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Original Article

Risk factors for severe hand foot and mouth disease

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Abstract ***Background***: Hand foot and mouth disease (HFMD) and herpangina are enteroviral infectious diseases caused mainly by Coxsackie virus A (CA) or enterovirus 71 (EV71). From 2000 to 2002, many complicated cases were reported in Japan, therefore a nationwide questionnaire survey was carried out to assess the situation. The subjects were patients with HFMD or herpangina, or other enterovirus infection from 2000 to 2002, who were either hospitalized over 24 h or who died. The response rates were 41.3% in 2000 and 2001 and 31.6% in 2002. The survey period included the year 2000, when HFMD epidemics due to EV71 occurred. To examine risk factors causing complications of enterovirus infection, severe cases of HFMD were focused on.

Methods: HFMD cases in 2000 were divided into two groups according to severity: 'more severe' and 'less severe'. 'More severe' was defined as 'fatal, involving sequelae, or involving hospitalization for 7 days or longer'. Statistical analyses were conducted with Epi info version 3.3 and the association between risk factors and severity was estimated.

Results: The number of patients with more severe and less severe cases was 96 and 103, respectively. There was no difference in sex, age, having siblings and family history between the two groups. There was a significant association between attending child care center and severe HFMD.

Conclusions: It is not clear why attending child care centers was associated with HFMD severity. Further study is needed.

Key words child care center, complication, enterovirus infection, EV71, hand foot and mouth disease, risk factor.

Hand foot and mouth diseases (HFMD) and herpangina are enterovirus infections mainly due to Coxsackie virus A (CA) or enterovirus 71 (EV71). Most of the infections remain mild, but over recent years complicated forms involving brainstem encephalitis or pulmonary edema have been reported from countries in the Western Pacific Region, including Japan.[1–3]. Complications in the course of enterovirus infections drew attention to these diseases when many children died in Malaysia in 1997,[1] and in Taiwan in 1998.[2] In the same period there were several reports from different parts of Japan. Osaka reported three fatal cases in 1997.[3] In 2000, complicated cases, including fatal ones, were reported mainly from the western part of Japan, including Hyogo,[4] Shiga[5] and Aichi prefectures.[6]

We carried out a nationwide investigation with questionnaires to assess the complete situation of the disease in Japan. The subjects had complicated cases of HFMD and herpangina, and others had no apparent symptoms of HFMD or herpangina, but were diagnosed as having enterovirus infections, which occurred during the period 2000–2002. The definition of complicated cases was 'hospitalization over 24 h or fatality'. The questionnaires were distributed to 3043 medical institutions with pediatric departments in October 2002. Collection of responses terminated at the end of June 2004. The 3 year period covered by the present study included the year 2000, when the HFMD epidemic caused by EV71 occurred in Japan. EV71 is known to have a high affinity for the nervous system, and a large number of patients with complicated cases of HFMD from 2000 were infected with EV71. The general findings from the present study were reported in Japanese by Taya *et al.*[7] The purpose of the present study was to examine risk factors causing complications in enterovirus infections.

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Methods

Of the data collected from the survey, the complicated cases of HFMD in 2000 were selected for a closer investigation. The subjects were divided into two groups according to the following definitions. The more severe cases were fatal cases, cases involving sequelae, or ≥7 days hospitalization. The subjects who did not fall into this first group were categorized as having less severe cases. The surveillance data from *Infectious Diseases Weekly Report* (IDWR) and *Infectious Agents Surveillance Report* (IASR) were used to calculate and compare the rate of complications for each year. We examined which characteristics were

related to severity by comparing the data from the more severe and less severe cases. Statistical analysis was performed with Epi info (version 3.3; Center for Disease Control and Prevention, Atlanta, GA, USA) to estimate the association between risk factors and complication.

Results

The response rates of the questionnaire survey were 41.3% for 2000 and 2001, and 31.6% for 2002. In total, data on 583 cases were collected. Of these, 272 were complicated cases associated with HFMD, 54 were herpangina cases and the remaining 257 were cases lacking apparent symptoms of HFMD or herpangina, but which were diagnosed as enterovirus infections. The manifestations of enterovirus infections such as HFMD, herpangina, and aseptic meningitis are monitored as specified under the Infectious Disease Law. Of the 272 complicated cases of HFMD, 226 cases occurred in 2000, 32 in 2001, and 14 in 2002. The total number of reported HFMD cases for each year was 216 154 in 2000, 134 927 in 2001, and 97 870 in 2002. From Table 1, it is apparent that the ratio of complicated cases to total HFMD cases reported in 2000 was significantly higher relative to the other 2 years. Table 1 also shows the information about pathogens, ages, duration of hospitalization, the number of sequelae, and fatal cases in the period 2000–2002. There were numerous reports of complicated cases of HFMD caused by EV71 in 2000. In the present survey the complicated HFMD cases consisted of 36 cases caused by EV71 versus one by CA16, during 2000. The isolation rate of EV71 was relatively high in the IASR of that year. There was no statistically significant difference in age, and duration of hospitalization, but four cases involving sequelae and one fatal case were found only in 2000.

Using the aforedescribed definition, there were 96 more severe cases and 103 less severe cases. Twenty-seven cases were not classified because the outcome and duration of hospitalization were unknown.

The incidence of both the more severe and less severe cases reached a peak in July (Fig. 1). Meningitis was the most common final diagnosis in both groups, but encephalitis was more frequent in the more severe cases (Fig. 2). There was no significant difference in the male:female ratios between the two groups (58:38 vs 63:40). There was also no statistical difference in age between the two groups ($P = 0.277$), as shown in Fig. 3. The proportion of children with peer group associations, meaning children who attended child care centers, kindergartens, or elementary schools, was 53% (51/96) and 54% (56/103) with regard to the more severe and less severe cases, respectively. The proportion of children attending child care centers, however, was larger for the more severe cases (35% vs 25%). There was no significant difference in the proportion of children with siblings, but the patients with the more severe cases tended not to have siblings. There was no significant difference in the proportion of patients with a family history of disease. The criteria for determination of the causative virus was based on detection of virus in cerebrospinal fluid (CSF), blood, throat swabs or stool, significantly rising antibodies in paired sera, or a single serum in which the NT antibody titer was elevated over 256. The number of cases in which the causative virus was confirmed was 26/96 (27.1%) for the more severe cases, and 11/103 (10.7%) for the less severe cases. The 26 isolates in the more severe group included 24 of EV71, one of CA16 and one of Echo virus 9. Eleven isolates from the less severe group were all confirmed as EV71.

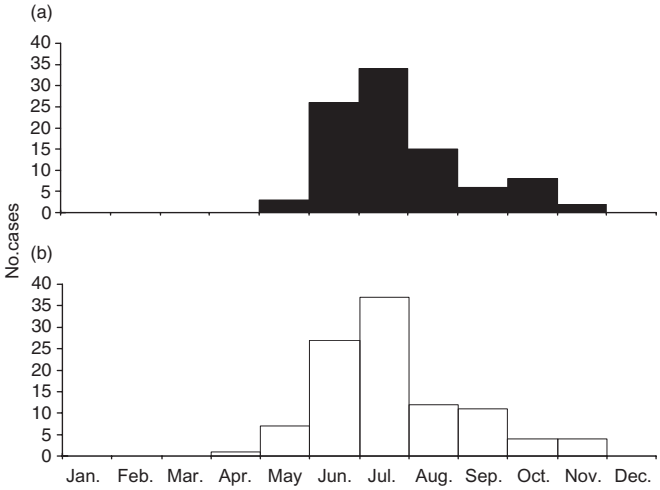

Fig. 1 Incidence of (a) more severe ($n = 96$) and (b) less severe ($n = 103$) hand foot and mouth disease reached a peak in July.

Table 2 lists the characteristics of five patients with extremely severe cases: one died, three had limb paralysis, and one had

Table 1 Complicated HFMD cases by year

		2000	2001	2002	*P*
		n = 226	*n* = 32	*n* = 14	
n : Reported cases		226:216 154	32:134 927	14:97 870	<0.001†
Pathogen	EV71:CA16 (Present survey)	36:1	0:0	1:0	
	EV71:CA16 (IASR)	364:195	18:290	20:367	
	P	<0.001		0.054	
Age, mean ± SD (years)		3.47 ± 2.41	3.47 ± 3.67	2.36 ± 2.27	0.22†
Mean hospitalization days ± SD (*n*)		6.75 ± 3.34 (208)	6.55 ± 2.57 (31)	5.46 ± 1.66 (13)	0.25†
Fatal or sequelae		5	0	0	0.067‡

†Kruskal Wallis test; ‡ratio to reported cases.
Reported cases: numbers from sentinel surveillance based on regulation of the Infectious Disease Law.
HFMD, hand foot and mouth disease; IASR, Infectious Agents Surveillance Report.

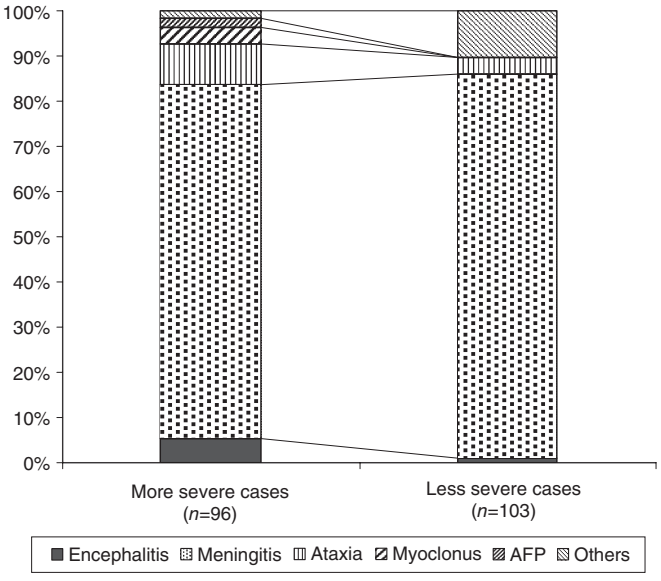

Fig. 2 Meningitis occupied the majority of diagnoses in both groups. Encephalitis, ataxia, myoclonus and acute flaccid paralysis (AFP) were more numerous in the more severe cases.

epilepsy; these were in the more severe group. The ratio of male to female was 2:3; the median age was 2 years (range, 5 months–12 years); two patients, including the one who died, had attended child care centers. EV71 was detected in three patients, and the cause was unknown for two patients.

Univariate analysis resulted in only one statistically significant association: between attending child care centers and developing a severe case of HFMD (odds ratio [OR]: 2.02; 95% confidence interval [CI]: 1.02–4.00, $P = 0.041$; Table 3). Multivariate analysis also identified child care center attendance as the only significant factor (adjusted OR, 2.96; 95%CI: 1.24–7.08, $P = 0.015$; Table 4).

Discussion

The investigation period was from 2000 to 2002. In 2000 there was a major epidemic of HFMD, with numerous reports of

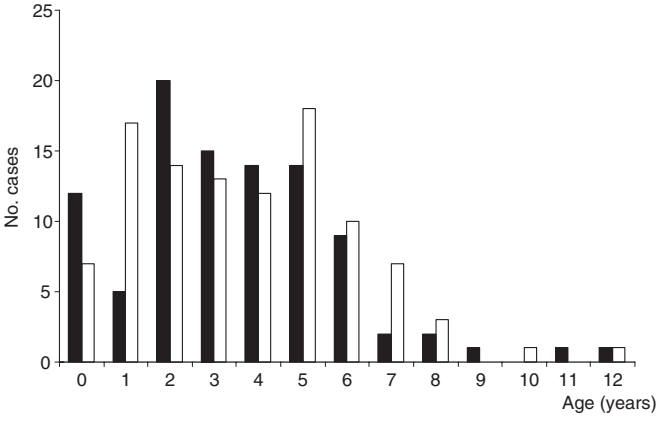

Fig. 3 There was no statistical difference in age between patients with (■) more severe ($n = 96$) and those with (□) less severe ($n = 103$) hand foot and mouth disease ($P = 0.277$).

Table 2 Fatal and sequelae cases of HFMD

Patient age	Sex	Diagnosis	Outcome	Hospitalization days	Pathogen	Peer group association	Sibling	Family history of HFMD
2 years 10 months	F	Encephalitis, meningitis, cerebellar ataxia	Died	2	EV71	Child care center	Younger sister	Yes
2 years 7 months	F	Encephalitis	Paralysis of left upper limb	8	Unknown	Unknown	Elder sister	Yes
0 years 5 months	M	Acute flaccid paralysis	Paralysis of right upper limb	17	EV71	not yet	Unknown	Unknown
12 years	F	Encephalitis, cerebellar ataxia, myoclonus	Epilepsy	25	Unknown	Unknown	Unknown	Unknown
2 years 7 months	M	Meningitis, cerebellar ataxia	Paralysis of right upper limb	17	EV71	Child care center	Elder sister	Yes

HFMD, hand foot and mouth disease.

Table 3 Analysis 1 (univariate)

Risk factor	More severe HFMD (n = 96)			Less severe HFMD (n = 103)			OR (more severe)	95%CI	P
	+	−	No data	+	−	No data			
Male	58	38	0	63	40	0	0.97	0.55–1.71	0.914
<1 year old	12	84	0	7	96	0	1.96	0.74–5.20	0.171
Peer group association[†]	51	14	31	56	18	29	1.17	0.53–2.59	0.697
Child care center	**34**	**31**	**31**	**26**	**48**	**29**	**2.02**	**1.02–4.00**	**0.041**
Kindergarten	8	57	31	12	62	29	0.73	0.28–1.90	0.512
Elementary school	9	56	31	18	56	29	0.50	0.21–1.20	0.119
Siblings	57	19	20	67	10	26	0.45	0.19–1.04	0.058
Family history[‡]	20	43	33	18	43	42	1.11	0.52–2.39	0.787

Bold, statistically significant at $P < 0.05$.

[†]Children belonging to the same generation who spend time together but who are not living together. It includes children attending child care center, kindergarten, or elementary school.

[‡]Any other family members had HFMD in the same period. +, presence of risk factor; −, absence of risk factor.

CI, confidence interval; OR, odds ratio.

complicated cases of HFMD. Although causative viruses were not detected in many cases, from the epidemiologic data it seemed that complicated cases were caused by EV71. From IASR data, EV71 was more common in 2000, and was even more common in complicated cases in the present study (Table 1). Other epidemiologic studies have also found a relationship between EV71 and severe disease. In the 1998 Taiwan outbreak, among patients from whom viruses were isolated, EV71 was present in 48.7% of outpatients with uncomplicated HFMD or herpangina, 75% of hospitalized patients who survived, and 92% of patients who died.[8] There are a few studies that also analyzed risk factors associated with complications. One study reported that hyperglycemia, leukocytosis and limb weakness were associated with pulmonary edema after central nervous system (CNS) involvement with EV71 infection.[9] Another study reported age <3 years, long duration of fever, early onset of CNS complications, and predominance of polymorphonuclear cells in the CSF were common in complicated cases.[10] Therefore, in order to analyze the risk factors independently from the influence of pathogens, it seemed reasonable to limit the subjects in the present study to those with HFMD in 2000, when EV71 was the common pathogen.

The following were limitations of the study. The response rate of the survey was 31.6–41.3%. Questions about clinical features and laboratory data were not included. The more severe cases and less severe cases were distinguished by the length of hospitalization, rather than a true measure of severity. A laboratory isolate was available for only 27% and 11% of patients with the more severe and less severe cases, respectively.

The proportion of virus confirmations was higher in the more severe group than in the less severe group. It is natural that the more severe the diseases become, the more the doctors seek the cause. It was judged, however, that statistical analysis could not be performed because data were too limited, and there were a multitude of factors, such as whether attempts were made to identify the causative virus or not, at which stage the specimen was taken, and which method was used for virus detection.

Age and sex were not statistically significant factors for severity. There was no significant difference in the overall proportion of peer group associations. The proportion of children attending child care centers, however, was significantly larger in the group with more severe cases (OR, 2.02; 95%CI: 1.02–4). On multivariate analysis this association was stronger (OR, 2.96; 95%CI: 1.24–7.08).

Of the 96 patients with more severe cases, only five had fatal cases or had sequelae, and all others were classified as having more severe cases because of the duration of hospitalization. When this point is considered, attending child care centers in itself may not be the risk factor, it may be an effect of the family situation. Perhaps the patients from child care centers could not be discharged from the hospitals until they had recovered completely because their parents could not care for them at home. In contrast, if child care center attendance was truly associated with severity, then infections under heavy contamination should be suspected as a cause. This includes both duration, as well as type of exposure (diapered vs toilet trained children). The characteristics of HFMD and other enterovirus infections include long-term secretion of virus. One study of EV71 secretion in children showed that some patients shed virus for 11 weeks.[11]

In the present study, attending kindergarten was not associated with increased severity of disease. In child care centers, in addition to being frequently diapered, children spend a longer time in

Table 4 Analysis 2 (multivariate)

Risk factor	Adjusted odds ratio	95%CI	P
<1 year old	2.02	0.58–7.03	0.269
Child care center	**2.96**	**1.24–7.08**	**0.015**
Not elementary school	1.09	0.38–3.13	0.088
Siblings	0.53	0.20–1.42	0.205

Bold, statistically significant at $P < 0.05$.

CI, confidence interval; OR, odds ratio.

close contact with peers compared to children in kindergarten. Once an outbreak occurs it is highly possible that children in child care centers are more exposed to infections under heavy contamination. In contrast, in the outbreak of HFMD due to EV71 in Taiwan, attending kindergarten and child care centers were both identified as risk factors for infection, and standard precautions and adequate isolation were recommended.[12] In Japan, the School Health Law does not specify an isolation period for HFMD.

Although the host–parasite relationship is responsible for the severity of infectious diseases, the data on the patients' immune state were not available from the questionnaire survey.

Conclusion

Based on the enterovirus surveillance data for the year 2000, when an HFMD epidemic occurred due to EV71, there was a statistically significant association between attending child care centers and severe HFMD. Further study is warranted to confirm this conclusion.

Fortunately we have not encountered another cluster of HFMD in Japan since 2000. If, however, another outbreak of HFMD due to EV71 occurs, active surveillance with thorough viral laboratory testing should be conducted. A cohort study using direct measures of disease severity, with complete reporting of risk factors, such as day care attendance, should be strongly considered.

Acknowledgments

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