Management of Severe Hand, Foot and Mouth Disease in Xiangyang, China during 2008-2013

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Abstract

Background Therapeutic strategies of severe hand, foot and mouth disease (HFMD) are inconsequent or deficient in evidence by now. **Methods** We have retrospectively analyzed HFMD outbreaks in Xiangyang from June 2008 to December 2013. All severe cases were enrolled to analyze the risk factors causing mortality and to compare the efficiency and outcome of some therapies by binary logistic regression. **Results** The HFMD involved 637 (1.26%) severe cases and 38 were fatal (0.75‰). Analysis indicate that age (<3y), EV71 (+), autonomic nervous system (ANS) dysregulation, pulmonary edema/haemorrhage, CRP (>40mg/L) and cardiac troponin I (cTnI) (>0.04ng/mL) are significant predictors of outcome for severe HFMD (all $P < 0.05$). IVIG and mechanic ventilation can significantly improve outcome of HFMD at early stage III (both $P < 0.05$) with odds ratios of 0.24 (95% CI: 0.10-0.57) and 0.01 (95% CI: 0.00-0.10) respectively. Methylprednisolone and milrinone administered at any stage did not make any significant differences on mortality (all $P > 0.05$). All therapies had no statistical significance on outcome at stage I and II (all $P > 0.05$). **Conclusions** Exactly recognition of the sever HFMD cases in early stage III and timely IVIG and mechanic ventilation application can significantly decrease mortality. Mechanic ventilation training program, and dispatching experts to county-level or district hospital when there are severe HFMD cases who lost transfer opportunity are two key successful administrative experience.

Background

Hand, foot and mouth disease (HFMD) is a contagious viral disease caused by more than 20 enteroviruses, including Enterovirus 71 (EV71), Coxsackievirus A16 (CVA16) and other enteroviruses. It usually affects infants and children younger than 5 years old. Symptoms of HFMD include fever, blister-like sores in the mouth (herpangina), and a skin rash. There is no specific treatment for the disease. Only a minority of HFMD sufferers require hospital admission, mainly as results of uncommon neurological complications (meningitis, encephalitis, or acute flaccid paralysis) or pulmonary edema/haemorrhage, which can even lead to death, particularly those aged no more than five years.

There are lots of outbreaks of HFMD in many cities and provinces in China in recent years [1-6]. It has been categorized as a category C notifiable disease since May 2, 2008 in China. The disease has a substantial burden throughout the country. Less is known what had caused different characteristics of descriptive epidemiology of HFMD between different area [1, 3-6], and therapeutic strategies of severe cases are inconsequent or deficient in evidence by now [7]. Xiangyang was one of the afflicted areas where continuous outbreaks occurred yearly from 2008 to 2013. We had retrospectively investigated some epidemiology characteristics of HFMD in Xiangyang, and had analyzed risk factors causing mortality and had compared some therapies in this study.

Methods

Study population and Data Collection

Xiangyang is a prefecture-level city in northwestern Hubei province, People's Republic of China, which administers 9 county-level divisions, including 3 districts, 3 county-level cities and 3 counties. It has a population of around 5.8 million people. Xiangyang has a monsoon-influenced, four season humid subtropical climate, with cold but comparatively dry winters, and hot, humid summers. Daily averages range from 2.6 °C in January to 27.3 °C in July, with an annual mean temperature of 15.5 °C. Rail, highway and airway are very convenient in Xiangyang, thus floating population is fairly large in this city.

HFMD case must be reported to the China Information System for Disease Control and Prevention (CISDCP) after being diagnosed in clinic. Severe HFMD case in Xiangyang, once been diagnosed, must be transferred instantly to the three class A tertiary comprehensive hospitals if possible according to the command from Health Authority. We had collected surveillance data on the prevalence of HFMD in Xiangyang from CISDCP from Jan 2008 to December 2013, as well as medical records of severe HFMD cases from the three hospitals in the same period. All dead HFMD cases before or in the course of transfer to the three hospitals had also been investigated and had undertaken etiological detection according to CDC order. We had collected variables of all severe and dead cases such as gender, age, stage of illness on admission, laboratory test results, medicines, ventilation parameters and outcome. Those survived severe cases had been followed up for sequelae by the end of December 2018.

Clinic Staging of Severe HFMD Case

HFMD with CNS involvement is defined as severe case. Clinical features predictive of CNS involvement include high fever lasting longer than three days, recurrent vomiting, lethargy, limb weakness, myoclonic jerks, positive of meningeal irritation sign and CSF pleocytosis [8]. Severe HFMD case is classified into three distinct stages on admission: stage I refers to those with central nervous system (CNS) involvement, including aseptic meningitis, encephalitis and acute flaccid paralysis; stage II refers to those with autonomic nervous system (ANS) dysregulation, including resting tachycardia, profuse sweating and hypertension and stage III refers to those with frank cardiopulmonary failure, pulmonary edema or haemorrhage [9,10], frequent seizures, severe unconsciousness, persistent hypotension and shock.

Sample Preparation and Detection

Serum samples from suspected HFMD cases were drew, for sentinel surveillance, to detect IgM antibody to EV71 with colloidal gold rapid test kit (WJ-20, Wantai, China), and IgM antibody to CVA16 with diagnostic ELISA kit (WQ-1096, Wantai, China). Throat and rectal swabs were also collected to withdraw RNA with Viral RNA Mini Extraction Kit (#52904, Qiagen, Germany), then use OneStep RT-PCR Kit (#210212, Qiagen, Germany) followed by electrophoresis to detect EV71, CVA16 and general enterovirus for dead and all (part in 2008) severe suspected HFMD cases. RT-PCR primers: EV up primer 5'- TCC GGC CCC TGA ATG CGG CTA ATC C -3', down primer 5'- ACA CGG ACA CCC AAA GTA GTC GGT CC -3'. EV71 up primer 5'- *GCAGCC* ∇ ∇ *GGC* ∇ *CAC* - 3', down primer 5-

– *A T TCAGCAGCTTGGAGTGC* – 3. CoX A16 up primer 5
 – *A T GGTGCTCCACTACAGC* – 3, down primer 5
 – *TCAGTG T GGCAGCTGTAGG* – 3. Laboratory tests such as blood cell counting, serum sugar, CRP, cardiac troponin I (cTnI) had also been done for severe inpatient HFMD cases.

Medicine Administration Methods

Intravenous immunoglobulin (IVIG) and methylprednisolone had been administrated to severe HFMD cases as soon as possible after having been diagnosed. Two different doses, recommended by national or provincial HFMD guidelines, could be selected alternatively: IVIG 2 g/kg iv drip singly, or 1 g/kg iv drip, qd for 2 days. Methylprednisolone 20 mg/kg iv drip singly, or 1-2 mg/kg iv drip, qd for 2 to 3 days. Milrinone is a positive inotropic cardiotonic agent with vasodilator properties. It inhibits cAMP phosphodiesterase activity in myocardium and vascular smooth muscle. It had been administrated in case of persistent resting tachycardia, hypertension or profuse sweating. Milrinone usage: loading dose 25-75 mcg/kg iv, and maintenance dose 0.25 to 1.0 mcg/kg per minute. The effects of three injections on mortality were compared between different doses at different stages.

Mechanic Ventilation Strategy

Protective-ventilation strategy [11] had been adopted by some doctors. Positive end-expiratory pressure (PEEP) was set 2-3 cm H₂O above the lower inflection point on the static pressure–volume curve, a tidal volume of less than 6-8 ml/kg, peak inspiratory pressure was less than 25 cm H₂O above the positive end-expiratory pressure value. Permissive hypercapnia and preferential use of pressure limited ventilatory modes were involved. PEEP being set at 10 cm H₂O above the lower inflection point for 20-40 minutes was applied on pulmonary edema/haemorrhage at the beginning of mechanic ventilation, accidental tube disconnect or extubation, after aspiration of sputum or in cases that pulmonary edema/haemorrhage had not been controlled or had reoccurred. On the contrary, high pressure ventilation, including PEEP above 15-20 H₂O and peak inspiratory pressure >40 cm H₂O, or volume control ventilation were also applied by other doctors. Mortalities were compared between protective ventilation and other ventilation strategies.

Statistical Analysis

We analyzed by binary logistic regression the risk factors causing mortality such as gender, age, stage of illness on admission, blood cell counting, serum sugar, CRP and cardiac troponin I (cTnI); and compared the efficiency of different doses of IVIG and methylprednisolone, milrinone and ventilatory strategies in severe HFMD cases at three stages of severe HFMD. The statistical analysis had been performed by SPSS Statistics Version 22 (IBM Inc.).

The different choices of medicines and/or doses between patients are derived from difference between national and provincial HFMD management guidelines. All therapies did not disobey national or provincial HFMD management guidelines, therefore informed consent has been waived by Ethics Committee of Baoan People’s Hospital.

Results

Prevalence of HFMD

Epidemiological investigation revealed that HFMD outbreaks in Xiangyang had gone through four stages in 6 years: sudden outbreak in 2008, then quickly aggravation year by year, sharply fall of morbidity after 2012 and then low-level tailing for several years. The HFMD involved 50651 cases, of which 637 (1.26%) were severe and 38 were fatal (fatality rate: 0.75‰). 91.14% were 5 years of age or younger, and 74.3% were 3 years of age or younger. EV71 and CVA16 were responsible respectively for 58.86% and 16.18% of all cases, 72.53% and 12.45% of the severe cases, and 94.73% and 2.63% of the deaths. Two peak incidence years had the highest EV71 positive rates: 83.70% in 2011 and 81.60% in 2012. Among the severe cases, the male-to-female ratio was 1.21:1 and the age ranged from 28 days to 9 years. EV71 was found to be the primary causative agent of HFMD epidemics from 2009 to 2013 (Fig. 1 & Table 1).

There are two outbreak peaks every year: higher peak in March to August, lower peak in October to December. Investigation shows that EV71 is the main virus that cause serious epidemics, severe morbidity and mortality of HFMD, and EV71 positive rate of severe HFMD cases had decreased coincident with the decrease of HFMD prevalence. (Fig. 1 & Table 1)

Fig. 1. The prevalence of HFMD in Xiangyang during 2008-2013.

Table 1. Analysis on severe, fatal and EV71 positive HFMD cases in Xiangyang during 2008-2013.

Risk Factors Analysis on the Fatality

We had investigated risk factors on the fatality of severe HFMD by binary logistic regression (Table 2). The results indicate that age (<3y), EV71 positive, ANS dysregulation, pulmonary edema/haemorrhage, CRP (>40mg/L) and cTnl (>0.04 ng/mL) are risk factors for severe HFMD (all *P* < 0.05), but gender, hyperglucose, leukocytosis (>13x10¹²/L) and thrombocytosis (>500x10⁹/L) are not at the 5% level. When age were categorized as <1y, 1-2y, 2-3y and >3y, no more significant difference were seen on fatality (*P* > 0.05).

Table 2. Risk factors analysis on fatality of severe HFMD by binary logistic regression.

Efficiency Comparison between Different Therapies

We had compared the efficiency of IVIG, methylprednisolone, milrinone and mechanic ventilatory strategies on severe HFMD at different stages by binary logistic regression (Table 3). The results show that IVIG and mechanic ventilation significant are relevant to outcome of severe HFMD in early stage III (both $P < 0.05$) with odds ratios (ORs) of 0.23 (95% CI: 0.10-0.57) and 0.01 (95% CI: 0.00-0.10) respectively. Protective-ventilation did not improve mortality comparing with common ventilation strategies ($P > 0.05$). Methylprednisolone and milrinone administered in any stage did not make any significant differences on mortality (all $P > 0.05$). All therapies had no statistical significance on outcome at stage I and II (all $P > 0.05$). No difference on mortality was found in our data between large and small doses of IVIG or methylprednisolone being administrated in any stage (all $P > 0.05$).

We have also compared these therapies by chi-square test, and have gotten almost the same results as binary logistic regression. Two cases, being at stage II on admission, had quickly deteriorated and died without mechanic ventilation.

Table 3. Efficiency comparison between different therapies on severe HFMD.

Prognosis Follow-up

Follow-up investigation by the end of December 2018 shows that 4 survivors with acute flaccid paralysis and 3 patients with unilateral abducens nerve paralysis had recovered within 2 to 5 months without further intervention, and no central nerve system sequelae or any complications was found on survivals who had received large dose of methylprednisolone.

Discussion

Our investigation reveals that elevated CRP, cTnI levels have been shown to be useful laboratory signals that may help doctors identify children at risk of systemic complication several hours before the onset of overt signs of disease progression. Hyperglucose and leukocytosis are not risk factors for poor prognosis, which is inconsistent with the report from Hainan, China [12]. Another study identified female sex, light-reflex insensitivity, tachycardia and higher serum lactate levels as independent risk factors; and longer onset-to-hospitalization time as an independent protective factor for death in children with critical and severe HFMD [13].

Our investigation revealed that IVIG and mechanic ventilation application as soon as possible to severe HFMD in early stage III had significantly improved pulmonary edema or haemorrhage, and had decreased mortality. Protective-ventilation strategy might outweigh other ventilation strategies in maintaining normal blood pressure, but no mortality difference between ventilation strategies was found. High airway pressure and PEEP may have extrapulmonary effects such as reducing the volume of venous return, increasing the afterload in the right atrium, decreasing cardiac output, decreasing visceral venous return, impairing renal function, and altered hormonal levels. PIP and PEEP should be regulated according to lower inflection point and upper inflection point on the static pressure-volume curve.

Milrinone is effective in bring down hypertension and sympathetic tachycardia, and methylprednisolone can exactly decrease high body temperature, which had been proved by many cases, but both had not contributed to the survival rate in our data. In contrast, a study in Taiwan (China) found that a milrinone-treated group was associated with reduced mortality corresponding to attenuated sympathetic activity and cytokine production in comparison with a non-treated group [14]. Elevated serum levels of inflammatory cytokines, including IL-3, IL-6, IL-12p40 and TNF- α , and decreased levels of serum biomarkers, including IL-1Ra, IL-8, IL-16, soluble ICAM-1, CXCL-1 and CCL27 were found in HFMD cases, which suggests systemic inflammation is involved in the etiology of HFMD. In contrast, the associated biomarkers had not made any difference in these patients treated with methylprednisolone [15], and methylprednisolone even had been associated with an increased risk of severe HFMD development [16]. Therefore further investigations are needed to associate the usefulness of steroid treatment on HFMD.

We also found that there are no enough evidences that urge us to use large doses instead of small doses of IVIG in any stage, nor should we perform mechanic ventilation or IVIG early at stage I or II of severe HFMD.

It usually takes 2 to 4 hours for severe HFMD to deteriorate from stage II to stage III, but less than one hour left at stage III for us to take action as quickly as possible. Severe cases should be thus monitored closely for signs indicative of CNS involvement, ANS dysregulation and the development of cardiopulmonary failure, and timely intervention or even mechanic ventilation is the key to reducing mortality associated with severe HFMD. Persistent high fever, vomiting, lethargy, agitation and irritability are indications of CNS involvement [8,17]. More specific neurological signs, such as myoclonic jerk (usually observed during the early stage of sleep, but also seen in severe cases when patients are awake), truncal ataxia and “wandering eyes” (rotary eye movement without fixation) are commonly observed in children in the severe cases [18]. With disease progression or increased severity affecting the ANS and leading to cardiopulmonary failure, signs such as mottled skin and dyspnea/tachypnea may also be evident at the stage III. We found that patients bringing up by grandparents especially by those too old to be alert or poor education is a risk factor of fatality, which due to delay in early recognition of severe case and loss of timely intervention.

Fatality cases of HFMD are the commonest cause that result in medical disputes and medical compensation in China in recent years. Our investigation found that 78% fatality cases before 2011 occurred on the way of, or within 12 hours after transfer to higher grade hospital, which was attributed largely to delay in applying mechanic ventilation. These cases might have deteriorated too fast or it was too late to have the opportunity to transfer to higher grade hospital. After recognition the truth, local Health Bureau had quickly equipped all paediatric departments with mechanical ventilators for all county-level and district hospitals, and emphasized early recognition of severe cases, compliance with indication and contraindication to transfer, and had held comprehensive trainings on mechanic ventilation management. Experts were dispatched to county-level or district hospital when there was severe HFMD who lost transfer opportunity. The fatality has decreased significantly when new policy being enforced in later years after 2011.

It is puzzling that the outbreaks of HFMD had been so severe in Xiangyang for several years, whereas adjacent areas had less impact, and severe morbidity and mortality among districts, county-level cities and counties were very different in Xiangyang. A study in Shandong province, China also showed spatiotemporal difference on HFMD prevalence [19]. We cannot convincingly interpret the difference are the results of climate, bad environment, insalubrity, large floating population and/or poor education.

IVIG and methylprednisolone had been used in many countries and districts on a presumptive basis, and had been demonstrated inconsistent results for efficacy on severe HFMD [8,20,21]. The efficacy of IVIG had been proved differ when medication in different stage of severe cases in our data, and no significant difference were found when analysis the efficacy of IVIG or methylprednisolone without staging, which may interpret the cause of inconsistent results above.

There are no fatality case at stage I and only 2 at stage II on admission, when more severe cases and fatalities being enrolled, and design of a randomized, double-blind, placebo-controlled trial being adopted, we presume that efficiency of IVIG and methylprednisolone administered at stage I or II on holding stage III at bay might appear. Studies also need be done to understand why these outbreaks occur and why some people have severe disease in the future.

Conclusions

Exactly recognition of the sever HFMD cases and timely IVIG and mechanic ventilation application in early stage III can significantly decrease mortality. Mechanic ventilation training program, and dispatching experts to county-level or district hospital when there are severe HFMD cases who lost transfer opportunity are two key successful administrative experience.

Abbreviations

ANS: autonomic nervous system; CI: confidence interval; CNS: central nervous system; Cox A16: Cocksackievirus A16; cTnl: cardiac troponin I; HEV71: Human enterovirus 71; HFMD: hand, foot and mouth disease; IVIG: intravenous immunoglobulin; MAP: mean airway pressure; OR: odds ratio

Declarations

Ethical approval and consent to participate

The study protocol was approved by Ethics Committee of Shenzhen Baoan People's Hospital (BYL20190401). It's a retrospective investigation and all therapies did not disobey national or provincial HFMD management guidelines, therefore informed consent has been waived by the Ethics Committee.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

All authors declare that they have no conflict of interest.

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Authors' contributions

JL and JQ designed the study, analyzed and interpreted the data, draft and revised the manuscript. FZ and RJ collected and interpreted clinic data. All authors read and approved the final manuscript.

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Tables

Table 1: Analysis on severe, fatal and EV71 positive HFMD cases in Xiangyang during 2008-2013

Year	All Cases	Severe cases (%)	Fatal cases (‰)	Pathogen checked cases (%) [*]	EV71 (+) cases (%)	Cox A16 (+) cases (%)	Others (+) case (%)
2008	2441	37 (1.52)	2 (0.82)	10 (0.41)	5 (50.00)	1 (10.00)	4 (40.00)
2009	4006	59 (1.47)	3 (0.75)	65 (1.62)	36 (55.38)	14 (21.54)	15 (23.08)
2010	5903	76 (1.29)	6 (1.02)	250 (4.24)	179 (71.60)	32 (12.80)	39 (15.60)
2011	16557	213 (1.29)	18 (1.09)	497 (3.00)	416 (83.70)	45 (9.05)	36 (7.24)
2012	17251	217 (1.26)	8 (0.46)	2668 (15.47)	2177 (81.60)	201 (7.53)	290 (10.87)
2103	4493	35 (0.78)	1 (0.22)	2458 (54.71)	688 (27.99)	706 (28.72)	1064 (43.29)
Total	50651	637 (1.26)	38 (0.75)	5948 (11.74)	3501 (58.86)	999 (16.80)	1448 (24.34)

^{*} ELISA test results, fatal and all (part in 2008) severe cases confirmed by RT-PCR.

Table 2. Risk factors analysis on fatality of severe HFMD by binary logistic regression

	Survival	Death	<i>P</i>	OR	95% CI
All severe cases	599	38			
Male	388	25	.36		
< 3 years	402	35	.03	9.54	1.20-75.80
ANS dysregulation	276	32	.02	5.77	1.40-23.85
Pulmonary edema/haemorrhage	73	36	.00	67.59	14.12-323.45
Hyperglucose	307	29	.38		
EV71(+)	326	36	.00	26.55	3.02-233.04
Leucocytosis (>13x10 ¹² /L)	376	32	.39		
Thrombocytosis (>500x10 ⁹ /L)	16	12	.82		
CRP (>40 mg/L)	73	25	.02	4.74	1.32-16.99
cTnI (>0.04 ng/mL)	31	29	.00	47.69	11.51-197.57

Abbreviation: ANS, autonomic nervous system. BNP, brain natriuretic peptide. CRP, C-reactive protein. cTnI, cardiac troponin I. OR, odd ratio. CI, confidence interval.

Table 3. Efficiency comparison between different therapies on HFMD

	Survival	Death	<i>P</i>	OR	95% CI
Stage 1	356	0			
IVIG (L/S/N)*	139/212/11	0/0/0			
Methylprednisolone (L/S/N)	252/98/6	0/0/0			
Mechanic ventilation (Yes/No)	0/0	0/0			
Milrinone (Yes/No)	0/0	0/0			
Stage 2	170	2			
IVIG (L/S/N)	102/68/0	1/1/0	0.76		
Methylprednisolone (L/S/N)	134/36/0	2/0/0	0.46		
Mechanic ventilation (Yes/No)	34/136	0/2	0.48		
Milrinone (Yes/No)	72/98	1/1	0.83		
Stage 3	73	36			
IVIG (L/S/N)	46/27/0	14/16/6	0.00	0.24	0.10-0.57
Methylprednisolone (L/S/N)	40/33/0	17/15/4	0.11		
Mechanic ventilation (Yes/No)	72/1	19/17	0.00	0.01	0.00-0.10
Milrinone (Yes/No)	34/39	14/22	0.45		
All severe cases	599	38			

*L/S/N: large dose / small dose / no dose.

Figures

Figure 1

The prevalence of HFMD in Xiangyang 2008-2013