Epidemiologic Research on Severe Cases of Enterovirus 71 Infection in 2008

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Abstract

There were 30 children being admitted to the Department of Pediatrics of Chang Gung Memorial Hospital, Kaohsiung due to severe enterovirus infection during January to May 10th, 2008. 25 out of 30 children were confirmed of enterovirus 71 infection by virology and serology and all were justified as positive cases by Centers for Disease Center (CDC), Department of Health. 25 severe cases of enterovirus 71 infection in this research all manifested with hand-foot-mouth disease. 20 out of 25 cases (80%) were less than 4 years-old. Among 25 cases, 16 were boys and 9 were girls. Male to female ratio was 1.8:1.0. The average period from onset of the disease to severe condition was 2.9 days. That is to say critical stage began in the third day. Myoclonic jerk happened in 76% of the severe cases. Significant elevation of blood sugar level and peripheral white blood cell counts in severe cases was noted ($P<0.005$). However, the average body temperature of the 25 severe cases in this research was not so high, which meant that it would be possible for an infected child to

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develop to severe condition even though his body temperature was not high. One of the clinical stage 3B children received extracorporeal membrane oxygenation (ECMO) therapy but remained helplessness. According to our recent experience, the prognosis was not good if the patient was in clinical stage 3B. One out of 25 children was dead. The mortality rate was 4%.

Our conclusion was that this year there would be an outbreak of enterovirus 71 infection. Children less than 4 years-old, especially boys, should be watchful if they were infected by enterovirus. Those who are taking care of infected children should pay much attention from the third day of onset of the disease. Not only watching out clinical symptoms and stages, but also monitoring higher blood sugar level and higher white blood cell counts as important index of severe cases. Only timely medication and therapy could we save back lives of the sick children.

Keywords: enterovirus, epidemiology, risk factors

Introduction

Enterovirus, a kind of virus with single strand RNA, belongs to picornaviridae which consist of poliovirus with 3 serotypes, coxsackievirus A with 23 serotypes, coxsackievirus B with 6 serotypes, echovirus with 31 serotypes, and 4 new kinds of enterovirus, type 68-71, that were found after 1960. Most of the enterovirus infection in children is mild or self-limited. The often seen manifestations are viral rashes, herpangina, hand-foot-mouth disease or viral meningitis. The most often seen is coxsackievirus A16 serotype. Since enterovirus 71 was found in a child with viral meningitis in California, USA, 1969 [1], it had continuously caused huge outbreak and high mortality rate in different countries like Melbourne, Australia in 1972; Swiss in 1974; and Japan in 1973 and 1978.

Severe neurologic complications were first seen in Bulgaria, which caused 44 deaths and turned the mortality rate to 30%. Then in 1978, 47 people died of the enterovirus infection in Hungary. Later relatively huge outbreaks of enterovirus infection happened in Hong-Kong, 1985 and in southern Australia, 1986. The outbreak of enterovirus infection in 1997 caused 28 deaths in Malaysia. The next year (1998) the enterovirus infected more than 120,000 people in Taiwan. There were 405 severely ill children and 78 out of them were dead, which turned the mortality rate to 19.3%. Enterovirus 71 was most seen in the expired sick children (37/78, 43.6%) [2-5]. Because of rapid clinical progress of the disease, most of the patients showed acute exacerbation of symptoms within 24 hours. There were even some patients died of pulmonary edema or pulmonary hemorrhage in 12 hours [6].

Many patients of enterovirus 71 infection here in Taiwan were noted in the beginning of 2008. Hand-foot-mouth disease dominated the clinical manifestations. Some severe cases then followed, which were most seen in Kaohsiung County, located in the southern part of Taiwan. By the past experience, if many cases appeared in seasons which were not supposed to be outbreak seasons that meant there would be a major outbreak this year. By the statistics supplied by CDC, Department of Health, there were 48 informed cases and 11 confirmed cases of severe enterovirus infection in 2006 respectively, while in 2007, the numbers of informed cases and confirmed cases were 49 and 12, respectively. That meant fewer numbers of infected cases in these 2 years. Most of the children less than 4 years-old had never been infected thus they had no antibodies against enterovirus 71. Once an outbreak happened, these susceptible hosts that had never been infected would turn out to be highly risky susceptible group [7]. By

Lin and Hwang, et al, in Taiwan, C2 gene subtype dominated in 1998 enterovirus infection outbreak, while B4 dominated the outbreak of enterovirus infection from 1999 to 2003. C4 followed the domination after 2004 [8]. B5 subtype would play a major role in the outbreak of the infection this year by the studies of CDC, Department of Health. The new subtype had never been found in the past 20 years in Taiwan and would thus cause a major outbreak. The more the number of the infected patients, of course, the more the number of the severe cases will appear. This was what official health authorities in charge and the public should be faced actively. We had done epidemiologic and clinical analysis for the 25 severe cases justified as positive cases of enterovirus infection by CDC, Department of Health from January to 10th May, 2008. Hereby we come up with the results for clinical practice reference.

Materials and Methods

1. Research Subjects:

   25 patients who were admitted to the Department of Pediatrics of Kaohsiung Medical Center, Chang Gung Memorial Hospital, clinically diagnosed as severe enterovirus infection and all had been informed and then justified as positive cases of enterovirus infection by CDC, Department of Health.

2. Period of Research:

   Patients infected by enterovirus and confirmed as severely infected cases from January 1st to May 10th, 2008.

3. Classification criteria for suspected cases of enterovirus infection complicated with severe symptoms:

   By classification principles set by CDC, March, 2008:

   I. Classification Evidence:

(1) Conditions of enterovirus infection complicated with severe symptoms

(2) Laboratory diagnostic results - as shown in report sheet of specimen examination

(* according to testing data by the laboratory contracted with CDC.)

1. Enterovirus antibody neutralization test (NT): whether there is more than 4 times elevation of convalescent titer of serum antibody comparing to acute stage titer
2. Enterovirus isolation in cell culture and differentiation of serotypes
3. Enterovirus reverse transcription polymerase chain reaction (enterovirus RT-PCR)

II. Definition of Case Classification:

(1) Excluded case

Those who do not meet the conditions of enterovirus infection complicated with severe symptoms

(2) Probable case

1. Those who meet the conditions of enterovirus infection complicated with severe symptoms and
2. 3 items of laboratory diagnostic results are all negative or positive RT-PCR only

(3) Confirmed case

1. Those who meet the conditions of enterovirus infection complicated with severe symptoms and
2. The laboratory diagnostic result is NT or culture for enterovirus positive

4. Methods:

For those who confirmed by tests and met the criteria of confirmed cases set

by CDC, we collected their disease histories, contact histories, physical examinations, clinical symptoms, complications, laboratory data, special tests, and image studies for detail statistic analysis and interpretation. Laboratory tests included general routine examinations like blood sugar level, liver function, CK, CK-MB, CRP, troponin-I, kidney function and so on.

Special tests included cerebrospinal fluid examination, viral culture and titration of antibodies. Magnetic resonance image (MRI) is the major part of the image studies.

5. Clinical stages:

The process of enterovirus 71 infection is clinically divided as 4 stages:

Stage 1: hand-foot-mouth disease or herpangina

Patients only had fever, anorexia, oral ulcer, bullous lesions or rashes in hands or feet.

Stage 2: encephalomyelitis

Patients already had some neurologic symptoms like irritability, somnolence, limb weakness, unsteady gait, myoclonic jerk and so on.

Stage 3: cardiopulmonary failure

Stage 3A: stage of autonomic nerve system imbalance

cold sweating, limb coldness, high blood pressure, high blood sugar, tachypnea, tachycardia and so on. Pulmonary edema or even hemorrhage would be noted in severely ill patients. Blood pressure would elevate first then lower down.

Stage 3B: heart failure stage

Tachycardia, blood pressure lowers down.

Stage 4: convalescent stage

Heart function recovered. If it is not possible to wean from ventilator,

tracheostomy should be considered for further rehabilitation program [4].

6. Statistics:

   Excel software is used for drawing statistics and SAS 9.1 version software is used for statistic testing while Student t-test is used for comparison in different groups for the statistic processing in this research.

Results

Children infected by enterovirus were almost always seen in outpatient department and ward since the end of 2007. The infected patients with severe symptoms were then seen in the middle of January, 2008. The Department of Pediatrics of Kaohsiung Medical Center, Chang Gung Memorial Hospital, experienced 25 proven cases of severe enterovirus infection through viral culture, RT-PCR or positive reaction to Enterovirus 71 antibody till May 10th, 2008. The detail information of the 25 patients including clinical stages, laboratory data, clinical diagnosis, and the result of cerebrospinal fluid were shown in Table 1 and Table 2. 80% (20/25) of the infected children with severe symptoms were less than 4 years old. The boys to girls ratio less than 4 years old was 2.3:1.0. In the overall 25 patients, 16 were boys and 9 were girls. Male to female ration was 1.8:1.0. The month distributions of appearance of severe cases were 6 in January, 2 in February, and 2 in March, respectively. There was no increasing number of infected patients because of Lunar New Year. Sudden increasing of the number of severe cases to 9 was seen in April. There were 6 severe cases from May 1st till May 10th (Figure 1). The relationship between clinical stages and age could be seen in Figure 2. Stage 3B cases were all less than 4 years old. The older children had mostly stage 2 diseases. There was no apparent relation between average body temperature and clinical stage of the 25 severe cases.

The average body temperature of the patients of stage 2, stage 3A, and stage 3B ranged from 38.1~38.4℃. Significant difference could be seen from the days of onset of the disease to severe symptoms and the clinical stages. The average days of stage 2 were 2.9 days, 3.4 days for stage 3A, and 2.3 days for stage 3B ($P<0.05$). That meant the third day from onset of the disease was a critical point. It was not uncommon to see myoclonic jerk in severe cases of enterovirus 71 infection. In this research, apparent myoclonic jerk showed in all infected children more than 3 years old. In the contrast, the chance of myoclonic jerk in the infected children less than 3 years-old ranged from 13% to 86% (Figure 3). The range of blood sugar level of most of the sick children was within 100~125 mg/dl. The higher the blood sugar level, the more severe the condition (Table 1). Blood sugar level of the sick children closely related to the clinical stages. The average blood sugar level of the stage 3B sick children was 245 mg/dl, which was significantly higher than that of 107.1 mg/dl of stage 2 and that of 98.3 mg/dl of stage 3A ($P<0.005$). White blood cell counts also related to the clinical stages. Although there were elevation of white blood cell counts in stage 2 (11,329/mm^3) and stage 3A (12,920/mm^3), both lower than that of the stage 3B (20,867/mm^3) significantly ($P<0.005$).

Magnetic resonance image (MRI) showed typical findings including brain stem encephalitis, abnormalities of caudate nucleus, pons, and spine in 4 out of 9 sick children with severe symptoms (Table 2). This was same with the case reports from Taiwan and Australia [9-11]. Only 1 death happened in the 25 severe cases. The mortality rate was 4%, which was far lower than that of the outbreak in the past and other reports [2, 12-17].

Discussion

The condition of enterovirus infection in 2008 showed up awfully. Infected patients were noted one by one from the beginning of this year. It was different from the situations in the past 10 years here in Taiwan that the infected patients began to be seen in every March to April, outbreak peak in May to June and another minor peak in October. In addition, severe cases were even noted in January that meant there would be an unusual trend of outbreak this year. The fact also demonstrated that the number of infected patients kept high till now (this May). It was worthy of gratification that there was no more huge outbreak happened because of family gathering during the festival period of the Lunar New Year even though the outbreak happened from the beginning of this year. In addition, there were few numbers of deaths of the infected patients. Till May 10^{th}, the number of informed cases of severely infected patients was 127 and the number of confirmed cases was 67. 2 patients were dead and the mortality rate was 3%. It meant that medical care systems in Taiwan had relative experience and excellent results in taking care of severe cases of enterovirus infection during the outbreak in the past 10 years.

The initial clinical manifestation of all the 25 severe cases in this research was hand-foot-mouth disease. From the situation of the outbreak this year, most of the infected patients manifested as hand-foot-mouth disease. Enterovirus 71 dominated in the viral culture. The 25 severe cases in this research were proved of enterovirus 71 infection through viral culture, RT-PCR, and antibody testing and all were justified as severely infected cases by CDC, Department of Health.

Four fifths (20/25) of the sick children were less than 4 years old. This was compatible with that there were few severe cases in the past 3 years and children

were short of antibodies against enterovirus 71 because of no contact of enterovirus infection. That also meant that chances for sick children less than 4 years old becoming severe cases were higher [20-21]. Out of the 20 cases, there were 14 boys (70%), which meant that boys less than 4 years old were high risk group. Analysis by month distributions of number of infected cases, a sudden increase number of infected cases in April should be attributed to warmer weather, more contact between children, and longer viral survival in the living environment. According to the past experience, the number of infected cases would increase in May and June. Stage 3B severe cases were most seen in patients less than 4 years old while stage 2 infected cases were more seen over 4 years old. The above data and phenomenon all showed that if children less than 4 years old were infected by enterovirus, especially type 71. Parents or medical staff should pay much attention to it that the chance becoming severe cases was higher than that of children over 4 years old. As of the average body temperature of the sick children, it was not the same as the previous reports claiming that high fever went first. The average body temperature of the sick children in this series ranged between 38.1℃~38.4℃. The chance becoming severe cases remained high even though the body temperature was not so high. The average days from onset of the disease to severe cases were 2.3 to 3.4 days. There was not significant difference of the average days between patients of stage 2, stage 3A, and stage 3B. The above data showed that we should remind parents or care takers of the sick children of the higher chance of becoming severe cases since the third day from onset of the disease. There was 100% chance for the severely sick children over 3 years old having myoclonic jerk. Owing to immature development of nervous system for those who were less than 3 years-old, the

chance of myclonic jerk ranged from 13% to 86%. No positive correlation was seen between the frequency and severity of myoclonic jerk.

Blood sugar level of most severely sick children in this research ranged between 100~125mg/dl. Only 3 patients had blood sugar level more than 150 mg/dl. Chance of becoming severe cases still remained high even though whose blood sugar level was not so high. The average blood sugar level of stage 2 and stage 3A patients almost kept in the normal range. But blood sugar level of stage 3B patients was significantly higher than that of the above 2 stages ($P<0.005$). This meant that we should pay much more attention to the chance becoming severe cases if blood sugar level was over 150 mg/dl [22]. In the contrast, it did not mean that it would not develop to severe cases if blood sugar level was not high. It was not uncommon that elevation of average peripheral white blood cell counts was usually seen in the severely infected children and that meant more significantly for stage 3B than stage 2 and stage 3A ($P<0.005$). Therefore, the average peripheral white blood cell counts over 20,000 /mm^3 should be another sign of becoming severe cases [22].

Conclusion to this research was that enterovirus 71 played a major role in severe cases. Boys less than 4 years old were high risk group. The major clinical manifestation was hand-foot-mouth disease. It might be possible for the patients to become severe cases from the third day of disease onset. High blood sugar level and high whit blood cell counts were important risk factors of severe cases.

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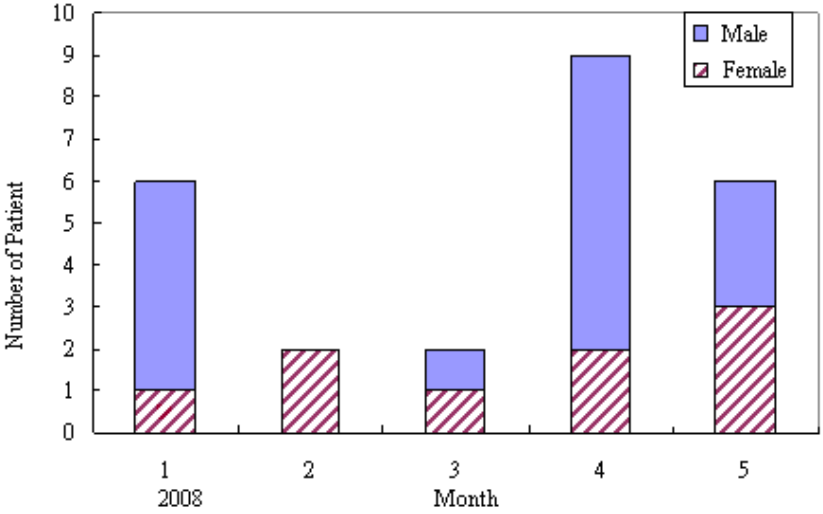

Figure 1. Distributions of Enterovirus 71 Infection by Month and Sex in 2008

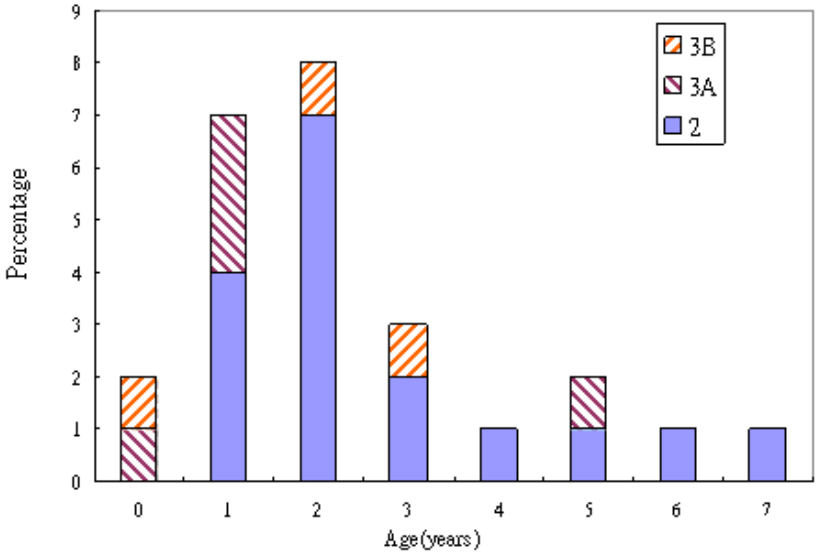

Figure2. Relationship between Age and Clinical Stages of Enterovirus 71 Infection in 2008

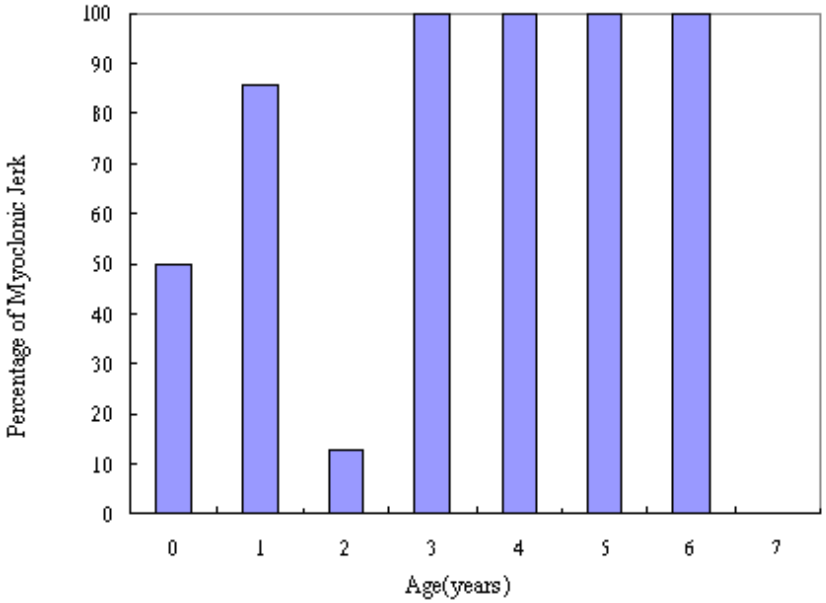

Figure 3. Relationship between Age and Myoclonic Jerk of Enterovirus 71 Infection in 2008

Table 1. Clinical Stages, Laboratory Tests, and Results of 25 Severe Cases of Enterovirus 71 Infection in 2008

Patients	Sex	Age (months)	Clinical Stage	Laboratory Tests					Current Status
				Glu	WBC	CK-MB	Trop-I	CRP	
1	M	3	3A	103	8900	5.4	0	6.9	
2	M	31	2	111	9900	7.4	0	7.4	
3	M	17	2	114	13500	7.7	0	1.1	
4	M	56	2	109	5900	11.8	0.01	39.4	
5	F	89	2	96	7300	not done	0	2	
6	M	18	2	101	5300	7	0	1.8	
7	F	21	2	114	13700	35.7	0	4.4	
8	F	31	3B	177	13500	not done	not done	0.2	
9	F	61	3A	73	11900	4.9	0	61.6	
10	M	24	2	102	11500	2.3	0	48.8	
11	M	35	2	74	15000	5.8	0	3.9	
12	M	25	2	105	27000	9.1	0	4.3	
13	M	40	3B	193	21900	22.3	0.59	2.1	expired*
14	M	3	3B	365	12900	17.5	1.44	2.1	
15	F	13	3A	not done	13000	16.9	0	12.7	
16	M	13	3A	96	11200	1.8	0	9.2	weakness of legs
17	F	70	2	122	9600	3.1	0	1.9	
18	M	15	2	126	19700	not done	not done	18.4	
19	M	47	2	125	10600	not done	not done	53.6	
20	M	80	2	114	10800	3.4	0	0.7	
21	M	17	3A	121	14700	7	0	11	
22	F	30	2	104	14600	5.7	0	19.6	
23	F	34	2	104	12800	not done	not done	6.4	
24	M	43	2	98	10200	1.8	0	9.9	
25	F	29	2	101	127	2.6	0	11.4	

*:this patient was applied with extracorporeal membrane oxygenation (ECMO).

Table 2. Clinical Diagnosis and Results of Cerebrospinal Fluid Tests and MRI of 25 Severe Cases of Enterovirus 71 Infection in 2008

Patient	Sex	Age (months)	Clinical Diagnosis	Tests of Cerebrospinal Fluid					
				Glu	Protein	lactate	WBC	DC (N/L/M)	(MRI)
1	M	3	HFMD, meningoencephalitis	51	77.3	11.4	4	6.0/1/3	
2	M	31	HFMD, meningoencephalitis	49	33.5	8.8	120	0/90/10	brain stem encephalitis
3	M	17	HFMD, meningoencephalitis	66	30.4	12.4	82	4/44/52	
4	M	56	HFMD, meningoencephalitis	81	25.7	15.3	3	2/1.0	
5	F	89	HFMD, acute cerebellar ataxia	54	27.8	12.3	8	2/98	suspect small old infarcts right cerebral peduncle; spine: unremarked
6	M	18	HFMD, left monoplegia	64	22.6	11.3	42	10/84/6	unremarked study
7	F	21	HFMD, meningoencephalitis	55	22	13.1	40	6/58/36	
8	F	31	HFMD, meningoencephalitis	112	17.9	16.3	1	0/1	encephalitis over caudate nucleus and nuclei over pons and medulla
9	F	61	HFMD, meningoencephalitis	not done	not done	not done	not done	not done	
10	M	24	HFMD, meningoencephalitis, Ataxia	64	40.6	15.1	280	20/52/28	unremarked study
11	M	35	HFMD, meningoencephalitis	48	40.9	18.4	38	38/56/6	
12	M	25	HFMD, Rhonbenencephilitis	65	27.5	13.6	46	2/92/6	T2: increased signal onpons and medulla pblongata, consistent with brain stem encephalitis
13	M	40	HFMD, myocarditis, pulmonary edema and hemorrhage, encephalitis, renal failure	not done	not done	not done	not done	not done	
14	M	3	HFMD, Rhonbenencephilitis	not done	not done	not done	not done	not done	bil subdural effusion, r/o memingeal lesion, medullary lesion due to enterovirus involvement
15	F	13	HFMD, meningoencephalitis	not done	not done	not done	not done	not done	
16	M	13	HFMD, meningoencephalitis	76	30.3	14.8	26	0/85/15	unremarked study
17	F	70	HFMD, meningoencephalitis	70	41.7	19.5	120	82/12/6.0	

Table 2. Clinical Diagnosis and Results of Cerebrospinal Fluid Tests and MRI of 25 Severe Cases of Enterovirus 71 Infection in 2008 (continue)

Patient	Sex	Age (months)	Clinical Diagnosis	Tests of Cerebrospinal Fluid					
				Glu	Protein	lactate	WBC	DC (N/L/M)	(MRI)
18	M	15	HFMD, meningoencephalitis, monoplegia	not done	not done	not done	not done	not done	unremarked study
19	M	47	HFMD, seizure	not done	not done	not done	not done	not done	
20	M	80	HFMD, meningoencephalitis	79	60.2	24.1	125	67/21/12	
21	M	17	HFMD, meningoencephalitis	68	34.3	24.4	180	17/38/45	
22	F	30	HFMD, meningoencephalitis	65	42.6	21.4	105	16/58/26	
23	F	34	HFMD, meningoencephalitis, seizure	79	20.7	18.2	18	1993/6/1	
24	M	43	HFMD, Rhonbenencephilitis	61	37.9	18	48	66/29/5	
25	F	29	HFMD, meningoencephalitis	64	49.2	14.1	170	22/76/2	