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

During April-July 1998, the Ministry of Health in Taiwan received approximately 90,000 reports of hand, foot, and mouth disease (HFMD) among young children based on passive surveillance from sentinel physicians. Approximately 320 children have been hospitalized with HFMD associated with suspected meningitis, encephalitis, or acute flaccid paralysis (AFP), and at least 55 have died. 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.

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. Cases of HFMD have been reported from all regions of Taiwan, including Taipei City, with most reported from the central and northern regions.

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 102.6°F (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/mm³ (normal: 5,000-10,000/mm³), a hemoglobin of 12.3 gm/dL (normal: 12-16 gm/dL), and a platelet count of 344,000/mm³ (normal: 150,000-400,000/mm³). There was no evidence of cerebral edema by computed tomography scan. Following a lumbar puncture, cerebrospinal fluid (CSF) examination showed a WBC count of 153/mm³ ([normal: 0-5/mm³]; 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 cardio-pulmonary 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 (EV71) using immunohistochemical staining with a monoclonal anti-EV71 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 a 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 102.2°F (39.0°C). A chest radiograph showed bilateral perihilar infiltrates. Laboratory findings included peripheral WBC of 5100/mm³ (84% neutrophils and 13% lymphocytes); hemoglobin, 9.3 gm/dL; and platelets, 84,000/mm³. Prothrombin time was 29.5 seconds (control: 10.8 seconds), and activated partial thromboplastin time was 45.3 seconds (normal: 20-34 seconds). Following a lumbar puncture, CSF examination revealed WBC of 205/mm³ (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 bradycardic episodes. Two blood cultures drawn on admission showed no growth of bacteria or fungi; viral cultures are pending. No autopsy was performed.

SUMMARY FINDINGS

All 55 previously healthy children initially developed an acute illness characterized by fever, or rash, 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 months; range: 3-151 months), 32 (58%) were male, and most lived in the central (27 [49%]) or northern (21 [38%]) regions of Taiwan. 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. Fourty-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. The last child who died was admitted on July 8.

EV71 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. In addition, one specimen was positive for EV71 by polymerase chain reaction.

**Reported by:** Ministry of Health, The Executive Yuan, Taiwan, Republic of China; clinicians and scientists from district, district teaching, and regional hospitals, Taiwan; Kaohsiung City Health Dept, Kaohsiung; Taipei City Health Dept, Taipei; Dept of Health, Taiwan Provincial Government; Academia Sinica. Infectious Disease Pathology Activity, Respiratory and Enteric Viruses Br, Div of Viral and Rickettsial Diseases, National Center for Infectious Diseases; Div of Applied Public Health Training, Epidemiology Program Office; and EIS officers, CDC.

**Editorial Note:** EV71 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.1,2 This is the third known EV71 outbreak resulting in rapid clinical deterioration and death among young children; previous outbreaks primarily among children aged <3 years 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; EV71 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 EV71 from case-patients) evidence suggest an association between EV71 infection and these deaths. However, further evidence is required to conclude that EV71 infection alone is responsible for all deaths reported from Malaysia or Taiwan. In Malaysia, various other potential causative agents were identified, and EV71 was isolated from only two of 11 specimens submitted to CDC. The EV71 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 EV71 infections and rapid death and to identify other potential factors or cofactors (eg, 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.

Clinicians and health-care providers who encounter similar deaths among children should report cases through their local ministry of health to CDC’s Respiratory and Enteric Viruses Branch, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases; telephone (404) 639-3596.

**MMWR.** 1998;47:629-632. 1 table, 1 figure omitted.

**REFERENCES**