 children. Sporadic cases appeared in May ($n=1$), June ($n=2$), and at the end of 2017 (October $n=3$, November $n=3$, and December $n=6$) (Figure 1).

All children were residing in the province of Vojvodina, although most cases (34/40.96%) were reported in Novi Sad. There were 44 (53.01%) boys and 39 (46.99%) girls affected. The majority of pa-

tients (60/72.29%) were below 6 years of age, while 38 (45.78%) children were below 2 years of age. The mean age was 4 years and 6 months, ranging from 5 months to 17.6 years. Household transmission of the disease was noted in 8 (9.64%) cases; child-to-adult transmission was present in 1 (1.20%) case and child-to-child transmission in the other 7 (8.43%) cases.

All patients had characteristic vesicular and/or maculopapular rash. Petechiae were present in 4 (4.82%) children. Rashes were most commonly distributed on the hands or/and feet (100%), followed by perioral distribution on the face in 42 (50.60%) children. Oral lesions were observed in 29 (34.94%), lesions on arms and legs were observed in 36 (43.37%), on the buttocks or napkin region in 18 (21.69%), and lesions on the trunk were present in 16 (19.28%) children. Onychomadesis was present in 9 (10.84%) children, and palmoplantar desquamation in 4 (4.82%) children. The rash was associated with pruritus in 18 (21.69%) children. Prodrome was present in a majority of children (59/71.08%).

Cases in the HFMD outbreak period (from June to September 2016) were compared with cases without an outbreak of HFMD. During the HFMD outbreak, children were significantly younger than children in the period without outbreak of HFMD (average age 3 y, 10 m vs. 6 y; $P=0.047$). There were no other significant differences between these 2 groups – they were similar according to demographics and clinical features (Table 1).

The most common prodromal symptom was fever, in 56 (67.47%) children. Three (3.61%) of them had febrile seizures (Table 2). High CRP was present in 17 (20.48%) children and leukocytosis in 6 (7.23%) children.

Secondary bacterial skin infections were observed in 14 (16.87%) children. Associated diseases were present in 7 (8.43%) children. Atopic dermatitis was present in 3 (3.61%) children; pediculosis, scabies, prurigo, contact dermatitis, and acne in 1 (1.20%) child each; asthma, lymphadenitis, thrombocytopenia, anemia, and urinary tract infection in 1 (1.20%) child each as well; one (1.20%) 17 year old boy was hospitalized with presumed immune disorder, with a diagnostic in progress, and he was taking azathioprine and prednisone.

Nine (10.84%) children with extensive HFMD skin involvement, fever, and accompanying symptoms were hospitalized. Children were treated with symptomatic medications and supportive measures, resulting in the resolution of symptoms. All children recovered completely.

Table 1. Demographic and clinical features of patients with hand-foot-mouth disease

	All cases	June- Sept 2016	Other cases	p value
Number of cases	83	56	27	
Age range	5 m - 17.6 y	5 m - 17.6 y	8 m- 17.2 y	
Age median	4 y, 6 m	3 y, 10 m	6 y	0.047
< 2 years	38 (45.78%)	26 (46.43%)	12 (44.44%)	
< 6 years	60 (72.29%)	44 (78.57%)	16 (59.26%)	
> 6 years	23 (27.71%)	12 (21.43%)	11 (40.74%)	
Sex				
Male	44 (53.01%)	32 (57.14%)	12 (44.44%)	0.350
Distribution				
Hands or/and feet	83 (100%)	56 (100%)	27 (100%)	1.00
Face and perioral distribution	42 (50.60%)	26 (46.43%)	16 (59.26%)	0.350
Oral lesions	29 (34.94%)	21 (37.5%)	8 (29.63%)	0.624
Lesions on arms and legs	36 (43.37%)	27(48.21%)	9 (33.33%)	0.242
Buttocks and/or napkin region	18 (21.69%)	12 (21.43%)	6 (22.22%)	1.00
Trunk	16 (19.28%)	11 (19.64%)	5 (18.52%)	1.00
Morphology				
Vesicular and/or maculopapular rash	83(100.00%)	56 (100.00%)	27(100.00%)	1.00
Petechiae	4 (4.82%)	3(5.36%)	1(3.70%)	1.00
Onychomadesis	9 (10.84%)	7(12.5%)	2 (7.41%)	0.711
Palmoplantar desquamation	4 (4.82%)	3(5.36%)	1(3.70%)	1.00
Pruritus	18 (21.69%)	13(23.21%)	5(18.52%)	0.779
Prodromal sym	59 (71.08%)	43(76.79%)	16(59.26%)	0.221
Fever	56 (67.47%)	40(71.43%)	16(59.26%)	0.321
Hospitalized	9 (10.84%)	8(14.29%)	1(3.70%)	0.260

DISCUSSION

HFMD is an acute febrile illness that commonly affects children younger than 5 years of age. The disease is caused by enteroviruses EV-71 and CV-A16, which may differ in their clinical course. EV-A71 infections are usually more severe than CV-A16 (1,2).

We presented a report of an outbreak of HFMD and its clinical features in Novi Sad, in the Republic of Serbia, during the summer of 2016. Our study describes the cases of 83 children with a clinical diagnosis of HFMD, observed during the period between January 2016 and December 2017, with the peak

of the incidence in the summer of 2016. The actual number of cases during the outbreak is likely to have been much higher, as many patients with mild symptoms may not have been referred to the Institute. The peak of the HFMD outbreak was reached in the period from June 2016 to September 2016, with its highest peak in the month of June (n=22). As in previous reports, we also observed the outbreak during summer months, with the peak occurring in June, as was reported in North China and France (2-4,6,7). During 2017, HFMD was detected in only 15 children. In a 7-year study (2011-2017) in Korea, a massive epidemic of HFMD was observed in 2016, decreasing in 2017, similar to our report (4).

Like in other studies, most patients (60/72.29%) were <6 years of age (3-5,8-10). The outbreak of HFMD occurred in younger children (average age 3.10 years) compared with sporadic cases of HFMD. Since HFMD is a highly contagious disease, outbreaks occur frequently in kindergartens. Therefore, it is important to educate health workers in primary health care and in kindergartens, as well as parents, on the transmission and prevention of disease, including enhanced personal hygiene practice and dis-

Table 2. Prodromal and accompanying symptoms in children with hand-foot-mouth disease

Symptom	n (%)
Fever	56 (67.47%)
Febrile seizures	3 (3.61%)
Pharyngitis	11(13.25%)
Tonsillitis	1 (1.20%)
Otitis	1 (1.20%)
Diarrhoea and other digestive signs	6 (7.23%)

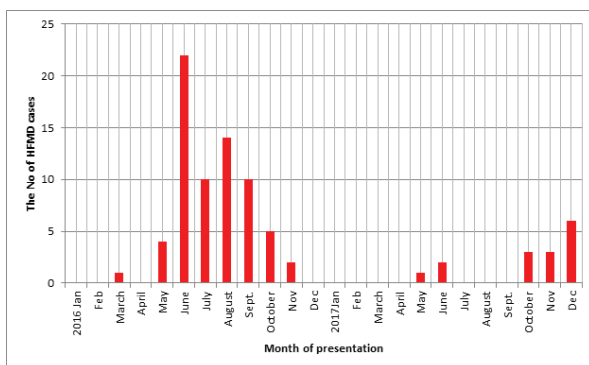


Figure 1. The number of hand-foot-mouth disease cases by season

infection of the environment. Surveillance and public health awareness would help keep the infection localized in order to prevent outbreaks.

A significant percentage of affected children (over 40%) were below 2 years of age. Although literature data from China showed that severity and mortality was higher in this age group, no severe complications or deaths were reported during our study period (10). The difference in mortality rate might be due to the causative agent. In China, EV-71 was encountered in most deaths, with no substantial effect of age.

According to the literature, both sexes are equally affected by HFMD, just like in our study, where 53.01% of affected children were boys and 46.99% were girls (3-5). Household transmission was documented in 9.64% cases. Intrafamilial cases were also reported in a study in Denmark (11).

The typical clinical features are sufficient to establish a correct diagnosis of HFMD, particularly in outbreak settings. Usually, children present with prodromal symptoms, followed by the appearance of a papulovesicular rash with a characteristic distribution involving the hands, feet, and mouth. Virological tests may be of use in atypical clinical presentations. As in an outbreak reported in India, we established the diagnoses based on typical clinical findings only (5).

Rashes were most commonly distributed on the hands and/or feet (100%), followed by perioral distribution (50.60%), while oral lesions were observed in only 29 (34.94%) patients. Other studies have reported a high prevalence of the involvement of the oral mucosa and less often of the face (5,6). Facial involvement in a distinct perioral distribution has often been described in outbreaks in France and Denmark; this is in accordance with our report (8,11).

Patients with classic HFMD have fever associated with a maculopapular or papulovesicular rash on the palms of the hands or the soles of the feet, along with mouth ulcers. This disease resolves spontaneously

within 7-10 days. It is relatively common for a patient to exhibit only one or two of these symptoms, which may explain the lack of oral lesions in our study (1).

Lesions were also observed on the arms and legs in 43.37% children, more than in a study in France (35.4%), and on the buttocks and/or napkin region in 21.69% children, which is less than reported in studies from France and India (5,6,8). In our report, 19.28% children had rashes extending to the trunk. Skin lesions involving the trunk in HFMD have been reported in India and France as well (6,8). The rash was associated with pruritus in 21.69% children, similar to a study by Nanda *et al.* in which approximately 24% of patients had pruritus (5). Consistent with previous reports, the majority of children (71.08%) in our study had prodromes. Most of them (67.47%) had fever, as reported in other studies (5-8). Other clinical features were uncommon.

HFMD is mostly a self-limiting illness that requires symptomatic treatment. Although the majority cases in our study were reported as mild, about 10% children required hospitalization due to an extensive skin rash, fever, and accompanying symptoms.

In recent years, the atypical form of HFMD, mostly caused by CV-A6, has been reported worldwide in children and adults, usually during the winter in temperate climates (8,11,13). The atypical form has more polymorphic lesions, which are much more extensive and lead to widespread exanthema. The majority of patients with atypical HFMD also had other symptoms, including fever (12,13). Atypical cutaneous presentations involved vesiculobullous and erosive lesions, purpuric or petechial eruptions, lesions similar to Gianotti-Crosti, and lesions resembling eczema herpeticum, termed eczema coxsackium in children with atopic dermatitis (13). In this report, petechial rash was found in 4.82% children.

Finally, 10.84% of our patients presented with onychomadesis, and 4.82% with palmoplantar desquamation. It is known that delayed cutaneous manifestations, such as onychomadesis and acral desquamation, may also occur in the preceding weeks and should raise suspicion of HFMD (14). Onychomadesis outbreaks following HFMD have been reported in Greece and many countries worldwide (15). Our data also suggest an association between onychomadesis and the outbreak of HFMD.

There were some limitations in our study, as many patients with mild symptoms may not have reported to the Institute, and thus under-reporting of cases is likely. Additionally, this was a study from a single tertiary-care university hospital. The retrospective nature of the study resulted in incomplete data capture.

Finally, the diagnosis of HFMD was established clinically, and virological confirmation was not available. However, the typical clinical features are sufficient to establish the correct diagnosis, particularly in an outbreak setting, as in our study.

CONCLUSION

Our results suggest that the outbreak of HFMD occurred in younger children (average age 3.10 years), who seem to be the most susceptible age group for HFMD infection. Taking into account that the diagnosis of HFMD is usually clinical, we believe that it is important for health professionals to be well-informed about the clinical features and the course of the disease. Good personal hygiene and the implementation of a surveillance system can help stop the spread of the disease and prevent outbreaks.

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