BRIEF COMMUNICATION

Hand, Foot and Mouth Disease Complicated with Central Nervous System Involvement in Taiwan in 1980–1981

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Sixteen cases from the 1980–1981 Taiwan outbreak of hand, foot and mouth disease (HFMD) associated with central nervous system involvement were identified: nine had polio-like syndrome, four had encephalitis or encephalomyelitis, one had cerebellitis, and two had aseptic meningitis. They all had fever, five (31%) had documented myoclonic jerk, and 15 (93%) had HFMD. Their mean blood leukocyte count was 12,490/μL, and five (31%) had leukocytosis (>15,000/μL); mean cerebrospinal fluid (CSF) leukocyte count was 156/μL, CSF protein was 57 mg/dL and CSF glucose was 57 mg/dL. Two patients with HFMD plus encephalitis died within 1 day of hospitalization, and one of them had acute cardiopulmonary failure mimicking myocarditis. Twenty years later, at least one male patient had sequelae of polio-like syndrome and was therefore exempted from military service. Clinical severity was comparable to the 1998 EV71 epidemic. [*J Formos Med Assoc* 2007;106(2):173–176]

Key Words: enterovirus 71, fatality, sequelae, severity

Did enterovirus 71 (EV71) commonly circulate in Taiwan before the 1998 outbreak? Chang et al initiated a seroepidemiologic study before and after 1998. They found that EV71 seroprevalence rates in 1997 among adults and children > 6 years of age were 57–67%.[1] Lu et al examined serial serum antibody titers to EV71 in 81 children born in 1988 who had yearly blood samples saved from 1989 to 1994, and again in 1997 and 1999.[2] They found that the annual incidence of EV71 seroconversion between 1989 and 1997 was 3–11%, and that by 1997, 68% of these children had serologic evidence of EV71 infection, defined as serotiter ≥ 8.[2] All this evidence indicates that EV71 has, in fact, been circulating in Taiwan before the 1998 epidemic.

Ho et al also reported outbreaks of EV71 infection in Taiwan in 1980 and 1986.[3] In 1980, there was an outbreak in Taipei, involving children who had poliomyelitis-like flaccid paresis associated with hand, foot and mouth disease (HFMD).[3] In Kaohsiung in 1986, EV71 was isolated from patients with HFMD.[3]

To elucidate the role of EV71 infection in 1980–1981, we conducted this retrospective study to evaluate cases of HFMD with central nervous system (CNS) complications in northern Taiwan in 1980–1981.

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Methods

Definition of clinical syndromes

We reviewed all 1980–1981 discharge notes from the Department of Pediatrics, National Taiwan University Hospital (NTUH). Cases of HFMD with CNS complications were selected and reviewed. Cases with CNS involvement as well as an epidemiologic link were also included. An epidemiologic link was defined as contact with HFMD cases within 1 week before disease onset. At that time, NTUH was one of the Taiwan medical centers with a virologic laboratory and the cell lines of viral isolation were HEP-2, human embryonic fibroblast cells and vero cells.

In HFMD, patients had oral ulcers and vesicular rash appearing on the hands, feet, knees, and/or buttocks. CNS involvement was indicated in five types of cases. Those with aseptic meningitis had headache and irritability along with cerebrospinal fluid (CSF) pleocytosis (> 5 leukocytes/μL) and without an altered level of consciousness. The second type involved encephalitis with altered level of consciousness plus CSF pleocytosis. Cerebellitis was defined as the presence of cerebellar ataxia and dis-coordination. Poliomyelitis-like syndrome was defined as acute limb weakness and decreased reflex and muscle strength. Finally, cases with encephalomyelitis had the occurrence of both encephalitis and poliomyelitis-like syndrome.

Data collection

Data were collected on age, sex, fever, peak body temperature, and all other symptoms and signs at presentation and during the whole treatment course. During hospitalization, data on heart rate, blood pressure, body temperature, mental status, muscle power, and breath sounds were collected. Laboratory data included white blood cell (WBC) count, differential WBC count, hemoglobin, platelet count, CSF WBC count, CSF glucose, and CSF protein. Leukocytosis was defined as WBC count > 15,000/μL on admission.

Results

Demography, clinical manifestations and syndromes

A total of 16 complicated HFMD cases were collected. Mean age at onset was 1.9 years (range, 3 months to 3 years 7 months). Male to female ratio was 9:7. Most (13) of them lived in northern Taiwan. Three lived in central Taiwan.

The clinical syndromes included nine cases complicated with polio-like syndrome, four with encephalitis or encephalomyelitis, one with cerebellitis, and two with aseptic meningitis. Only one case (Case 6) of aseptic meningitis did not have preceding HFMD but an epidemiologic link, that is, his older sibling had HFMD 3 days before his illness.

Demography, clinical manifestations, and laboratory data from the 16 cases are listed in the Table. All had fevers. Myoclonic jerk was documented in five (31%). Fifteen (93%) patients had skin rash over their palms, knees, buttocks and/or soles; and 14 (87%) had oral ulcers. Mean leukocyte level was 12,490/μL. Five (31%) had leukocytosis (> 15,000/μL). Mean CSF WBC count was 156/μL, CSF protein was 57 mg/dL and CSF glucose was 57 mg/dL.

Clinical outcomes

Noteworthy sequelae occurred in the patients with polio-like symptoms. Two additional cases (Cases 7 and 8) of HFMD plus encephalitis were fatal.

In the first fatal case (Case 7), there was acute cardiopulmonary failure mimicking myocarditis and death occurred within 1 day after hospitalization. The 1-year-and-9-month-old boy was brought to the NTUH emergency services on September 29, 1980. He had developed fever up to 39°C, had vesicular eruption over the feet and hands, had been vomiting for 4 days, and displayed consciousness disturbance of half a day's duration. During hospitalization, disturbance of consciousness, trismus, upward gaze, myoclonic jerk, and tonic spasms of the extremities were observed. Mild tachypnea and moist rales on auscultation were found. WBC count was 21,700/μL (23% bands,

Table. Demography, clinical manifestations and laboratory data of complicated hand, foot and mouth disease in 1980–1981 in Taiwan

Case	Age	Sex	Onset	Neurologic symptoms	WBC count (/μL)	CSF WBC count (/μL)	Neurologic diagnosis
1	1 yr 6 mo	F	HFMD	Left upper limb paralysis, lethargy	13,500	177	Encephalomyelitis
2	3 yr 3 mo	M	HFMD	Lethargy, dysphagia, dysarthria, ataxia, right upper limb paresis	8700	51	Encephalomyelitis
3	7 mo	F	HFMD	Right upper limb paresis, myoclonic jerk during sleep	9500	2	Polio-like syndrome
4	1 yr 5 mo	F	HFMD	Right upper limb paresis	14,000	208	Polio-like syndrome
5	1 yr 3 mo	M	HFMD	Vomiting	12,500	450	Aseptic meningitis
6	3 yr 2 mo	M	Elder sister had HFMD	Myoclonic jerk during sleep	10,000	130	Aseptic meningitis
7	1 yr 9 mo	M	HFMD	Trismus, myoclonic jerk during sleep, seizure, consciousness disturbance	21,700	280	Encephalitis plus cardiopulmonary failure mimicking myocarditis
8	3 yr	F	HFMD	Seizure, opisthotonus, consciousness disturbance	16,000	310	Encephalitis
9	2 yr 2 mo	M	HFMD	Right lower limb paralysis	8500	210	Polio-like syndrome
10	10 mo	F	HFMD	Left upper paresis, myoclonic jerk during sleep	17,300	110	Polio-like syndrome
11	3 yr	M	HFMD	Right arm paralysis	7200	8	Polio-like syndrome
12	3 yr	M	HFMD	Lethargy, ataxia, left upper limb paresis	9800	24	Polio-like syndrome
13	2 yr	F	HFMD	Left leg paresis	9700	11	Polio-like syndrome
14	3 mo	M	HFMD	Left upper limb paresis	8200	154	Polio-like syndrome
15	1 yr 7 mo	M	HFMD	Myoclonic jerk during sleep, ataxia	16,300	326	Cerebellitis
16	1 yr 8 mo	F	HFMD	Ataxia, lower limb paresis	16,950	42	Polio-like syndrome

WBC = white blood cell; CSF = cerebrospinal fluid; HFMD = hand, foot and mouth disease.

47% neutrophils, 10% monocytes, 18% lymphocytes). Aspartate transaminase was 51 IU/L. CSF WBC count was 280/μL (60% lymphocytes, 40% neutrophils), and CSF glucose was 10–20 mg/dL. One day later, there was sudden onset of facial paleness, cold and clammy extremities, tachycardia (up to 210 beats/minute), blood in the sputum and nasogastric tube, and high fever (up to 41.6°C). Consciousness deteriorated and pinpoint pupils were observed, with a sluggish light reflex. Despite resuscitation efforts, he died 4 hours after intubation. All the bacterial cultures of the blood, CSF and urine were negative.

The second fatal case (Case 8) was a 3-year-old girl brought in with oral ulcers, vesicles over the palms and soles, and fever of 3 days' duration. Her elder sister also had HFMD at that time. The patient had lower limb weakness and tremors while standing. She was taken to emergency services after an episode of upward gaze and general convulsions. WBC count was 16,000/μL (8% bands, 70% neutrophils). CSF WBC count was 310/μL (70% lymphocytes, 30% neutrophils) and CSF glucose level was 50 mg/dL. After hospitalization, her consciousness deteriorated, there were intermittent seizures, severe vomiting with coffee-ground-like substances, tachypnea and tachycardia, and she passed away 11 hours after intensive care.

All nine cases of HFMD plus polio-like syndrome continued to have limb weakness on discharge. Twenty years later, at least one male (Case 9) had sequelae of limb weakness and atrophy. As a result he was exempted from Taiwan's mandatory 2-year military service.

Discussion

The 1997 seroepidemiologic studies suggested that EV71 had circulated for years before the 1998 outbreak in Taiwan.[1,2] This study confirmed that assumption clinically. Severe EV71 cases were present in Taiwan at least as far back as 1980, with deaths and permanent handicaps known.

This was a clinical, rather than laboratory-based, study. At that time, EV71 was isolated from five cases in this series but not all of them (data not shown). Virologic laboratory technique was not as advanced and reliable in the 1980s as it is now, and it was difficult to cultivate EV71. Despite these drawbacks, we still point out the value of this study to document the 1980 EV71 infection in Taiwan. It also indicates that EV71 cases were missed or underdiagnosed in the past or in areas lacking a virologic laboratory.

In the NTUH records, two of the 16 patients with CNS complications died. The mortality rate was therefore similar to that of the 1998 EV71 epidemic (78/405) ($p = 0.73$, χ^2 test).[3] The two patients who died in 1980 also had neurologic involvement and leukocytosis, and died from sudden cardiopulmonary failure as did those cases in 1998.[4] One was suspected to have myocarditis clinically. However, there was no cardiac echo and cardiac enzyme data at that time, so myocarditis could not be confirmed and the manifestation could be brainstem encephalitis-induced cardiopulmonary failure mimicking myocarditis. This was also the initial suspected cause of death during the 1998 epidemic. Neurologic involvement was evidenced by limb weakness, upward gaze, pinpoint pupils, seizures, trismus, myoclonic jerk, and CSF pleocytosis. Cases in this study were all younger than 4 years of old, which was also the most common age group of enterovirus CNS infections in and after 1998. All the clinical features were also similar to those observed during the 1998 epidemic in Taiwan and thus indicate that the severity of EV71 infections in 1980–1981 was similar to that of the 1998 EV71 epidemic.[3–5]

Leukocytosis was commonly found in EV71 CNS cases with cardiopulmonary failure,[4] but marked elevation of band form was rarely reported. Case 7 had an elevated percentage of band form WBC, up to 23%, and this might be related to severe viral infection-related severe inflammatory response syndrome since all the bacterial cultures were negative. The CSF glucose level in this case was very low, which has also seldom been reported. The low CSF level might be related to increased intracranial pressure, which decreased blood–brain perfusion and resulted in low CSF glucose.

Now that the poliovirus has been eradicated, EV71 has come to medical attention as the most important enterovirus related to fatality and sequelae. We speculate that this is not a new situation, but that EV71 also previously caused severe disease and paralysis in vulnerable children. At the time when virologic laboratories were unavailable, and there was difficulty in differentiating EV71 infection from poliomyelitis, it would have been easy to mistake EV71 infections for poliomyelitis. This study provides some evidence for this speculation.

In conclusion, as a result of this study, it is now apparent that at least as far back as 1980, there were fatalities and handicaps in Taiwan due to EV71 infections. These 1980–1981 infections were of a similar severity to those seen in the 1998 EV71 epidemic.

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