



LETTER

A case-control study of risk factors for severe hand-foot-mouth disease in Yuxi, China, 2010–2012

Dear Editor,

Here, we report the risk factors for severe hand-foot-mouth disease (HFMD) determined by our case-control study. Our findings could help disease prevention and intervention initiatives. Patients with severe HFMD display fatal clinical manifestations with sequelae, requiring ≥ 7 days of hospitalization. A total of 249 severe cases treated at Yuxi Children's Hospital were included in the case group, and 512 common cases were included in the control group. The demographics and characteristics of these patients, including disease course, medical treatment, and virus type, were assessed. Statistical analyses were conducted using SPSS (version 19.0) software. Based on our research, six independent variables, including age, residence, pathogen, type of hospital first visited, respiratory infection 1 month prior, and contact with confirmed cases 1 week prior, are identified as the risk factors for severe hand-foot-mouth disease.

High HFMD incidence occurs in China between April and July (Tan X, et al., 2011). By July 5, 2013, 4,909 cases had been diagnosed at Yuxi Children's Hospital in 2013. Compared with the corresponding period in 2012, the incidence increased to 32.86%. The arid climate of this region might exacerbate the incidence (Ma E, et al., 2010). Since 2009, HFMD has been classified as a category C notifiable infectious disease by National Health and Family Planning Commission of the People's Republic of China (NHFPCC) (NHFPCC, 2010; NHFPCC, 2009).

HFMD occurs mainly in children (Ruan J R, et al., 2012). Clinical complications include fever and rash or herpes on the hand, foot, and mouth. Patients with severe HFMD might occasionally develop symptoms like pulmonary edema, myocarditis, and encephalitis (Lee M S, et al., 2006). HFMD and herpangina are enteroviral infectious diseases that are mainly caused by Coxsackie virus A16 (CA16) or enterovirus 71 (EV71) (Papenburg J, et al., 2012). Human EV71 is an HEV-A species. Since 2007, multiple outbreaks have occurred and demonstrated increasing morbidity and mortality (Wang Y, 2013). In 2010–2012, many complicated cases were reported in Yuxi and therefore, a questionnaire survey was administered to assess the situation. In order to determine the risk factors that cause the complications of enterovirus

infection, severe cases of HFMD were the primary focus.

We studied the severe HFMD cases reported by Yuxi Children's Hospital in 2010–2012. We used common HFMD cases as the controls in order to maintain the 1:2 ratio required by the survey. Severe cases were clinically defined by nervous system involvement, respiratory dysfunction, and circulatory dysfunction. Biochemical tests confirmed peripheral leukocytosis, cerebrospinal fluid (CSF) abnormalities, and hyperglycemia; and magnetic resonance imaging (MRI) confirmed cerebrospinal abnormalities.

According to the Guidelines of Hand-Foot-Mouth Disease Control and Prevention issued by NHFPCC, we investigated severe cases after obtaining parental consent. Throat swabs were simultaneously collected and analyzed using fluorescent real-time polymerase chain reaction (NHFPCC, 2009).

23,563 HFMD cases were reported in Yuxi from 2010 to 2012, including 258 severe ones. The annual average incidence of HFMD was 366.28 per 1,000,000 (422.08 in 2010 vs 365.19 in 2011 vs 311.56 in 2012). Through analyzing these HFMD cases and the 2010–2012 annual incidences, it was found that epidemiological trends were steady. The number of severe cases decreased with the decrease in the total number of HFMD cases. This indicated that the existing prevention and control measures were effective. Of 23,563 HFMD cases, 12,632 were boys and 10,931 were girls, demonstrating an average male-to-female sex ratio of 1.16 (1.07 in 2010 vs 1.19 in 2011 vs 1.22 in 2012). The age distribution was described as follows: 3,055 cases in 0–1-year-olds (12.97%), 8,661 cases in 1–2-year-olds (36.76%), 8,897 cases in 2–3-year-olds (37.76%), 1,724 cases in 3–4-year-olds (7.32%), and 1,226 cases in 4–11-year-olds (5.20%). In total, 87.48% of children with HFMD were < 4 years of age.

Through analyzing the monthly distribution of HFMD cases, it was shown that HFMD infection demonstrated a significant seasonal pattern. It was obvious that incidence peaked between April and July during the study years. Incidence also peaked during November to December, when it is winter in Yuxi. The diverse and stereoscopic climate—which is defined by a moderate or tropical monsoon climate in some regions of Yuxi, such

as Yuanjiang and Xinping—results in widespread HFMD infection (Hii Y L, et al., 2011). Conversely, the Chinese Center for Disease Control and Prevention reported that peak HFMD incidence occurs in summer. Accordingly, we issue two warning newsletters about controlling and preventing HFMD in a year.

From 2010 to 2012, HFMD pathogens had been detected in Yuxi using nucleic acid testing (NHFPC, 2009). We tested 761 specimens, and the percentages of CA16, EV71, and other EV strains were 38.42%, 45.18%, and 16.40 % respectively.

In total, 258 severe HFMD cases were reported at Yuxi Children's Hospital between January 1, 2010 and December 31, 2012, among which 249 demonstrated valid responses and were defined as the case subjects. Taking into account patient compliance, 512 (283 boys and 229 girls) out of 520 normal cases demonstrated an effective response and were randomly included in the control group.

According to our univariate analysis (Table 1), the average age of children in the severe case group was 3.1 ± 1.7 years (range = 5 months to 10 years), while children in

the control group were 3.1 ± 1.6 years (range = 5 months to 10 years). A significant age difference exists between the two groups ($P < 0.05$). Accordingly, we must provide better health and food hygiene education to the parents of young children. There was no significant difference in terms of the sex ratio, breast feeding or premature delivery. We also investigated clinical symptoms, treatments, pathogens, and health conditions. First, the percentage of sporadic cases and rural children was significantly higher in the case group than in the control group ($P < 0.01$). Health education must be emphasized in these areas. Second, pathogen monitoring of severe HFMD cases indicated that EV71 infection was an important risk factor, accounting for 83.78% of the severe HFMD cases. Third, most of children with severe HFMD developed respiratory illnesses ≤ 1 month prior to HFMD onset ($P < 0.01$). 10% of severe cases were in contact with a confirmed case ≤ 1 week prior to HFMD onset. In addition, the important clinical indexes include fever, convulsion, and hand or foot shaking. Six independent variables, including age, residence, pathogen, type of hospital first visited, respiratory infection 1 month prior, and contact with

Table 1. Associated risk factors according to the univariate analysis

Risk factors	No. severe cases (n=249)	No. common cases (n=512)	χ^2	<i>P</i>
Age				
0-4 year	202	373	6.21	0.01 < <i>P</i> < 0.05
>5 year	47	139		
sex			0.03	> 0.05
Male	136	283		
Female	113	229		
Residence areas			29.84	< 0.01
Rural	182	268		
Urban	67	244		
Breast feeding			2.09	> 0.05
No	24	68		
Yes	225	444		
Premature delivery			0.02*	> 0.05
No	246	505		
Yes	3	7		
Pathogen			13.13	< 0.01
EV71	62	118		
CA16	8	53		
Other EV	4	24		
Fever			270.96	< 0.01
Non-fever	8	186		
<39°C	111	245		
≥39°C	130	81		
Convulsions			609.87	< 0.01
No	29	506		
Yes	220	6		
Hand or foot shaking			606.41	< 0.01
No	32	508		
Yes	217	4		
Hospital first visited			314.44	< 0.01
Community or individual physician	164	31		
Municipal or county	85	481		
Respiratory infection 1 month prior			308.57	< 0.01
Yes	145	15		
No	104	497		
Contact with confirmed cases 1 week prior			251.00	< 0.01
Yes	139	27		
No	110	485		

*Determined using the calibrated chi-square test.

confirmed cases 1 week prior, were selected for inclusion in the multivariate analysis. Significance of these risk factors was confirmed again.

Since HFMD broke out in Anhui province in 2008, severe cases and deaths have been reported in many places on the Chinese mainland (Xu Q H, et al., 2008). Numerous severe cases and 9 deaths occurred in Yuxi in 2009. Therefore, it is important to study the risk factors associated with severe HFMD and take appropriate preventative measures.

Our findings confirm that EV71 virus infection is an important risk factor for the development of severe HFMD ($P < 0.01$). This is consistent with other studies conducted in the Asia-Pacific region (Ooi M H, et al., 2009). The EV71 vaccine also effectively prevents and controls severe HFMD (Lee B Y, et al., 2010). Immunity against enteroviruses obtained from the mother might slowly attenuate with age, even though the child's own immune system has not fully developed (Zhu Q, et al., 2013). Our ongoing studies on adult-child serological enterovirus monitoring support this view.

Also according to our study, the average age of the severe cases was lower than that of the control group. Obviously, children > 5 years demonstrated a lower incidence of severe HFMD.

The diagnosis and treatment level of the hospital first visited has a marked impact on severe HFMD development. Most severe cases were first treated in community or individual clinics, where doctors are often unable to diagnose children with inconspicuous herpes. Doctors without sufficient experience often diagnose HFMD as common pediatric fever. Especially in rural areas, misdiagnoses and delayed diagnoses are common. Doctor training in rural areas needs to be strengthened.

Most children with severe HFMD developed respiratory illnesses 1 month prior to HFMD onset ($P < 0.05$). The studies by Ruan J R also report similar trends (Ruan J R, et al., 2012). HFMD-causing enteroviruses are mainly transmitted via the fecal-oral route. Respiratory tract HFMD is important epidemiologically, and respiratory illness could also affect HFMD infection. Clinicians need to pay attention to nursing children and the treatment of respiratory illnesses.

Typical clinical symptoms include fever, convulsions,

and hand or foot shaking. Corticosteroid injections are needed when body temperature is > 39 °C. The experts at Yuxi Children's Hospital also recommend the timely use of mannitol to reduce intracranial pressure.

FOOTNOTES

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All the authors declare that they have no competing interest. Additional informed consent was obtained from all patients for which identifying information is included in this article.

Ze Liu¹, Shukun Wang¹, Rusong Yang¹, Xia Ou^{2✉}

1. Yuxi City Center for Disease Control and Prevention, Yuxi, Yunan 653100, China;

2. Basic Medical College, Kunming Medical University, Kunming, Yunnan 650500, China

✉Correspondence:

Phone/Fax: +86-871-5922865, Email: mybelieze@yeah.net

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