

Hand, Foot and Mouth Disease: University Malaya Medical Centre Experience

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Summary

The prevalence of HFMD as well as the causative agents was unknown in peninsular Malaysia prior to May 1997. From May 1997 to June 2001, 585 patients suspected to have enterovirus infections, with 467 patients clinically diagnosed as having HFMD, were investigated in the diagnostic virology unit of the University Malaya Medical Centre. Data from this study showed that HFMD is endemic in Malaysia with the occurrence of two outbreaks during the study period. In each outbreak, a number of viruses were isolated but enterovirus 71 was the main virus isolated in both outbreaks. Echovirus 7 (Eo7) was isolated from 5 patients with HFMD in the second outbreak, a clinical entity that has not been attributed to it previously. Children aged 4 years and below, particularly those between 1 and 2 years of age, were in the main group of patients affected by the illness. HFMD by itself and without neurological involvement was relatively benign and self-limiting. There was no significant difference in the virus isolation rate with respect to gender and ethnic groups. Virus isolation was attempted in a total of 764 clinical specimens consisting of 342 stool specimens, 285 oral secretions specimens and 137 vesicular fluid specimens. Oral specimens gave the highest virus isolation rate (33.3%) followed by vesicular specimens (27.0%). Stool specimens only yielded an isolation rate of 14.0%.

Key Words: Hand-foot-mouth disease, Enterovirus 71, Coxsackie A16 virus, Echovirus 7

Introduction

Human enteroviruses are small, single-stranded positive sense RNA viruses in the family *Picornaviridae*. It comprises 68 serotypes identified by conventional serum neutralization test¹. Clinical entities typically associated with particular enterovirus serotypes, except polioviruses, are rare although there are defined clinical diseases that are usually caused by a limited number of different enterovirus serotypes. One of the most distinct examples is hand, foot and mouth disease (HFMD), a febrile

papulovesicular eruption that is most frequently associated with coxsackievirus A16 (CA16) infection. Other serotypes of coxsackie A viruses (4, 5, 9 and 10) and enterovirus 71 (EV71) have also been reported to cause HFMD besides being associated with other types of disease manifestations^{1,2}.

Prior to May 1997, HFMD was a relatively unknown and understudied disease in Malaysia. Interest in the disease picked up when a large outbreak of HFMD resulted in a number of

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deaths in children due to acute involvement of brain stem in 1997^{3,4}. Both CA16 and EV71 were isolated from cases of HFMD but only EV71 was isolated from fatal cases^{3,4}. A similar outbreak of HFMD with fatalities recurred in 2000 in peninsular Malaysia. In the University Malaya Medical Centre (UMMC), besides CA16 and EV71, echovirus 7 (Eo7) was also isolated. Historically, Eo7 has been implicated in mild febrile exanthematous diseases mainly in children although there were a number of previous reports of human fatalities^{5,8}. However, in the 2000 HFMD outbreak, Eo7 was the sole agent isolated from several fatal cases with brain stem encephalitis⁹.

As with other countries in the region, specimens from HFMD cases were not routinely investigated. From May 1997 to June 2001 when there were reports of severe HFMD outbreaks, clinical specimens consisting of oral secretions (mouth swab and throat swab), stool (rectal swab), vesicular fluid, cerebrospinal fluid (CSF)

and postmortem tissues from patients suspected to be infected by enteroviruses were submitted to UMMC for investigation by virus isolation using Vero (ATCC, CCL-81), Vero E6, Hep-2 and RD cells. The identification of the virus was made using a range of commercial typing monoclonal antibodies (Chemicon Co. USA) by indirect immunofluorescence test. Of the 585 patients, 467 patients were diagnosed as having classical HFMD, 4 HFMD cases with neurological involvement, 87 other illnesses, 12 were contacts of HFMD and 15 with no specific diagnosis (Table I). The types of viruses isolated from the clinical specimens of each clinical category of patients are shown in Table I. Overall, EV71 was the most common virus (128/198) isolated followed by CA16 (20/198). Unlike earlier reports of HFMD due to CA16, the predominant virus in this study was due to EV71. This study also showed that Eo7 was the cause of HFMD in 5 patients, a clinical entity that has not been reported before.

Table I
The Type of Virus Isolated from Each Clinical Category of Patients with Clinical Diagnosis of Enterovirus Infections

[^] Clinical Diagnosis	No. Tested	No. Isolated	CA16	EV71	Eo7	*EV	Adenovirus	#HSV-I
HFMD	467	162	18	108	5	6	4	21
HFMD with CNS infection	4	4		3	1			
CNS infection	16	6		5	1			
Myocarditis	8	2		2				
Respiratory infection	3	2				2		
Sepsis	2	1			1			
Enterovirus infection	56	10		5		3		2
Febrile convulsion	1	1		1				
Steven-Johnson syndrome	1	1		1				
Contacts of HFMD	12	3		2	1			
No clinical diagnosis	15	6	2	1	3			
Total	585	198	20	128	12	11	4	23

[^]Abbreviation: HFMD = hand, foot and mouth disease; CNS = central nervous system

*EV = other types of enterovirus

#HSV = herpes simplex virus

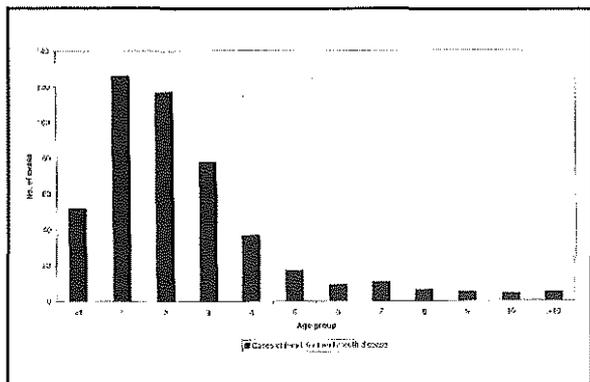


Fig. 1: Cases of hand, foot and mouth disease by age-group.

Among the 467 patients with HFMD, 301 were males and 166 patients were females, giving a male to female ratio of 1.81:1. 289 of the affected patients were Malays, 149 were Chinese, 17 were Indians and other races accounted for the remaining 12 cases. The positive virus isolation rate was 35.2% (106/301) for males and 33.7% (56/166) for females. The positive virus isolation rates for various ethnic groups were Malays 35.6% (103/289), Chinese 32.9% (49/149), Indians 41.2% (7/17) and other ethnic group 25.0% (3/12) respectively. There was no significant difference in the isolation rate with respect to gender ($\chi^2=0.05$, $p=0.8247$) and ethnic group ($\chi^2=0.5$, $df=3$, $p=0.9189$).

The distribution of cases of HFMD by age groups is shown in Figure 1. Children aged 4 years and below comprised 87.8% (410/467) of the total number of HFMD cases and the children between 1 and 2 years of age constituted 52.0% (243/467) of the total number of cases. Thus, HFMD essentially affected very young children, particularly those between 1 and 2 years of age.

During the study period, virus isolation was carried out on a total of 764 specimens from the 467 patients with HFMD. Oral specimens gave the highest yield (33.3%) followed by vesicular fluid specimens (27.0%) (Table II). Herpes simplex virus type I was isolated from a number of oral samples. The result may reflect silent excretion of virus in these patients or the patients may actually be suffering from acute gingivostomatitis due to this virus but were misdiagnosed as HFMD. Virus isolation was attempted on 192 serum samples but no virus was isolated and Eo7 was isolated in one of the 3 CSF samples.

Five of the patients who were initially diagnosed as having HFMD subsequently showed evidence of neurological involvement and succumbed to the illness. EV71 was isolated from postmortem brain stem and spinal cord tissues of 3 patients and Eo7 was isolated from the CSF of one and postmortem biopsied brain stem tissue of another patient.

Table II
Number of Clinical Specimens from Cases of Hand, Foot and Mouth Disease for Virus Isolation

Type of specimens	No. Tested	No. +ve (%)	CA16	EV71	Eo7	*EV	Adenovirus	#HSV-I
Rectal swab (stool)	342	48 (14.0)	1	42	1	2	2	
Oral secretions	285	95 (33.3)	11	56	3	2	2	21
Vesicular swab	137	37 (27.0)	8	26	1	2		
Total	764	180 (23.6)	20	124	5	6	4	21

*EV = other types of enterovirus

#HSV = herpes simplex virus

In summary, the prevalence and aetiological agents of HFMD were unknown in peninsular Malaysia prior to May 1997. Data from this study showed that HFMD is endemic in Malaysia with occurrence of two outbreaks since 1997. In each outbreak, a number of viruses could be isolated but EV71 was the main type of virus isolated in both outbreaks. Young children, especially those below the age of 4 years, were mainly affected by the illness. HFMD by itself and without neurological involvement was relatively benign

and self-limiting. Virus isolation was better achieved from oral secretions than other types of clinical specimens.

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