Original Article

The Comparative Study on Two Models of Syndrome Differentiation of the Hand, Foot and Mouth Disease: An Investigation Analysis of the Signs and Symptoms on 2 325 Cases

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Objective To realize the characteristics of “zheng” differentiation-treatment for hand, foot and mouth disease (HFMD), a new methodology of syndrome differentiation for different stages of HFMD has been explored.

Methods Total of 2 325 cases with HFMD were recorded by distributing them into exterior syndrome stage, interior syndrome stage, severe syndrome stage and recovered syndrome stage, respectively, and the main symptoms and subsidiary symptoms of different stages of HFMD have been observed. The major and minor pathogenesis of HFMD in different stages were obtained, and compared with the “2010 Guideline for the Diagnosis and Treatment of HFMD”.

Results It was found that the major pathogenesis of exterior stage was defined as “the invasion of the wen-evil to the defender of the body with the collaterals got involved”, and the minor as “qi deficiency”; in interior stage, “the fury of Gan-Yang” was the main pathogenesis, and “qi in chaos and qi deficiency” was the minor; in severe syndrome stage, “the damage of heart, liver and lung” was the main pathogenesis, and “qi in chaos” was the minor; and the pathogenesis of recovered stage was “qi-yin deficiency”. Compared with the “2010 Guideline for the Diagnosis and Treatment of HFMD”, it showed that “the obstruction of the fei-pi qi by the mixture of shi-re evil” and “the mixture of shi-re” in vivo was quite difficult to be explained in completely different context in the general situation; in the severe stage, the TCM clinical characteristics of syndrome differentiation might lose; in the early acute severe cases, the phenomenon that xin-yang and fei-qi almost ran out was difficult to be observed, then, the line between the severe and the acute severe became vague.

Conclusions The theory of syndrome differentiation by stages of HFMD was reasonable in the actual situation of clinical description on HFMD which was expected to be further tested and widely applied in the “zheng” differentiation-treatment of HFMD in the future.

Key words: Hand, foot and mouth disease (HFMD); Syndrome differentiation in classification; Syndromes differentiation by types; Syndrome factors

Hand, foot and mouth disease (HFMD) is a kind of human common infectious disease that is mainly caused by Coxsackie virus A16 (CA16)

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and enterovirus 71 (EV-71), and usually affects infants and children under the age of three. The main clinical manifestations were rashes and blister-like sores on the hand, foot, buttocks and mouth cavity, and fever; partial cases were with neurological, respiratory and circulatory system symptoms; and few severe cases were with brainstem encephalitis, neurogenetic pulmonary edema, which were even life-threatening.¹⁻⁴ At present, the etiology, pathology and treatment of syndrome differentiation of HFMD still remained in the expertise-based phase. To realize the characteristics of the “zheng”

differentiation-treatment of the HFMD by exploring a new methodology of syndrome differentiation for stages, 2 325 cases with HFMD collected from Shenzhen Third People's Hospital, Hunan Children Hospital, Beijing You An Hospital, Beijing Ditan Hospital affiliated to Capital Medical University and Wuhan Medical Treatment Center from January, 2007 to December, 2011 were used to make retrospective study, and the etiology-pathogenesis development rules and appropriate syndrome differentiation of clinical stages of HFMD were discussed with the syndrome study survey method.

MATERIALS AND METHODS

Diagnostic standard

The diagnostic method was meet the standard provided by "2010 Guideline for the Diagnosis and Treatment of HFMD" authorized by the Ministry of Health of China.^{5,6}

Data collection and classification

The questionnaire of symptoms and transmission rules of HFMD was designed based on the exterior syndrome stage, the interior syndrome stage, the severe syndrome stage and the recovered syndrome stage. The cases information was filled in and the main contents included: (1) name, sex and age; (2) clinical manifestations in different stages of disease, such as fever, dysphoria, fatigue, coughing, abdominal pain, appetite, limb shaking and frightened shiver; (3) laboratory examination, including complete blood count, blood biochemical analysis, chest radiography, electrocardiography and so on; (4) the courses of disease in each stage and the duration of fever. Total of 2 510 cases of questionnaires were investigated, and only 2 325 cases were recorded for the incomplete information of the HFMD. The data of cases information were calculated and the syndromes frequencies were listed with clustering analysis of syndrome elements. The major and minor pathogenesis was defined and the main and accompanied symptoms were summarized.

General data of cases

Among all the cases, 1 491 were males and 834 were females. There were more males than females ($M : F = 1.79 : 1$), and the mean age was 27.78 ± 19.01 months. Age group ranged from 1 month to 35 years old. There were 1 407 cases in the common type, 777 in severe type, and 141 in critical type (including 56 deaths).

Clinical staging

The "Skin-Channels and Collaterals-Zangfu" transmission model based on the Internal Classic theory in "Huang Di Nei Jing" was applied to make the following staging.⁷

Exterior syndrome stage

The symptoms of this stage were fever with chillness followed by primordial skin rashes or sores, poor spirit, fatigue, cough, and poor appetite, which were caused by the invasion of exogenous pathogenic factor to the Taiyin meridian. There were no symptoms of exogenous evil spreading into the zangfu, such as high fever, limb shaking and frightened shiver. This stage was equivalent to the pre-eruptive stage or the eruption stage of HFMD. Partial cases were merely appeared as rashes or herpetic angina, and most of the cases were cured in this stage.

Interior syndrome stage

It was the turning stage that from the exogenous evils invading from meridians to zangfu to the forming of scab and the recovering of the normothermia, during which the signs and symptoms of the respiratory, digestive and neurological systems pathological changes occurred: continuous high fever, cough, abdominal pain, vomiting, frightened shiver, limbs shaking and flaccid paralysis. This stage was quite similar to the neurological involvement period, during which a few cases were neurologically damaged within 1 to 5 days of the course and most of the cases could be cured.

Severe syndrome stage

The severe syndrome stage was quite similar to pre-cardiorespiratory failure or cardiorespiratory failure period, and majority occurred within five days of the course. The clinical symptoms of this stage were accelerated breathing and heart rate, in a cold sweat, pallor or pattern skin, limbs coldness, elevation of blood pressure and blood glucose, and would go on to develop tachycardia (some cases were bradycardia), tachypnea, cyanosis of lips, coughing pink frothy sputum or bloody sputum, continued low blood pressure or shock. There were also some cases of which severe brain function failure was the main manifestation, with the unobvious pulmonary edema, accompanied with the frequent convulsion, serious disturbance of consciousness, respiratory central circulatory failure and so on.

Recovered syndrome stage

During this stage, rashes scabbed, the body temperature was getting normal, the neurological involvement symptoms and cardiopulmonary function

began to recover, except a few cases would remain the sequela of neurological involvement. This stage was equivalent to the recovery phase when the temperature was getting normal and the rash scabbed.

Syndrome factors distribution

The common signs and symptoms of HFMD were analyzed and reduced to different syndromes factors (as shown in Table 1) based on the “syndrome elements differentiation theory”,⁸ and some corresponding adjustments have been made according to the problems occurred during the application of syndrome elements concept.

The theory basis of this paper was: “determination of pathogenic factors based on the differentiation of symptoms and signs”. To realize the convenient application of the “main decoction plus-minus” in the different clinical stages, the major and the minor pathogenesis of different stages (the exterior syndrome stage, the interior syndrome stage, the severe syndrome stage and the recovered syndrome stage) have been obtained, through the pathogenesis research and frequency calculation of signs and symptoms of HFMD.

According to the principle of syndrome factors differentiation, feng, re and shi belong to the different nature of disease. But the analysis of the symptoms and pathogenesis in the clinical medicine signs was indivisible or overlapped, such as the unsurfaced fever, tenesmus, and blister-like sores couldn't be simply divided into shi or re; as aversion to wind and fever in the syndrome of feng-re invades the exterior, feng and re had already been linked together clinically, for the deliberate separation of which would lead it divorce from the clinical practice.

The same symptom could be caused by several

different pathogenesis and should be distributed to different syndrome factors. Owing to retrospective study, concrete analysis of each sign and symptom was unsufficient and repetitive computation was adopted in this paper. For example, fever was divided into the two syndrome elements of feng-re and shi-re; coughing into feng-re and disorder of qi movement; lassitude and sloppy stool into shi-re and qi deficiency; lethargy into qi deficiency and yang exhaustion.

RESULTS

Exterior syndrome stage

The results showed that 2 286 cases (2 286/2 325, 98.32%) might have small body rashes or blister-like sores on the skin, blister-like sores on the mouth mucosae and tongue surface, accompanied with fatigue, loss of appetite, salivation or throat burning pain, fever, chillness, runny nose, red tongue and white greasy tongue coating, and 418 cases (17.98%) had almost no significant discomfort or was only with mild lassitude. The exterior syndrome stage lasted from 10 hours to 180 hours and the mean time was 106.73 ± 33.45 hours. As shown in the Table 2, the main manifestations of this stage were body rashes (95.27%), blister-like sores (84.77%), fever (82.02%), oral and throat pain (65.33%), fatigue (57.72%), followed by the symptoms such as poor appetite (36.69%), coughing (24.30%), chillness (4.22%) and runny nose.

From the distribution of syndrome and sign factors, it was found that the basic factors were feng-re, shi-re, qi in chaos and qi deficiency (as shown in Table 3). The high frequent syndrome factors were feng-re (40.19%) and shi-re (38.06%), followed by qi-deficiency (13.35%) and qi in chaos (8.40%).

Table 1. The syndrome (signs and symptoms) factors distribution of 2 325 cases

Syndrome elements		Signs and symptoms
Pathogenic factor	Feng-re	Fever, aversion to wind or cold, headache, sore throat, cough, rashes, dry stool, yellow urine
	Shi-re	Fever (or unsurfaced fever), heavy head or body, fatigue, sloppy stool, blister-like sores
	Disorder of qi movement	Cough, dyspnea with rapid and short breath, loss of appetite, vomiting (including projectile vomiting), abdominal distention or pain, dry or wet rales in double lungs
Zangfu in chaos	The fury of Gan-Yang peripheral circulatory disturbance	Headache, limb shaking, frightened shiver, convulsion, neck rigidity, flaccid paralysis, projectile vomiting
		Lethargy, limbs coldness
Healthy-qi deficiency	Qi-deficiency	Fatigue, weakness, loss of appetite, sloppy stool
	Yin deficiency	Night fever abating at dawn, thirsty, dry stool, dry skin
	The failure of yang-qi	Coma, weakness, dyspnea with rapid and short breath, lethargy, coughing of pink frothy sputum, limbs in a cold sweat, cyanosis, pallor or pattern skin

Table 2. Exterior syndrome stage: frequencies of symptoms and signs for 2 325 cases

Symptoms and signs	Frequencies (times)	Ratios (%)
Fever	1 907	82.02
Chillness (aversion to wind)	98	4.22
Fatigue	1 342	57.72
Coughing	565	24.30
Oral and throat pain	1 519	65.33
Poor appetite	753	36.69
Body rashes	2 215	95.27
Blister-like sores	1 971	84.77

Table 3. Exterior syndrome stage: syndromes factors distribution of 2 325 cases

Syndromes elements	Frequencies (times)	Syndromes elements frequencies/total (%)
Feng-re	6 307	40.19
Shi-re	5 973	38.06
Disorder of qi function	1 318	8.40
Qi-deficiency	2 095	13.35
Total frequency	15 693	100.00

Table 4. Interior syndrome stage: the frequencies of symptoms and signs for 918 cases

Symptoms	Frequencies (times)	Ratios (%)
High fever	911	99.24
Fatigue	665	72.44
Coughing	309	33.66
Oral and throat pain	670	72.98
Loss of appetite	826	89.98
Abdominal pain	75	8.17
Vomiting	395	43.03
Dry stool	169	18.41
Sloppy stool	129	14.05
Dyspnea with rapid and short breath	22	2.40
Lethargy	76	8.28
Headache	220	23.97
Heavy of head and limbs	14	1.53
Limbs coldness	19	2.07
Limb shaking	845	92.05
Frightened shiver	643	70.04
Convulsion	22	2.40
Flaccid paralysis	18	1.96
Body rashes	899	97.93
Blister-like sores	826	89.98

The results indicated that the main pathogenesis of exterior syndrome stage was the feng-re or shi-re evils invaded into the body, hurt skin and channels at first, accompanied with the wei-yang deficiency. Although the pathogens attacked the surface of the body, typical exterior syndrome manifestation such as chillness and headache could hardly be observed, indicating that the exogenous pathogen was close to the warm or heat nature. At this stage the major pathogenesis was

the invasion of the wen-evil to the defender of the body with the collaterals involved, and the secondary pathogenesis was the health-qi deficiency.

The interior syndrome stage

Of 2 325 patients, 1 407 patients with common types of HFMD were recovered during the exterior syndrome stage, and other 918 cases were into the interior syndrome stage. Male/female ratio was 1.89 : 1; average age

was 26.59 ± 14.18 months; the shortest disease course was 1 day, and longest was 18.4 days (mean 159.16 ± 45.74 hours). As shown in Table 4, the main clinical manifestations were high fever (99.24%), body rashes (97.93%), blister-like sores (89.98%), limb shaking (92.05%), loss of appetite (89.98%), oral and throat pain (72.98%), fatigue (72.44%), frightened shiver (70.04%), secondly in vomiting (43.03%), coughing (33.66%), headache (23.97%), dry stool (18.41%) or sloppy stool (14.05%). In sum, the syndrome features of the interior syndrome stage could be summarized as “the invasion of the re evil into the lung and spleen”, followed by “the internal stirring of liver feng”. “The invasion of the re evil into the lung and spleen” referred that almost all the patients had fever and most in continued high fever (71.84%); almost all the patients were with body rashes or blister-like sores, which were widely spread over hand, foot, oral, elbow, knee, buttock, perianal and back, and the commonest sites were in hand, foot, and oral pharyngeal (a solid elevation of skin, with a rigidulous tactility and red infiltration around); most cases were with loss of appetite, oral and throat pain, vomiting, coughing, headache, dry or sloppy stool and so on. The “internal stirring of liver feng” referred that almost all the patients had symptoms of frightened shiver and limb shaking, and the severe cases were even with neck rigidity and convulsion. It was important to emphasize that once manifestations such as lethargy, flaccid paralysis, convulsion, neck rigidity and limbs coldness appeared, strong vigilance should be warranted to avoid the occurrence of the critical period, the manifestations of which were excessive heat and limbs coldness, the disturbed mind, and the lung-qi depletion.

Syndrome factors analysis showed that re evil (26.41%, feng-re transmission to the interior from the exterior) and shi-re (28.01%) were the main factors in syndrome factors distribution (as shown in Table 5). Skin rashes have remained due to the pathogen stagnation in the exterior-muscle. When warm pathogen transmitted to the lung and spleen sequentially with the obstruction of qi-function (13.52%), the zangfu would be in chaos, which manifested as coughing, vomiting, loss of appetite and abdominal pain; when warm pathogen reversely transmitted to the heart and liver and stirred up liver feng (17.81%), symptoms such as convulsion, limbs shake, frightened shiver and flaccid paralysis would occur; yang syncope (0.78%) and health-qi deficiency (13.46%) would lead to lassitude, lethargy, sloppy stool and limbs coldness. In a word, the main pathogenesis of the interior syndrome

stage were the internal stirring of liver feng due to the pathogen heat invaded into the interior of the body, the minor was the orbit of qi in disturbance and exhaustion of health-qi.

Severe syndrome stage

Among 918 cases of the interior syndrome stage, 777 cases were recovered (84.64%) and 141 cases (15.36%) came into the severe syndrome stage (namely the critical type). There were 83 males and 58 females, with the mean age of 21.18 ± 17.05 months. The main clinical manifestations were frightened shiver (98.58%), loss of appetite (94.32%), high fever (89.36%), body rashes (78.01%), blister-like sores (58.16%), lethargy (71.63%), limbs coldness (67.38%), fatigue (61.70%), and the minor were coughing pink frothy sputum (43.96%), cyanosis (32.62%), rales in double lungs (29.78%), dyspnea with rapid and short breath (26.95%), pallor pattern skin (22.70%), coma (17.02%), flaccid paralysis (12.77%) and so on (as shown in Table 6).

The characteristics of the patients in this stage were mind damaged, high fever, and convulsion. Mind damaged referred to the neurological symptoms at different levels, which were caused by the excessive pestilent invasion into jue-yin meridian. At the same time, most of them were with persistent high fever, the body temperature of most of them reached over 39 degrees. It was also observed that the patients of the interior stage and severe syndrome stage all had frequent frightened shiver and limb shaking, but the symptoms such as limb coldness (67.38%) and pallor patterns skin were more often observed in the patients of severe syndrome stage than that of the interior stage, and 43.97% patients of the severe stage coughed with pink frothy sputum, which was the indication of critical conditions such as exhaustion of lung-qi and the yang-qi, and needed to be given emergency treatment at once.

According to the syndrome factors analysis, severe syndrome stage could be mainly summarized as follows: first was the invasion of the exterior pathogen to the inside of the body (most of the exterior pathogen was the re evil (16.00%), and the minor was the shi-re (11.57%), which also manifested as re predominating over shi); the second was the healthy-qi deficiency, including qi deficiency (16.62%), exhaustion yang and the qi-consume (20.47%); and the third was zangfu in chaos, which appeared with the fury of Gan-Yang pathogen (9.16%), yang syncope (11.31%) (as shown in Table 7). Taking all into consideration, the fulminant

Table 5. Interior syndrome stage: the frequency distribution of syndrome factors for 918 cases

Syndrome elements	Frequencies (times)	Syndrome elements frequencies/total frequencies (%)
Pathogenic re	3 178	26.41
shi-re	3 371	28.01
Qi in chaos	1 627	13.52
The fury of Gan-Yang	2 143	17.81
Yang syncope	95	0.78
Qi deficiency	1 620	13.46
Total frequency	12 034	100.00

Table 6. Severe syndrome stage: frequencies of symptoms and signs for 141 cases

Signs or symptoms	Frequencies (times)	Ratios (%)
High fever	126	89.36
Fatigue	87	61.70
Lethargy	101	71.63
Coma	24	17.02
Limbs shaking	13	9.22
Flaccid paralysis	18	12.77
Projectile vomiting	8	5.67
Frightened shiver	139	98.58
Coughing	2	1.42
Rales in double lung	42	29.78
Dyspnea with rapid and short Breath	38	26.95
Coughing pink frothy phlegm	62	43.97
Loss of appetite	133	94.32
Nausea	2	1.42
Abdominal distension	2	1.42
Dry stool	10	7.09
Yellow urine	28	19.86
Pallor pattern skin	32	22.70
Limbs coldness	95	67.38
Cyanosis	46	32.62
Body rashes	110	78.01
Blister-like sores	82	58.16

evil would lead to the reversion to heart and liver, and would manifest as skittishness, muscles jitter, headache, projectile vomiting and flaccid paralysis, when the internal liver-feng being stirred up; when invaded to the heart (or pericardium), would result in the hoodwinked mind, the weakness and decline of the heart-yang, yang exhaustion and qi depletion, and the clinical manifestations were lethargy, coma, speedy heart rate, dark skin, limbs coldness, then the breath got out of the lung, even manifested as bloody pink frothy sputum overflow and feeble and impalpable pulse. Comprehensive speaking, the main pathogenesis was

the fulminant evil and the harm of heart, liver and lung (deficiency of heart-yang, internal liver feng stirred up and the depletion of lung-qi), the minor was qi in chaos.

Recovered stage

The signs of the recovered stage were the body temperature recovery and rash scabby. For most patients in this phase had been discharged from hospital, efficient statistical data of the recovery phase could not be collected totally, and only 30 cases were recorded by the writer for preliminary statistics. The time started approximately from seventh day after the

Table 7. Severe syndrome stage: the frequency distributions of syndrome factors for 141 cases

Syndrome elements	Frequencies (times)	Ratios of elements (%)
Pathogenic re	311	16.00
shi-re	225	11.57
Qi in chaos	289	14.87
The fury of Gan-Yang	178	9.16
Yang syncope	220	11.31
Healthy-qi deficiency	323	16.62
Yang exhaustion, qi depletion	398	20.47
Total frequency	1 944	100.00

Table 8. Recovered syndrome stage: frequencies of signs and symptoms for 30 cases

Signs and symptoms	Frequencies (times)	Ratios (%)
Night fever abating at dawn	5	16.67
Fatigue	14	46.67
Loss of appetite	10	33.33
Thirsty	6	20.00
Dry stool	3	10.00
Sloppy stool	2	6.67
Skin dry	4	13.33

Table 9. Recovered syndrome stage: frequency distributions of syndrome factors for 30 cases

Syndrome elements	Frequencies (times)	Syndrome elements frequencies/total frequencies (%)
Qi-deficiency	26	59.10
Yin deficiency	18	40.90
Total frequency	44	100.00

onset (6.78 ± 1.85 days). At this stage, the spirit state, appetite, and sleep of the patients all turned better compared with that of the interior syndrome stage, but were not completely recovered when compared with the normal child, for symptoms of fatigue, loss of appetite, thirsty, night fever abating at dawn, and dry stool still remained. Syndrome factors analysis suggested that the pathogenesis of this stage could be summarized as the deficiency in both qi and yin (as shown in Tables 8, 9).

Results of comparison with the basis of “the Guideline for Diagnosis and Treatment of HFMD”

Common type

There were 1 407 common type patients, in which the ratio of males and females was 1.98 : 1, and the mean age was 28.35 ± 22.22 years. It was found in this research that almost all the HFMD cases manifested the red rashes (98.66%) or blister-like sores (87.97%) on the characteristic sites (hand, foot, knee, buttocks and oral cavity), accompanied with fever (72.90%), lassitude

(43.05%), coughing (31.55%), poor appetite or food refusal (32.75%), salivation, throat pain or chillness, runny nose. Partial cases (418/1 407) had no obvious unwell or was merely in slight lassitude. The syndromes factors distribution of this phrase was equal to the exterior syndrome stage. It was worthwhile to point out that:

(1) In this study, the common type was further divided into more types. However, it was difficult to divide the common type into the types of shi-re of lung-spleen and retention of shi-re, for the symptoms and signs of them were merely different in degree. The same problem also existed between the types of feng-re and shi-re for skin rashes and blister-like sores were coexisting on the same sufferer at the same stage, while other symptoms of two types could not be distinguished obviously.

(2) In the recovered syndrome stage, though the signs and symptoms of most cases have not been recorded, their pathogenesis and syndromes were significant different, as the recovered period performance of the 30 cases showed. In the 2010 guideline, the syndromes of recovered stage has been paid equal attention with the

common type, severe type and critical type, with the unclear and nondescript limits.

Severe type

There were 777 cases in the severe type, in which the male-female ratio was 1.91 : 1, the mean age was 26.63 ± 14.82 months, and the mean course was 158.24 ± 45.72 hours. It was shown in the investigation results that the main manifestations were fever (98.97%), skin rashes (98.19%), limb shaking (92.15%), blister-like sores (89.45%), loss of appetite (88.93%), lassitude (72.97%), frightened shiver (71.94%), oral and throat pain (70.91%), vomiting (41.96%), and coughing (32.95%), and the distribution of the syndrome factors was quite similar to that of interior syndrome stage. It was worthy to point out that the pathogenesis features of the exterior syndrome stage for severe type cases were different from those of the interior syndrome stage, and changed along with the development of pathogenic conditions. If syndromes were generally differentiated on the basis of 2010 guidelines, the feature of TCM as “different treatments at different times” would lose, leading to absence of the differentiation between the exterior and interior syndrome stages. Especially, it was debatable whether the lingjiao gouteng decoction (one decoction of the wind-dispelling formula) could be used before the clue as stirred up of liver feng appeared in the exterior syndrome stage.

Critical type

Syndrome factors analysis and investigation results of the critical type were the same with those of the severe syndrome stage. The disease situation of the HFMD critical type was so complicated and changeable that careful designs of a disease model for the HFMD critical type were in requirement. The deficiency of heart-yang and consume of lung qi were impossible to be found in the early period of the critical type and the patients could not be diagnosed as the critical cases before the index of all kinds had achieved yet. Obviously, there were other TCM methods to diagnose and treat the HFMD patients who were in the early period of critical type, and the deficiency heart-yang and the consume-of lung qi were unable to include all patients' situations of this period. The problem has also been found in the critical syndromic survey that the difference between the critical and severe type was not clear when all symptoms and signs in the early period were summed up.

DISCUSSION

The HFMD treatment with TCM methods could be traced back to 20 years ago; however, there was

still no uniform view for the pathogenesis and the dialectical treatment of the HFMD.⁶ It is pointed out in the guideline of diagnosis and treatment of HFMD that HFMD could be divided into four types (the common type, the severe type, the critical type and the recovered type) for diagnosis and treatment, the division of which has adopted the method of type classification.⁵ In our previous study, a symptoms' survey of 2 024 HFMD cases was made according to the pre-rashes period, rashes period and the recovered period, looking forward to find out a proper staging model for diagnosis and treatment in TCM, but the patients diagnosed as the critical type in the Western medicine didn't get enough attention in this staging model.⁹ In this paper, the sequential meridians transmission model of “skin-channels and collaterals -zangfu”, which was constructed based on the idea of classics in “Huang Di Nei Jing”, and the syndromes' survey had been made according to the “exterior syndrome stage, interior syndrome stage, severe syndrome stage and recovered syndrome stage”.⁷ The results were compared with the type model of “Guideline for the Diagnosis and Treatment of HFMD” (common type, severe type and critical type), and it was found that the former was more confirmed with the feature of occurrence and development, as well as the changes law of etiology and pathogenesis of HFMD. However, there were still many questions should be discussed when introducing a new model.

Up to now, there were two kinds of opinions about the pathogenesis of skin rashes in HFMD: one was “pathogenic factor attacked qi and nutrient aspect, and internal pathogens broke out”, and another was “feng-re with shi stagnation on the surface of the skin”.⁷ Our opinion was similar to the latter, and managed to classify the skin rashes as one of exterior syndromes, in view of four reasons for this: (1) skin rashes showed up in the prophase of HFMD, like as in some exanthematous virus diseases (nettle rash, measles, crystalli and so on), skin rashes were always the initial symptom; (2) only the skin rash accompanied with the lung infection (transmitting to zangfu) was the symbol of the patient's condition worsening, and most of the other cases could be recovered from the exterior stage of HFMD; (3) the location of skin rashes was on the surface (skin or mucosa); (4) in the traditional Chinese medical theory, skin rashes were erupted by the feng re in taiyin meridian, which suggested that rashes were related to the invasion of feng re towards hand-taiyin meridian, while blister-

like sores manifested as the attack of the shi-re to the foot-taiyin-meridian. The pathogenesis of skin rashes could be explained as newly re evil entered into the branches of channels. In this symptoms' investigation, it was found that the majority of the common type cases of HFMD could be recovered from the exterior stage and pathogen did not further transmit to zangfu. Moreover, in the survey classifying to the pre-rash, rash and rash scabbed groups, it was found that HFMD patients often had no pre-rash manifestations, which showed that the exterior syndrome of HFMD (including other exanthematous viral infectious diseases) was different from general exogenous diseases, and the exterior syndrome stage of HFMD could present with fever but often did not manifest aversion to cold or wind with the initial typical skin rash, which would be recovered rapidly in a week.

What was the signal of the transmission to zangfu in HFMD? In this syndrome differentiation model of HFMD investigation, it was suggested that the transmission of the warm or re evil from the skin surface or channels to the corresponding zangfu (lung, intestine, spleen and stomach) was the end of the exterior syndrome and the beginning of interior syndrome. The methods to distinguish symptoms should be its pathogenesis in the course of HFMD disease. For example, coughing could be divided into the exterior syndrome or interior syndrome period according to the difference of the diseased positions (meridian or zangfu). Coughing caused by itching and sore throat belongs to the channels pathological changes and was exterior syndrome, while the coughing caused by internal heat of lung belonged to the zangfu pathological changes and was the interior syndrome.

The difference between “Zheng” and “disease” (Western medicine) could be described as: “Zheng” was the space distribution of the disease signs (symptom, sign, and experimental test results) at a certain time point, while “Disease” was the time distribution of the disease signs at a certain space limit. The staging syndrome differentiation model was put forward as the guideline of infectious disease HFMD, compared with the typing diagnosis and treatment model in the “2010 Guideline for the Diagnosis and Treatment of HFMD”, and would be more valuable to the zheng differentiation-treatment of infectious diseases in TCM. The disadvantages of the typing model have been shown as follows: in the common type cases, the differences between shi-re of lung-spleen and steaming of shi-re could not be further

distinguished; and the severe type cases may loss the TCM clinical characteristics which was suitable to the treatment at right time and climate; and in the early stage of the acute severe type cases, it was difficult to find out heart-yang and lung-qi exhaustion, which could resulted in the unclear boundaries between severe and acute severe cases. According to which, the theory of differentiation by stages of HFMD was conform to the feature of HFMD occurrence, development and the evolvement rule of etiology and pathogenesis, which could make a foundation for the long and reasonable choice of the TCM syndrome differentiation model of infectious diseases.

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REFERENCES

1. Ho M, Chen ER, Hsu KH, Twu SJ, Chen KT, Tsai SF, et al. An epidemic of enterovirus 71 infection in Taiwan. *N Engl J Med* 1999; 341(13): 936-942.
2. Ni H, Yi B, Yin J, Fang T, He T, Du Y, et al. Epidemiological and etiological characteristics of hand, foot, and mouth disease in Ningbo, China, 2008-2011. *J Clin Virol* 2012; 54(4):342-348.
3. Vijayaraghavan PM, Chandy S, Selvaraj K, Pulimood S, Abraham AM. Virological investigation of hand, foot, and mouth disease in a tertiary care center in South India. *J Glob Infect Dis* 2012; 4(3):153-161.
4. Zou XN, Zhang XZ, Wang B, Qiu YT. Etiologic and epidemiologic analysis of hand, foot, and mouth disease in Guangzhou city: a review of 4 753 cases. *Braz J Infect Dis* 2012; 16(5):457-465.
5. The Ministry of Health Expert Group. The guideline of diagnosis and treatment of HFMD [EB/OL]. [2010-04-21]. <http://www.moh.gov.cn/publicfiles/business/htmlfiles/mohyzs/s3586/201004/46884.htm>.
6. Chen Y, Chen Y, Tao Rf. Reading the guideline of diagnosis and treatment on HFMD in 2010. *Shi Jie Gan Ran Za Zhi (Chin)* 2010; 10: 104-108.
7. Nie G, Hong K, Nie F. The hypothesis of transmission model “skin-meridian-zangfu”. *Huan Qiu Zhong Yi Yao (Chin)* 2011; 4 (5):354-357.
8. Zhu WF. Syndrome elements differentiation theory. Beijing: The People's Medical Publishing House 2008:189-229.
9. Hong K, Nie F, Nie G, Li HJ, Yuan H, Zhu QJ, et al. Etiology and mechanism and syndromes differentiation in periods on 2024 HFMD patients. *Huan Qiu Zhong Yi Yao (Chin)* 2012;5(5):332-336.