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Deaths Among Children During an Outbreak of Hand - Foot - Mouth Disease -- Taiwan, Republic of China, February-July 1998

During February-July 1998, the Ministry of Health in Taiwan received 314 children have been hospitalized with hand, foot, mouth disease (HFMD) associated with suspected meningitis, encephalitis, or acute flaccid paralysis (AFP), and 55 have died (Table 1). Cases of HFMD have been reported from all regions of Taiwan, including Taipei City, with most reported from the central and northern regions. The first case was reported in February 1998 and the peak incidence was between May 24 and 30 (Figure 1). All 55 previously healthy children initially developed an acute illness characterized by fever, or mouth ulcers. Approximately 2-7 days (median: 3 days) after onset of illness, case-patients were hospitalized for rapid cardiopulmonary failure. In 41 case-patients, death occurred within 24 hours of hospitalization despite respiratory and cardiovascular support. Of the 55 children, 43 (78%) were aged <3 years (median age : 17 mouths; range : 3-151 mouths), 32 (58%) were male, and most lived in the central (27 [49%]) or northern (21 [38%]) regions of Taiwan (Figure 2). Reasons for seeking medical attention included respiratory distress (17 [31%]) or an altered level of consciousness (14 [25%]) . Thirteen (24%) children were comatose on admission (Table 2). Forty-four (80%) case-patients either died in the emergency department or were admitted directly to an intensive-care unit. All case-patients required intubation for respiratory distress during their illness. EV7 1 was identified in the central nervous system tissue from one autopsy (case 1) and in preliminary studies was isolated from 14 specimens from the 55 case-patients.

This report describes the clinical course of two fatal cases and presents summary findings from an ongoing clinical, epidemiologic, and laboratory investigation of the 55 deaths (Figure 1). A case was defined as refractory shock following a prodromal acute illness characterized by fever or rash that resulted in the death of a previously healthy child.

Case Reports

Case 1. On June 5, fever and headache developed in a 7-year-old girl from Taipei City. On June 6, she vomited and complained of tinnitus but was mentally alert. On June 8, she was admitted to a local hospital for suspected aseptic meningitis with a temperature of 102.6F(39.2 C), nuchal rigidity, tonsilar enlargement, and a vesicular rash on the soles of her feet. Laboratory findings included a white blood cell (WBC) count of 14,300/mm^3 (normal: 3900/mm^3-10,600/mm^3), a hemoglobin of 12.3gm/di (normal: 12-16 gm/dl), and a platelet count of 344,000/mm^3 (normal: 150,000-400,000/mm^3). There was no evidence of cerebral edema by computerized tomography scan. Following a lumbar puncture, cerebrospinal fluid (CSF) examination showed a WBC count of 153/mm^3 ([normal : 0-5/mm^3] differential, 70% neutrophils), a protein of 43 mg/dl (normal: 8-32 mg/dl), and a glucose level of 76 mg/dl (normal : 50-80 mg/dl). Approximately 10 hours after admission, the patient coughed up blood-tinged sputum and perioral cyanosis, tachypnea, and coarse rhonchi were observed. A chest radiograph revealed dense, bilateral pulmonary infiltrates. She was intubated and mechanically ventilated and developed hypotension and bradycardia. She died June 8, following repeated attempts at cardiopulmonary resuscitation.

Autopsy findings included acute encephalomyelitis, mild interstitial pneumonitis, and pulmonary hemorrhage. No histopathologic evidence of myocarditis was detected. Neurons in areas of inflammation and tissue necrosis were positive for enterovirus 71 (EV7 1) using immunohistochmical staining with a monoclonal antiEV7 1 antibody.

Case 2. On May 16,fever developed in a previously healthy 7-month-old girl from central Taiwan. On May 20, she had episodes of vomiting, respiratory distress, and a seizure. On physical examination at local hospital, the patient was tachycardic (heart rate of >200 beats per minute) and cyanotic, with gasping respirations and bilateral coarse rhonchi. She had a temperature of 102.2F (390 C). A chest radiograph showed bilateral perihilar infiltrates. Laboratory findings included peripheral WBC of 5 100/mm^3 (84% neutrophils and 15% lymphocytes); hemoglobin, 9.3 gm/dl and platelets, 84,000/mm^3. Prothrmbin time was 29.5 seconds (control: 10.8 seconds), and activated partial thromboplastin time was 45.5 seconds (normal: 20-34 seconds). Following a lumbar puncture, CSF examination revealed WBC of 205/mm^3 (94%lymphocytes), protein of 43 mg/dl, and glucose level of 90 mg/dl. She was intubated and received cardiovascular support with dobutamine and dopamine. Approximately 5 hours after admission, bradycardia and hypotension developed, and she required resuscitation. She died on May 21, following multiple bradycardiac episodes. Two blood cultures drawn on admission showed no growth of bacteris or fungi, viral cultures are pending. No autopsy was performed.

Reported by: Department of Health, The Executive Yuan, Taiwan, Republic of China.

Sources from: Taiwan Provincial Health Government; Taipei City Health Department; Kaohsiung City Health Department; Clinicians from District, District Teaching, and Regional Hospitals, Taiwan.

Editorial Note

EV7 1 is one of two etiologic agents of epidemic HFMD and has been associated with other febrile rash illnesses, aseptic meningitis, encephalitis, and a syndrome of AFP similar to that caused by poliovirus[(2)] This is the third known EV7 1 outbreak resulting in rapid clinical deterioration and death among young children , previous outbreaks primarily among children aged <3years occurred in Bulgaria during May- September 1975 (44 cases)[(3)] and in Malaysia during April-June 1997(28 cases). In Bulgaria, the outbreak was characterized by rapid onset of central nervous system disease (described as "medullary involvement")[(3)] EV7 1 was isolated from 27 of 29 fatal cases. In Malaysia, clinical presentations were similar to the case-patients in Taiwan. The outbreak involved children who had febrile illnesses, oral ulcers, or hands or feet rash followed by rapid clinical deterioration[(4)]. Most died within 24 hours of admission to area hospitals. Immunohistochemical evidence of EV71 infection was detected in central nervous system tissues from four of five case-patients. Other viruses isolated from Malaysian case-patients included echovirus 25, adenovirus, and coltivirus (L. Munn Sann, Malaysia Ministry of Health, personal communication, 1997).

The etiologies of the deaths in Malaysia and Taiwan are still under investigation. The epidemiologic (presence of concomitant HFMD outbreaks), clinical (presence of HFMD rash in most case-patients), and virologic (isolation of EV7 1 from case- patients) evidence suggest an association between EV7 1 infection and these deaths. However, further evidence is required to conclude that EV7 1 infection alone is responsible for all deaths reported from Malaysia or Taiwan. In Malaysia, various other potential causative agents were identified, and EV7 1 was isolated from only two of 11 specimens submitted to CDC. The EV7 1 isolates recovered from case-patients in Taiwan are genetically distinct from the strains from patients in Malaysia. Case- control studies are under way in Taiwan to further assess the associations between EV7 1 infections and rapid death and to identify other potential factors or cofactors (e.g. toxins, medicines, or environmental exposures) that might contribute to the disease process. Laboratory studies also are under way to further characterize the viral agents recovered, and clinical review of suspected cases is in progress.

References

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Table 1. Residence Distribution of Hospitalized Hand-Foot-Mouth Disease Cases in Taiwan, February-July 1998, Taiwan

County	male	Female	Total	No. death
Keelung C.	2	0	2	0
Taipei C.	23	29	52	4
Taipei Co.	32	20	52	5
Taoyuan Co.	18	10	28	10
Hsinchu Co.	4	2	6	0
Hsinchu C.	6	2	8	2
Miaoli Co.	1	4	5	2
Taichung Co.	18	9	27	6
Taichung C.	6	8	14	1
Nantou Co.	9	3	12	7
Changhua Co.	17	15	32	9
Yunlin Co.	1	4	5	2
Chiayi Co.	2	3	5	0
Chiayi C.	0	1	1	1
Tainan Co.	7	3	10	2
Tainan C.	3	2	5	1
Kaohsiung C.	11	7	18	0
Kaohsiung Co	4	3	7	0
Pingtung Co.	4	5	9	2
Ilan Co	2	0	2	1
Hualien Co	0	3	3	0
Taitung Co	5	4	9	0
Unknow	1	0	1	0
Total	176	138	313	55

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Table 2. Number and Percentage of Children* with Selected Signs and Symptoms Who Died During an Outbreak of Hand-Foot-Mouth Disease — Taiwan, Republic of China, February-July, 1998

Characteristic	No.	(%)
Symptoms		
Fever	53	(96)
Vomiting	35	(64)
Poor feeding	27	(49)
Dyspnea	23	(42)
Increased sleepiness	17	(31)
Cough	14	(26)
Irritability	11	(20)
Generalized weakness	14	(26)
Diarrhea	7	(13)
Rhinorrhea	6	(11)
Signs		
Skin/Mucous membranes		
Hand or foot rash	32	(58)
Mouth ulcers	28	(51)
Herpangina	8	(15)
Respiratory		
Rales	26	(48)
Rhonchi	21	(39)
Retractions	17	(32)
Cardiac		
Central cyanosis	28	(52)
Peripheral cyanosis	22	(41)
Neurologic		
Somnolent or lethargic	24	(44)
Comatose	13	(24)
Alert	9	(17)
Nuchal rigidity	7	(13)
Seizure	7	(13)
Focal paralysis or weakness	1	(2)

*N=55

Figure 1. Epidemic Curve of Hospitalized Hand-Foot-Mouth Disease in Taiwan, February-July, 1998

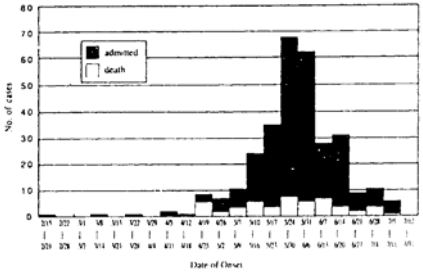

Figure 2. Residence Distribution of fatal Hand-Foot-Mouth Disease Case in Taiwan, February-July, 1998