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Epidemiological characteristics, etiological pathogen and meteorological factors analysis of hand, foot and mouth disease (HFMD) in Western Hainan Province, China, 2010-2016.

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Abstract

Objectives: This study tries to analyse the epidemiologic, etiologic Characteristics and Hand, Foot and Mouth Disease (HFMD), as well as its correlation with meteorological factors.
Methods: The epidemiological data of HFMD was retrieved from the Hainan Center for Disease Control and Prevention for retrospective analysis. Feces of severe patients and randomly mild patients were collected for enterovirus detection by RT-PCR. Meteorological data including temperature, barometric pressure and amount of precipitation and wind speed of Western Hainan province were collected. Univariate analysis and multivariate linear regression analysis were used to determine the relationship between meteorological factors and the incidence of HFMD.
Results: A total of 13133 cases were identified in West of Hainan province from January, 2010 to December, 2016. A majority of the patients (97.3%) aged under 5 years old with an incidence of 123.5/100 000. The incidence of HFMD showed a significant increase in spring and reached the peak between spring and summer, and decreased at the end of summer. Male occupied about 66.6% of total patient and severe cases accounts for 2.1%. Pathogen analysis of 989 cases showed that Coxsackie A (CV-A), enterovirus 71 (EV71) accounts for 87.7% of all cases. Spearman rank correlation demonstrated that the incidence rate of HFMD had a significant relationship with temperature (rs=0.895, P<0.001), barometric pressure (rs=-0.731, P=0.007), amount of precipitation (rs=0.881, P<0.001). However, the multivariate linear regression analysis only confirmed statistical significance of temperature and HFMD.
Conclusions: The epidemiological characteristics of HFMD patients in West of Hainan province is similar with the whole situation of china. The type of CV-A and EV71 are the major pathogen causing HFMD. Temperature probably is an independent risk factor for the incidence of HFMD.

Keywords: Epidemiology, Etiology, Meteorological factors, Hand, foot and mouth disease (HFMD), China.

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Introduction

Hand, Foot and Mouth Disease (HFMD) is a highly contagious disease mostly affects children under the age of 5 y old, which is caused by a series of virus including enterovirus 71 (EV71), coxsackievirus A16 (CA16), CA6, CA10 [1]. HFMD acquires its name for its mild and self-limited symptoms and signs of fever, skin eruptions on hands and feet as well as the vesicles in oropharynx [2]. However, some cases can show sever life-threatening complications such as pulmonary edema, meningitis, cephalitis [3].

It is proven that the HFMD breaks out in summer and autumn. Obviously, HFMD is highly affected by spatial and meteorological factors. Numerous studies have reported that there is a strong correlation between the morbidity of HFMD and meteorological factors [4]. However, these studies mainly focus on Northern half of China, whose meteorological factors differ a lot from Southern China [5]. Furthermore, there is limited and scant data about HFMD cases in West of Hainan Province. Hainan Province is located in the most Southern part of China mainland, belonging to the tropical zone, where there is abundant amount of precipitation [6]. In this study, we briefly analysed the epidemiologic, etiologic characteristics of HFMD patients from Jan, 2010 to Aug, 2016. We also tried to investigate the influence of meteorological factors on the incidence of HFMD.

Methods

Clinical and meteorological data collection

All patients of HFMD in West of Hainan Province were identified by Department of Internal Medicine of the People's

Hospital of Danzhou. All clinical data of this study were retrieved form National Notifiable Disease Reporting System (NNDRS). A total of 13133 cases were identified in this study, all patients should have complete demographic data. Meteorological data including average atmospheric temperature, barometric pressure, amount of precipitation and wind speed were obtained from Hainan Meteorological Bureau. The diagnostic criteria and the division standard of mild or severe cases refer to "Diagnosis and Treatment Guidelines of HFMD" formulated by the Ministry of Health of China in 2008 [7].

Sample acquisition

Fecal specimens of HFMD patients from several hospitals located in West of Hainan Province were collected in the acute period and stored at -70°C refrigerator immediately. All severe patients and part of mild patients were selected for further investigation. The samples were sent to the Clinical laboratory of the People's Hospital of Danzhou for etiological identification [8].

Etiological identification

10% PBS was used to suspend the fecal specimens and then the sample was shocked for 20 min, followed by centrifuge (1500 g, 30 min). The clear pending was collected for test. MagNA Pure LC total nucleic acid isolation kits (MagNA Pure LC 2.0; Hoffmann-La Riche, Switzerland) was used to extract RNA of the samples according to the manufacturer's instruction. The extracted RNA samples were dissolved at -80°C. Common pathogen genes including pan-EVs, EV71, CA16, CA10 and CA10 were detected in the samples by Fluorescence Reverse Transcription-Polymerase Chain Reaction (RT-PCR). When specimen is positive for pan-EVs but negative for EV71, CA16, CA10 and CA10 nucleic acid, semi-nested RT-PCR was used to amplify the *VP1* gene of EVs. The product of amplification was sequenced and the genotype of EVs was confirmed using online BLAST (blast.ncbi.nlm.nih.gov/Blast.cgi) [9].

Statistical analysis

SPSS version 22.0 software (IBM Corp., Armonk, NY USA) was applied in the analysis of data. Descriptive statistical method was used to analyse the characteristic of HFMD patients. Chi-square test was used to check the difference of categorical variables. Quantitative variables were described as ($\bar{x} \pm s$). Spearman rank correlation analysis was applied to determine the relationship between the incidence of HFMD and single meteorological factor. Multi-linear regression analysis was used for multiple analysis. All analysis was two-sided and the$\alpha$was set as 0.05.

Results

Epidemiological features

Between January 2010 and December 2016, there is a total of 13133 cases happening in West of Hainan province recorded of CDC of Hainan province, with an average incidence of 123.5/100 000 in the entire population. Most of the patients are males (n=8764, 66.6%), and most of patients aged under 5 y old. The average age of all patients is (1.83 ± 1.77 y) old. Severe cases accounts for about 2.14% of all (Table 1).

Pathogen distribution

There are a total of 374 cases including all of the severe patients were collected of their fecal sample for test. The results were shown in Table 2.

Univariate analysis of incidence of HFMD and single meteorological factor

Spearman rank correlation analysis shows that the incidence of HFMD was positively correlated to temperature, amount of precipitation ($P<0.05$), and is negatively correlated to barometric pressure ($P<0.05$). However, there was no statistically significant relationship between wind speed and HFMD cases ($P>0.05$, Table 3).

Multivariate analysis of incidence of HFMD and single meteorological factor

Multivariate analysis results showed that temperature is the independent risk factor for the incidence of HFMD ($P<0.05$, Table 4).

Table 1. *Epidemiological characteristics of HFMD patients in West of Hainan province from 2010 to 2016.*

Variable		2010	2011	2012	2013	2014	2015	2016	Total
Age (years old)	<1	270	320	280	380	480	214	270	1944
	1~5	1603	1811	1634	2136	2442	1209	1603	10835
	>5	39	45	47	59	46	118	39	354
Gender	Male	312	1324	1648	1543	1750	1850	636	8751
	Female	137	626	764	418	825	1118	184	4382
Clinical manifestations	Severe	10	38	44	50	48	62	30	282

Mild	439	1912	2176	1961	2575	2968	820	12851
total	449	1950	2220	2011	2623	3030	850	13133

Table 2. *Etiological composition of HFMD patients in West of Hainan province from 2010 to 2016.*

Pathogen	2010	2011	2012	2013	2014	2015	2016	Total
EV71	16	41	28	41	27	39	25	218
CA16	7	7	7	7	7	12	7	54
CA10	1	3	0	5	1	6	2	18
CA6	5	3	2	1	2	9	4	25
Others	1	2	10	9	14	5	5	46
Co-infection	1	2	1	2	2	3	2	13
Total	30	58	49	65	53	74	45	374

Table 3. *Meteorological data and HFMD cases between 2010 and 2016 in West of Hainan province.*

Month	Temperature (°C)	Barometric pressure (kpa)	Amount of precipitation (mm)	Wind speed (m/s)	HFMD cases (n)
January	16.3	1028	16.5	7.1	344
February	17.6	1022	26.5	5.4	255
March	20.5	1021	34.3	8.6	593
April	22.4	1014	56.8	6.5	691
May	24.5	1008	110.5	9.8	1271
June	26.5	1003	186.7	8	1872
July	27.8	1003	465.4	7.1	2167
August	28.9	1010	521.1	5.4	1286
September	27.6	1016	120.2	5.6	1805
October	23.3	1022	110.2	6.5	1390
November	21.1	1024	43.3	7.8	966
December	18.5	1028	14.3	6.9	546
rs	0.895	-0.731	0.881	0.102	-
P	<0.001	0.007	<0.001	0.753	-

Table 4. *Multivariate analysis results of incidence of HFMD and meteorological factor.*

Factor	B	SE	β	t	P
Constant	429.062	25383.172		0.017	0.987
Temperature	139.694	51.487	0.936	2.713	0.030
Barometric pressure	-2.775	23.848	-0.039	-0.116	0.911
Amount of precipitation	-0.318	1.064	-0.086	-0.298	0.774
Wind speed	47.450	93.742	0	.506	0.628

Discussion

Although the HFMD disease has been reported since 1957, it still has no specific medication or vaccines. As a result, it is quite important for human beings to make the prevention. Descriptive epidemiology about HFMD has been done in many places globally. However, every study shows its own characteristics. Huang [10] studied the epidemiological and etiological characteristics of HFMD in Henan Province of China from 2008 to 2013. It can be seen that a total of 400264 cases including 22,309 severe and 141 fatal cases; the author also found that the incidence peaked in April and May. Yao [11] analysed the epidemiological data of HFMD in Jiangsu Province of China, a relatively South province compared to Henan province as well. And the author found something different that a presence of delayed peak of incidence in summer. Although it is well recognized that the HFMD disease mostly break out in summer and autumn, it could vary a lot amongst different places. The peak in our study mostly concentrates on June and July, which can be explained by executive meteorology of different location. Zhou [12] collected 213617 cases of HFMD during 2008-2014 in Wenzhou, a South city of China; the results showed that HFMD more frequently in males than in females and 92.68% of the HFMD patients were children aged<5 y. The results were in congruence with ours, and we reported a proportion of

males as 66.6%. HFMD disease barely happens on people over 5 y old. Although most of the cases only have mild symptoms, there are also severe patients, even vital ones of them. For severe patients, they are under high risk of neurologic or cardiopulmonary complications, which is the major cause of HFMD-associated mortality. In our study, the results showed 2.14%. Studies have reported different percentage of severe cases, but it ranges from 3%-10% [7,13,14].

In recent years, the pathogen leading to HFMD remains stable but also shows some changes [15]. Enterovirus 71 (EV71) and Coxsackievirus A16 (CA16) are the predominant pathogens causing HFMD all over the world [16]. Our study of all samples from all severe case and part of mild patients all confirmed the common sense. EV71 accounts for 58.3% of all pathogenic viruses, while CA16 does for 14.4%. Bian [17] reported a new pathogen leading to HFMD, CA6, also contributing to some outbreaks of HFMD in Europe, North America and Asia. We have found several HFMD cases are caused by CA6, with similar situation of CA10. We also focused on the relationship between the meteorological factors and the incidence of HFMD, considering the seasonality and some characteristics of this disease. Zhang [18] studied meteorological factors and HFMD in details that temperature, relative humidity and wind speed might be risk factors of children HFMD in Shenzhen. Zhang completed the similar study in another province, Guangdong of China, drawing a different conclusion that temperature, sunshine, wind speed may play a role in the incidence of HFMD. However, there is no previous study focusing on HFMD in West of Hainan Province. We conducted univariate and multivariate analysis in different ways on the correlation between the morbidity of HFMD and meteorological factors. The univariate results demonstrated that temperature, amount of precipitation and barometric pressure are all correlated to the incidence of HFMD, which agree with other studies. However, the multi-linear regression study found temperature is the only factor positively related to HFMD. It is believed that the temperature between 10-25°C facilitate the progress of HFMD for its beneficial for viruses to survive and reproduce.

Nevertheless, our study has its own disadvantages. First, we may have caused some bias in search of pathogens because we collected all severe patients and little mild ones, which might contribute to inevitable bias. Second, we considered not enough meteorological factors, especially the humidity and sunshine, which are also significant to onset or progress of a disease. Last, we combined all data of 7 y, making a general description but neglect the difference during the long time span.

In conclusion, the epidemiological characteristics of HFMD patients in West of Hainan province share the tendency with the whole country, and CV-A and EV71 are the major pathogen causing HFMD. Temperature is the most probable independent risk factor for the incidence of HFMD.

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