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AN EPIDEMIC OF ENTEROVIRUS 71 INFECTION IN TAIWAN

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ABSTRACT

Background Enteroviruses can cause outbreaks of hand-foot-and-mouth disease (characterized by vesicular lesions on the hands, feet, and oral mucosa) or herpangina, usually without life-threatening manifestations. In 1998 an epidemic of enterovirus 71 infection caused hand-foot-and-mouth disease and herpangina in thousands of people in Taiwan, some of whom died.

Methods We assessed the epidemiologic aspects of this outbreak. Cases of hand-foot-and-mouth disease or herpangina in ambulatory patients were reported to the Taiwan Department of Health by a mean of 818 sentinel physicians. Severe cases in hospitalized patients were reported by 40 medical centers and regional hospitals. Viruses were isolated by 10 hospital laboratories and the department of health.

Results The sentinel physicians reported 129,106 cases of hand-foot-and-mouth disease or herpangina in two waves of the epidemic, which probably represents less than 10 percent of the estimated total number of cases. There were 405 patients with severe disease, most of whom were five years old or younger; severe disease was seen in all regions of the island. Complications included encephalitis, aseptic meningitis, pulmonary edema or hemorrhage, acute flaccid paralysis, and myocarditis. Seventy-eight patients died, 71 of whom (91 percent) were five years of age or younger. Of the patients who died, 65 (83 percent) had pulmonary edema or pulmonary hemorrhage. Among patients from whom a virus was isolated, enterovirus 71 was present in 48.7 percent of outpatients with uncomplicated hand-foot-and-mouth disease or herpangina, 75 percent of hospitalized patients who survived, and 92 percent of patients who died.

Conclusions Although several enteroviruses were circulating in Taiwan during the 1998 epidemic, enterovirus 71 infection was associated with most of the serious clinical manifestations and with nearly all the deaths. Most of those who died were young, and the majority died of pulmonary edema and pulmonary hemorrhage. (N Engl J Med 1999;341:929-35.)

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SINCE it was first recognized in California in 1969,¹ enterovirus 71 infection has been reported in at least 12 small and large outbreaks throughout the world.² Like other types of enteroviral infections, enterovirus 71 infection may be asymptomatic or may cause diarrhea; rashes; vesicular lesions on the hands, feet, and oral mucosa (hand-foot-and-mouth disease); herpangina; aseptic meningitis; encephalitis; myocarditis; or some combination of these conditions. Although hand-foot-and-mouth disease is usually considered a benign disease without neurologic complications, Ishimaru et al.³ described two outbreaks in Japan of over 1000 cases with frequent involvement of the central nervous system. Enterovirus 71 has also been associated with several clinical syndromes: acute flaccid paralysis mimicking paralytic poliomyelitis, bulbar and brainstem encephalitis, the Guillain-Barré syndrome,^{4,5} and rapidly fatal pulmonary edema and hemorrhage.⁶ Outbreaks of enterovirus 71 infection that caused more than 20 deaths occurred in Bulgaria in 1975,⁷ Hungary in 1978,⁸ Malaysia in 1997,⁹ and Taiwan in 1998.⁹ In Malaysia and Taiwan, most of the patients who died had hand-foot-and-mouth disease or herpangina and died of pulmonary edema and hemorrhage or after the onset of brain-stem encephalitis.^{6,10}

Vaccination with the Sabin vaccine is the only preventive public health measure taken against enteroviruses in Taiwan.¹¹ Sporadic outbreaks of various types of enteroviral infection occur almost yearly, but an epidemic of the proportion of that of 1998 is un-

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precedented. Because enterovirus 71 can cause serious complications and death, we wanted to examine the 1998 outbreak in depth. Despite the absence of a national surveillance system for enteroviruses other than polioviruses, we sought to reconstruct the epidemiology of the outbreak using clinical reports from the national sentinel-physician reporting system, reports from hospitals of cases of severe hand-foot-and-mouth disease, and reports from hospital laboratories of the isolation of enteroviruses.

METHODS

Epidemic Surveillance

Taiwan has a population of approximately 21,178,000. The main island is divided into 22 cities and counties. These are grouped into four regions with the following constituent cities and counties: the northern region (Taipei, Keelung, Hsinchu, Taipei County, Taoyuan County, and Hsinchu County), the central region (Taichung, Miaoli County, Taichung County, Nantou County, and Changhua County), the southern region (Kaohsiung, Tainan, Chiayi, Yunlin County, Chiayi County, Tainan County, Kaohsiung County, and Pingtung County), and the eastern region (Ilan County, Hualien County, and Taitung County). The national department of health is the highest public health authority. Each city or county has a health bureau and various numbers of health stations. There are 9427 pediatricians, internists, general practitioners, family physicians, and ear, nose, and throat specialists on the island.

The system of reporting cases to the department of health during the 1998 epidemic has been described previously.¹² This department enlists 850 sentinel physicians from all 22 cities and counties. Each week they report suspected cases of infectious diseases among their ambulatory patients. Diseases such as influenza-like respiratory tract infections, acute diarrhea, chickenpox, measles, and pertussis were reportable before the 1998 epidemic but not hand-foot-and-mouth disease or herpangina. Because of the perception that cases of hand-foot-and-mouth disease and herpangina were becoming prevalent, beginning March 3, 1998, they were included in reports. The total numbers of sentinel physicians in 1998 in the northern, central, southern, and eastern regions were 258, 211, 296, and 85, respectively. The mean number of physicians reporting during 1998 was 818, which is 8.7 percent of all primary physicians.

Patients who were hospitalized for hand-foot-and-mouth disease or herpangina were reported to the department of health by Taiwan's 14 teaching hospitals and 54 regional hospitals, each with a capacity of at least 300 to 1000 beds. Forty hospitals reported one or more cases, submitted their records to the department of health for analysis, and specified whether the cases were severe.

Clinical Definitions

Patients with hand-foot-and-mouth disease had vesicular lesions on their hands, feet, mouth, and frequently, buttocks. Lesions in the mouth were often ulcerated. Herpangina is a vesicular enanthem of the fauces and soft palate, often accompanied by fever, sore throat, and pain on swallowing. Most patients with these manifestations alone were seen only as outpatients.

Patients were hospitalized if in addition to hand-foot-and-mouth disease or herpangina they had signs or symptoms indicating more serious illness. These included high fever (temperature of at least 38°C), vomiting, tachypnea, and indications of neurologic complications (encephalitis, aseptic meningitis, or acute flaccid paralysis) or cardiopulmonary complications (pulmonary edema, pulmonary hemorrhage, or myocarditis). Patients with any of these complications were considered to have severe cases.

Encephalitis was characterized by a disturbance in the level of consciousness, such as lethargy, drowsiness, or coma. Aseptic

meningitis was characterized by headache, meningeal signs, and mononuclear pleocytosis. Pulmonary edema was characterized by respiratory distress, tachypnea, tachycardia, frothy sputum, and rapidly progressing, patchy, diffuse pulmonary infiltrates and congestion on a chest film. Pulmonary hemorrhage was defined as bleeding during tracheal aspiration. Acute flaccid paralysis was defined as the acute onset of paresis or paralysis of one or more skeletal-muscle groups, usually of one or more limbs. Myocarditis was characterized by evidence of decreased contractility on echocardiography, arrhythmia, an enlarged heart, and elevations in cardiac enzymes that are markers for cardiac damage.

Isolation and Identification of Enteroviruses

Viral laboratories were located in 10 hospitals and in the department of health. Clinical specimens were often sent from smaller to larger centers for identification. Detailed data were available from two medical centers (Chang Gung Children's Hospital, a 3875-bed hospital in Lin Ko, near Taipei in the north, and Cheng Kung University Medical Center, an 839-bed hospital located in southern Taiwan) and are reported here. Specimens from these two hospitals consisted of throat swabs, stool, cerebrospinal fluid, and in rare cases, blood samples. They were from inpatients or outpatients suspected of having enteroviral infection. Most of the patients had hand-foot-and-mouth disease or herpangina, with or without complications.

The methods used to identify enteroviruses differed in the various laboratories. Monolayers of Vero, rhabdomyosarcoma, and MRC-5 cells were most commonly used for viral isolation. An immunofluorescence assay was used for identification. Cultures that showed a cytopathic effect characteristic of enteroviruses were screened for enteroviruses with use of an enterovirus screening set (catalog number 3365, Chemicon International, Temecula, Calif.), which included pan-enterovirus, coxsackievirus B, echovirus, and poliovirus blends. Coxsackievirus A16 and enterovirus 71 were identified with the use of monoclonal antibodies 3323 and 3324. The former can be used to identify either virus, whereas the latter is specific for enterovirus 71. The identification of enterovirus 71 was confirmed by a neutralization test with a polyclonal rabbit antiserum against enterovirus 71, which had been prepared during a previous outbreak in 1986 (provided by Kuei-Hsiang Lin, Kaohsiung Medical College, Kaohsiung, Taiwan), or a rabbit anti-enterovirus 71 serum (kindly provided by H. Shimuzi, Laboratory of Enteroviruses, National Institute of Infectious Diseases, Tokyo, Japan). Final enterovirus typing was done by neutralization testing with the use of polyclonal antiserum (American Type Culture Collection, Rockville, Md.).

Statistical Analysis

Differences in frequencies or proportions were analyzed with use of the χ^2 test with Yates' correction. Relative risks were calculated according to standard methods.

RESULTS

Cases

Figure 1 shows the number of cases of hand-foot-and-mouth disease and herpangina reported by sentinel physicians from the week of March 29, 1998, through the week of December 27, 1998. Beginning with a handful of cases, the number peaked at 15,758 cases during the week of June 7. The peak was reached a week earlier in the central region and a week and half later in the southern region. A total of 98,004 cases were reported between March 29 and July 25, during the first wave of the epidemic. The first wave encompassed all four regions of Taiwan. The second wave was largely limited to the

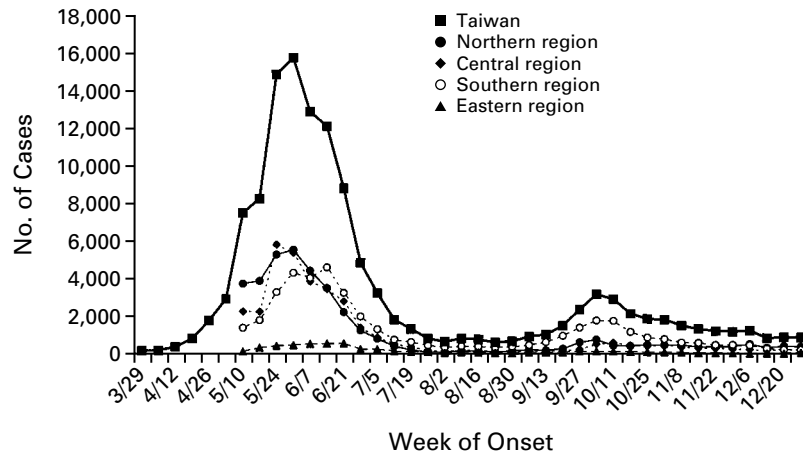


Figure 1. Number of Cases of Hand-Foot-and-Mouth Disease and Herpangina Reported in Taiwan as a Whole and in Each of Its Four Regions by Sentinel Physicians from the Week of March 29, 1998, through the Week of December 27, 1998. The total number of cases was 129,106.

TABLE 1. ENTEROVIRUSES ISOLATED FROM INPATIENTS AND OUTPATIENTS AT TWO MEDICAL CENTERS IN TAIWAN FROM MAY TO DECEMBER 1998.*

ENTEROVIRUS ISOLATED	TOTAL No. OF PATIENTS (N=782)	TYPE OF PATIENT		RELATIVE RISK (95% CI)†	P VALUE
		INPATIENT (N=669)	OUTPATIENT (N=113)		
		number (percent)			
Enterovirus 71	469	414 (61.9)	55 (48.7)	1.27 (1.04–1.55)	0.01
Coxsackievirus A16	226	184 (27.5)	42 (37.2)	0.73 (0.56–0.95)	0.04
Other	87	71 (10.6)	16 (14.2)	0.75 (0.45–1.24)	0.90

*The data were obtained from Chang Gung Medical Center and Cheng Kung University Medical Center.

†Values are the relative risk of isolating the virus from inpatients as compared with outpatients. CI denotes confidence interval.

southern region, lasted from September 6 to December 12, and included 24,166 cases. It peaked at 3177 cases during the week of October 4. The total number of cases reported during the two waves from March 29 through the end of the year was 129,106.

Isolates

Table 1 shows the data on the enteroviruses isolated from outpatients and inpatients suspected of having uncomplicated or severe enteroviral infection at two large medical centers, one in the north and one in the south. From May through December 1998, isolates of enteroviruses were obtained from 782 patients, with the greatest number — 371 iso-

lates — obtained in June (data not shown). The frequency of isolates of enterovirus 71, coxsackievirus A16, and other enteroviruses varied significantly between outpatients and inpatients ($P < 0.05$ by the χ^2 test). The relative risk of an enterovirus 71 isolate was higher among inpatients than outpatients, whereas the relative risk of a coxsackievirus A16 isolate was higher among outpatients (Table 1). Other enteroviruses isolated were untyped viruses; coxsackievirus B1, B2, B3, and B5; echovirus 6, 7, 11, 22, and 27; and poliovirus (Sabin-vaccine strain). These data suggest that in addition to enterovirus 71, coxsackievirus A16 and perhaps other enteroviruses were circulating in the community, but that enterovirus 71 was more prevalent among severely ill, hospitalized patients.

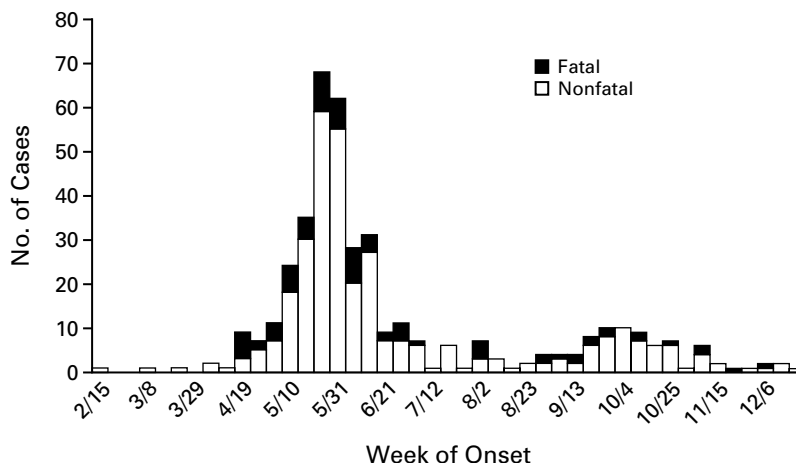


Figure 2. Number of Cases and Outcome of Severe Hand-Foot-and-Mouth Disease and Herpangina in Taiwan from the Week of February 15, 1998, through the Week of December 20, 1998. A total of 78 patients died, and 327 survived.

That the isolation of these viruses was associated with true infection was occasionally confirmed by the demonstration of specific antibodies. For example, eight patients who died at Chang Gung Children's Hospital and from whom enterovirus 71 was isolated had specific neutralizing-antibody titers greater than 1:16 (Chang L-Y, Shih S-R: personal communication).

Incidence and Severity of Infection

The number of cases of severe hand-foot-and-mouth disease and herpangina and the number that were fatal are shown in Figure 2. The peak incidence occurred in early June, around the same time as the peak in uncomplicated cases of hand-foot-and-mouth disease (Fig. 1). A smaller peak is evident in October, representing, as in the case of uncomplicated hand-foot-and-mouth disease, cases from southern Taiwan. There were 405 severe cases, 78 of which were fatal. The smaller number of cases during the second peak was largely restricted to the southern region, which includes the second largest city in Taiwan, Kaohsiung.

Table 2 shows the incidence of severe cases and case fatality rates in the four regions of Taiwan. The number at risk in each region is given. The northern region, which includes Taipei, had the largest number of severe cases. The incidences were not significantly different among the regions. The cases were evenly distributed relative to the population of each region. However, the case fatality rates differed significantly among the regions. The central region, which includes the city of Changhua, had the highest case fatality rate — 31.0 percent. The lowest rate — 7.7 percent — was in the eastern region, the least populated region.

TABLE 2. INCIDENCE OF CASES OF SEVERE HAND-FOOT-AND-MOUTH DISEASE AND HERPANGINA AND CASE FATALITY RATES, ACCORDING TO THE GEOGRAPHIC REGION OF TAIWAN.

REGION OF TAIWAN	NO. AT RISK*	NO. OF CASES	INCIDENCE†	NO. OF DEATHS	CASE FATALITY RATE‡
			no. of cases/ 1000		percent
Northern	2,012,802	167	0.083	29	17.4
Central	1,293,462	100	0.077	31	31.0
Southern	1,342,779	125	0.093	17	13.6
Eastern	234,397	13	0.055	1	7.7
Total	4,883,440	405	0.083	78	19.3

*The population at risk consists of children under 15 years of age.

†P=0.2 for the differences among the regions.

‡P<0.001 for the differences among the regions.

Children less than one year old were most likely to be hospitalized. Most of those hospitalized (314 of 393 [80 percent]) were five years of age or younger.

Of the 78 patients who died, 71 (91 percent) were five years of age or younger. The case fatality rate was significantly higher among children less than one year old than among those who were older. The death rate among children who were one year old or younger was therefore investigated in greater detail. There were 6 deaths among the 38 children who were 6 months of age or younger (16 percent) and 25 deaths among the 58 children who were 7 to 12 months of age (43 percent, P<0.01). Thus, there were fewer deaths in the youngest age group.

TABLE 3. CLINICAL COMPLICATIONS IN 96 PATIENTS WITH SEVERE ENTEROVIRAL INFECTION.

COMPLICATIONS*	NO. OF PATIENTS (%)	ENTEROVIRUS 71 (N=78)	number of isolates	
			COXSACKIEVIRUS A16 OR A24, COXSACKIEVIRUS B5, OR ECHOVIRUS 6 OR 7 (N=9)	OTHER ENTEROVIRUSES (N=9)
Encephalitis	39 (41)	30	5	4
Encephalitis and pulmonary edema or hemorrhage	25 (26)	25	0	0
Aseptic meningitis	11 (11)	5	1	5
Pulmonary edema or hemorrhage	10 (10)	9	1	0
Myocarditis and encephalitis	2 (2)	2	0	0
Myocarditis	1 (1)	1	0	0
Acute flaccid paralysis and encephalitis	1 (1)	1	0	0
Acute flaccid paralysis	1 (1)	1	0	0
Other	6 (6)	4	2	0

*The categories of complications are mutually exclusive.

Clinical Complications

Table 3 shows the clinical complications and types of viruses isolated from 96 patients with severe infections. Only one virus was isolated from each patient. Seventy-two patients had hand-foot-and-mouth disease (75 percent), and 11 had herpangina (11 percent) (data not shown). Each complication or combination of complications shown in Table 3 is mutually exclusive. The complications are listed in decreasing order of frequency. The overall frequency of enterovirus 71 isolates in these patients was 81 percent. Enterovirus 71 was isolated from all 25 patients with encephalitis and pulmonary edema or hemorrhage. Enteroviruses other than enterovirus 71 were more frequently isolated when the complication was either encephalitis (9 of 39 [23 percent]) or aseptic meningitis (6 of 11 [55 percent]). There was a significant difference in the frequency of enterovirus 71 isolates between patients with pulmonary edema or hemorrhage (34 of 35 [97 percent]) and patients with aseptic meningitis (5 of 11 [45 percent], $P<0.01$).

Of the 78 patients who died, the results of viral cultures were available for 68. Thirty-one patients had negative cultures, and 37 had positive cultures. Altogether, 65 patients (83 percent) died of pulmonary edema or hemorrhage, making this the most frequent lethal complication. Most were three years old or younger and died within one to two days after admission. Except for one patient with coxsackievirus B5, all patients who died of pulmonary edema or hemorrhage were infected with enterovirus 71 (32 of 33 [97 percent]). Of the 37 isolates obtained from patients who died, 34 (92 percent) were enterovirus 71. Of 59 isolates obtained from patients with

severe infections who survived, 44 (75 percent) were enterovirus 71. Taken together, the data suggest that the frequency of enterovirus 71 isolates increased as the severity and lethality of complications increased, ranging from aseptic meningitis to encephalitis, pulmonary edema or hemorrhage, and encephalitis and pulmonary edema or hemorrhage.

DISCUSSION

Between April and December 1998, thousands of people throughout Taiwan were infected by a number of enteroviruses, including enterovirus 71. Before that time, outbreaks of enterovirus 71 infection had occurred in Taiwan in 1980 and 1986. In 1980, there was an outbreak in Taipei involving approximately 20 children who were three or four years old and who had poliomyelitis-like flaccid paresis associated with hand-foot-and-mouth disease or herpangina; none of the children died. Enterovirus 71 was isolated from five patients (Lee C-Y: personal communication). In 1986 enterovirus 71 was isolated from patients with hand-foot-and-mouth disease or herpangina in Kaohsiung (Hwang K-P: personal communication).

The state of immunity of the Taiwanese population to enterovirus 71 before 1999 was unknown. Preliminary seroepidemiologic studies conducted early in 1999 with serum obtained from subjects before and after the epidemic showed that about half the adult population in northern Taiwan had antibodies against enterovirus 71 before the epidemic. The susceptible population during the epidemic primarily consisted of young children (Chang L-Y: personal communication).

There are still many unresolved questions about

this epidemic. Why did enteroviruses that were fairly prevalent suddenly cause such a large epidemic, particularly given the apparent immunity of most of the population? What was the precise mechanism of transmission? The rapidity of spread suggests a respiratory or droplet mechanism, but precise data are not available. Was a particular strain of enterovirus 71 imported that was unusually virulent? Many groups in Taiwan are studying the molecular genetics of strains involved in the epidemic, but definite conclusions are not yet available.

The primary clinical marker of enteroviral infection during this epidemic was hand-foot-and-mouth disease or herpangina. The 129,106 cases reported by sentinel physicians represent only a fraction of the total. If these physicians, representing 8.7 percent of all primary physicians on the island, saw 8.7 percent of outpatients, the true number of cases of hand-foot-and-mouth disease or herpangina in Taiwan would be 1,483,977. The vast majority of patients were ambulatory, had self-limited infections, and required little or no medical attention. Hand-foot-and-mouth disease or herpangina is caused by coxsackievirus A and other enteroviruses, including enterovirus 71.^{2,13} The viruses isolated by two major diagnostic laboratories, which processed samples from inpatients and outpatients, suggest that in addition to enterovirus 71, at least coxsackievirus A16 was also active during the epidemic.

Hospitalized patients with severe disease represented a small but important proportion of those infected and were uniformly distributed throughout the island. The case fatality rate was highest in the central region. The reasons for this are obscure. There were no known risk factors for severe or fatal infection, although many were considered. Severe cases occurred primarily in children who were less than 15 years old. The case fatality rate was highest among children who were 7 to 12 months old.

Ever since its recognition, enterovirus 71 has been associated with hand-foot-and-mouth disease as well as a variety of serious, often life-threatening, syndromes. But hand-foot-and-mouth disease is not an invariable sequela of enterovirus 71 infection. Almost all the deaths during the 1975 epidemic in Bulgaria were in infants given a diagnosis of "bulbar encephalitis" that was initially thought to be poliomyelitis.⁷ Hand-foot-and-mouth disease, herpangina, and pulmonary edema or hemorrhage were not seen during the epidemics in Bulgaria and Hungary.^{7,8}

Landry et al.² described a case of enterovirus 71 infection in a four-year-old girl with signs "suggestive of noncardiogenic pulmonary edema," who died of disseminated intravascular coagulation. The four patients who died of encephalomyelitis and pulmonary edema due to enterovirus 71 in the Malaysian epidemic more closely resembled the typical patients in the Taiwan epidemic. They were young, died soon

after the onset of illness, and had few organ systems involved.¹⁴ Acute pulmonary edema or hemorrhage was the predominant, and often the only, sign at presentation. At autopsy, the patient described by Landry et al.,² the four Malaysian patients,¹⁴ and the patient described by Chang et al.⁶ (who was part of the 1998 Taiwan epidemic) all had lesions of the central nervous system, including the pons, medulla, and spinal cord. Although the pathogenesis of pulmonary edema and hemorrhage in enteroviral infections is not well understood, Chang et al. suggested that lesions of the spinal cord and medulla disturb the autonomic nervous system and lead to neurogenic pulmonary edema.⁶ No evidence of viral infection was found in the lungs of their patient. This theory is consistent with the basic neurotropism of enteroviruses and the studies of pulmonary edema in patients with bulbar poliomyelitis.¹⁵ Baker studied 10 such patients from a series of 150 patients with bulbar poliomyelitis and found that all 10 had involvement of the dorsal nuclei of the vagus and the vasomotor (medial reticular) nuclei in the medulla oblongata.¹⁵

An alternative theory is that systemic viral sepsis leads to the capillary leak syndrome. This possibility could account for the hyperglycemia, metabolic acidosis, elevated levels of cytokines, and shock seen in affected patients. A third possibility is hypersensitivity or immunopathology related to superinfection by enterovirus 71 in a patient sensitized by a concurrently active enterovirus, such as the related coxsackievirus A16. The dengue shock and hemorrhagic syndrome is endemic in Asia and is thought to be due to superinfection with one dengue virus in a patient already infected with another type of dengue virus.¹⁶

In conclusion, our analysis of the 1998 Taiwan epidemic suggests that clinicians and epidemiologists throughout the world should be aware of the capacity of enterovirus 71 to cause large epidemics as well as sporadic cases. The infection may be fatal in young children.

APPENDIX

The following investigators and institutions also participated in the Taiwan Enterovirus Epidemic Working Group: Tzou-Yien Lin, Chang Gung Children's Hospital; Chin-Yun Lee, College of Medicine, National Taiwan University; Wen-Tsong Chao, Changhua Christian Hospital; Ching-Shiang Chi, Taichung Veterans General Hospital; Ching-Chuan Liu, Cheng Kung Medical College; Kao-Pin Hwang, Kaohsiung Medical College Hospital; and Mei-Shang Ho, Institute of Biomedical Science, Academia Sinica.

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