The 1998 Enterovirus 71 Outbreak in Taiwan: Pathogenesis and Management

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The most recently discovered enterovirus, enterovirus 71 (EV71), is neurotropic and may cause severe disease and sudden death in children. In 1998, a large outbreak of enterovirus infection occurred in Taiwan that resulted in 405 severe cases in children and 78 deaths. Of the 78 children who died, 71 (91%) were 5 years old. EV71 was the primary agent in fatal cases of infection. Most of these patients died within 1–2 days of admission to the hospital. We hypothesize that EV71 directly attacks the central nervous system and causes neurogenic pulmonary edema and cardiac decompen-sation through the mechanism of sympathetic hyperactivity and inflammatory responses. Early recognition of risk factors and intensive care are crucial to successful treatment of this fulminant infection. After poliovirus is eradicated, EV71 will become the most important enterovirus that affects children, and development of a vaccine may be the only effective measure against it.

The classic enteroviruses include poliovirus (3 serotypes), coxsackievirus group A (23 serotypes), coxsackievirus group B (6 serotypes), and echoviruses (31 serotypes). Since the 1960s, 4 new enteroviruses have been discovered, which are designated by serial number only (enteroviruses 68–71).

Enterovirus usually causes mild and self-limited infections in children (e.g., viral exanthema, herpangina, hand-foot-and-mouth disease [HFMD], or aseptic meningitis). The newly discovered enterovirus 71 (EV71) is characterized by neurotropism and may cause severe disease or sudden death. EV71 was first isolated from a child with aseptic meningitis in 1969 [1]. Since then, EV71 has been found in many parts of the world. There are 2 patterns of outbreak. One involves sporadic cases or small outbreaks with occasional mortality; this has occurred in the United States, Sweden, Japan, and Australia [2–5]. The other pattern involves an epidemic outbreak with high mortality, which occurred in Bulgaria in 1975 (44 deaths) [6], in Hungary in 1978 (47 deaths) [7], in Malaysia in 1997 (at least 31 deaths) [8], and in Taiwan in 1998 (78 deaths) [9]. In this article, we describe the EV71 outbreak in Taiwan in 1998 and discuss the pathogenesis and management of the disease and future perspectives on treatment and prevention.

1998 EPIDEMIC IN TAIWAN

Since 1988, the Department of Health in Taiwan has enlisted 850 sentinel physicians (8% of all primary care physicians) from all 22 cities and counties to assist in surveillance for important infectious diseases. Each week, these physicians submit clinical reports of suspected cases of infectious disease. Through this system, the health care authority became aware that the number of reported cases of HFMD and herpangina had increased beginning 3 March 1998. The first and biggest wave of the epidemic peaked at 15,758 cases during the week of 7 June. Cases were seen in all 4 regions in-Taiwan. The second and smaller wave was largely lim-
Table 1. No. of patients with severe, culture-proven enterovirus infection who exhibited various clinical syndromes during the 1998 enterovirus 71 (EV71) epidemic in Taiwan.

<table>
<thead>
<tr>
<th>Clinical syndrome</th>
<th>All patients (n = 96)</th>
<th>Patients infected with EV71 (n = 78)</th>
<th>Patients infected with other enteroviruses (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalitis</td>
<td>67</td>
<td>58</td>
<td>9</td>
</tr>
<tr>
<td>Alone</td>
<td>39</td>
<td>30</td>
<td>9</td>
</tr>
<tr>
<td>With pulmonary edema</td>
<td>25</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>With myocarditis</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>With acute flaccid paralysis</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Aseptic meningitis</td>
<td>11</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Pulmonary edema/hemorrhage&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Acute flaccid paralysis</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

NOTE. Adapted from [9], with permission.

<sup>a</sup> Without encephalitis.

itted to the southern region. This wave peaked at 3177 cases during the week of 4 October. The total number of cases reported from 29 March through the end of 1998 was 129,106.

During the epidemic, 405 severe cases of enterovirus infection occurred in children, 78 (19%) of which were fatal. Severe cases involved pulmonary edema; cardiac insufficiency; and neurologic complications, such as encephalitis, meningitis, and polio-like syndrome. The peak incidence occurred in early June, at approximately the same time as the peak in uncomplicated cases of HFMD and herpangina. Children <1 year old were most likely to be hospitalized. Of the 78 patients who died, 71 (91%) were ≤5 years old, and 65 (83%) had pulmonary edema. Most of these patients died of fulminant disease within 1–2 days after admission to the hospital.

Among the 405 patients with severe cases, 96 patients had positive results of viral culture, and 78 (81%) of these 96 patients had samples that yielded EV71 [9]. Among patients with severe EV71 infection, the majority (67 [86%] of 78 patients) had encephalitis as a complication of infection; pulmonary edema, alone or in conjunction with encephalitis, was the second most common complication (35 [45%] of 78 patients) (table 1).

Huang et al. [10] described 3 neurologic syndromes that were seen during the 1998 EV71 outbreak in Taiwan: aseptic meningitis, acute flaccid paralysis, and rhombencephalitis (brain-stem encephalitis). In 90% of the patients with neurologic involvement, rhombencephalitis was the primary manifestation. The clinical spectrum of rhombencephalitis is shown in table 2.

**VIROLOGIC FEATURES**

The results of viral cultures from throat or rectal swabs were available for 68 of the 78 patients who died during the 1998 EV71 outbreak in Taiwan. Thirty-seven of these patients had positive results of viral culture (table 3). Cultures for 34 (92%) of those 37 patients yielded EV71 isolates. Furthermore, 418 strains of enterovirus were isolated in Chang Gung Children’s Hospital (Taoyuan, Taiwan) during the outbreak (table 4); 177 strains (42%) were EV71, 73 strains (17%) were coxsackievirus A16, and 168 strains (40%) were other enteroviruses. All the enterovirus isolates from patients at Chang Gung Children’s Hospital with fatal cases of infection were EV71. EV71 was the primary agent in fatal cases, but many other enteroviruses co-circulated during the outbreak.

In our experience at Chang Gung Children’s Hospital during the 1998 epidemic, the rate of EV71 isolation from throat swabs was 90% (105 of 117 samples), and the rate of EV71 isolation from rectal swabs was 32% (37 of 117 samples) [11]. This implies that the fecal-oral route and respiratory droplets are both possible routes of transmission. Of the 38 samples of CSF submitted for viral culture, only 1 CSF specimen taken during autopsy yielded positive results. Like poliovirus, EV71 is difficult to isolate from CSF specimens.

To understand the virologic source of mortality, Shih et al. [12], from Chang Gung Children’s Hospital, analyzed the nucleotide sequence of VP1, which is important to serotypic specificity, and the 5′ noncoding region (NCR), which is important to replication efficiency. Phylogenetic analysis of both VP1 and the 5′-NCR of 9 EV71 isolates from patients with fatal cases and 7 isolates from patients with uncomplicated HFMD showed that all but 1 isolate were of genotype C. The single distinct isolate (TW-1998-1743), isolated from a patient with uncomplicated HFMD, belonged to genotype B, as did 1 strain (TW-1986-253) isolated from a patient in southern Taiwan in 1986 [12]. Shimizu
Table 2. Clinical spectrum in 37 patients with enterovirus 71 rhombencephalitis during the 1998 epidemic in Taiwan.

<table>
<thead>
<tr>
<th>Grade of disease</th>
<th>No. (%) of patients</th>
<th>Clinical manifestations</th>
<th>Outcome and condition at 6 months’ follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>20 (54)</td>
<td>Myoclonic jerk with tremor/ataxia</td>
<td>All patients recovered, except 1, who had persistent myoclonus</td>
</tr>
<tr>
<td>II</td>
<td>10 (27)</td>
<td>Myoclonic jerk with cranial-nerve involvement</td>
<td>Neurologic sequelae in 2 patients</td>
</tr>
<tr>
<td>III</td>
<td>7 (19)</td>
<td>Transient myoclonus followed by rapid onset of respiratory distress, cyanosis, shock, and apnea</td>
<td>Death within 12 h of admission in 5 patients; both survivors were dependent on ventilatory support</td>
</tr>
</tbody>
</table>

**NOTE.** Summarized from [10], with permission.

et al. [13] analyzed EV71 isolates from patients with fatal cases and patients with nonfatal cases of HFMD during EV71 epidemics in Malaysia, Japan, and Taiwan and found temporal, as well as geographic, heterogeneity of isolates.

Shih et al. [12] further analyzed complete sequences of 2 EV71 strains isolated from the spinal cord of a patient with a fatal case of HFMD and from vesicles in a patient with mild HFMD. We confirmed a high degree of identification (97%–100%) in nucleotide sequence throughout the entire genome, except in the focal regions of 3C-encoding viral proteinase and the 3′-NCR, where the nucleotide homology was 90%–91%. No clear marker of neurovirulence has been identified yet.

EV71 has been isolated continually in Taiwan since 1998. The results of phylogenetic analysis of these isolates is shown in figure 1. Most isolates from the years 1999, 2000, and 2001 belong to genotype B.

**PATHOGENESIS**

The pathogenesis of EV71-related fatalities remains unclear; a proposed pathogenesis is shown in table 5. Most patients in the 1998 epidemic who had fatal cases of infection died of pulmonary edema and cardiac decompensation. Virologic and pathologic findings indicate that the CNS, especially the brain stem, is the primary location of invasion, and there is no evidence of myocarditis. Most of the patients who died during the 1998 epidemic in Taiwan presented with signs of excessive sympathetic hyperactivity, which might have resulted in an excessive release of catecholamine and cortisol and led to systemic reactions, such as tachycardia, cold sweating, hypertension, and hyperglycemia. We postulate that EV71 involvement in the medullary vasomotor center results in neurogenic pulmonary edema and, finally, cardiovascular collapse [16]. The pathogenesis may be similar to Baker’s observation [17] of extensive damage to vasomotor centers in the medulla in 10 patients with fatal cases of bulbar poliomyelitis associated with pulmonary edema.

Our preliminary data showed that patients with fatal cases of encephalomyelitis complicated with pulmonary edema had extremely high levels of IL-1, IL-6, and TNF-α. The systemic inflammatory response may have some role in this and needs further study.

**CLINICAL STAGES AND MANAGEMENT OF EV71 INFECTION**

**Stage 1: HFMD/Herpangina**
1. Patients require symptomatic treatment only.
2. Children with signs and symptoms of CNS involvement, such as vomiting, limb weakness, drowsiness, and seizure (including myoclonic jerk), should be identified and admitted to the hospital [16].

Most patients who present in stage 1 recover without sequelae within 1 week. Only a very few progress to the next stage.

**Stage 2: Encephalomyelitis**
Most patients present with subtle neurologic symptoms or signs (e.g., drowsiness, limb weakness, ataxia, and myoclonic jerks) during stage 2, and some may develop flaccid paralysis.

**PATHOLOGY**

Autopsy of an 8-year-old girl who died in Chang Gung Children’s Hospital during the 1998 EV71 epidemic revealed extensive inflammation throughout the CNS [14]. The degree and extent of inflammation were more severe in the brain stem and spinal cord. The involved neurons showed degeneration and necrosis with neuronophagia. Perivascular cuffing with mononuclear cells was present. The lungs primarily revealed marked pulmonary edema with multifocal hemorrhage. The heart showed mild hypertrophy, with a small focus of mononuclear cell infiltration in the myocardium of the right ventricle, but no evidence of myocarditis.

The virus was isolated from various CNS tissues, including the frontal and parietal lobes of the brain, the pons, the medulla, the cerebellum, and the cervical, thoracic and lumbar spinal cord, as well as from the CSF, whereas viral cultures of tissues from the visceral organs, including the heart, lungs, liver, kidney, and pancreas, yielded negative results. In general, the autopsy findings were very similar to those from autopsies of the 4 patients in Malaysia who had fatal cases of infection during the 1997 EV71 epidemic [15].
Table 3. Results of virologic studies for 37 patients with fatal cases of enterovirus infection who had positive results of viral culture during the 1998 enterovirus 71 (EV71) outbreak in Taiwan.

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>EV71</th>
<th>Coxsackievirus B5</th>
<th>Other enteroviruses</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary edema</td>
<td>32</td>
<td>1</td>
<td>0</td>
<td>33</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>34</td>
<td>1</td>
<td>2</td>
<td>37</td>
</tr>
</tbody>
</table>

1. Fluid restriction should be initiated.
2. Osmotic diuretics should be given to patients who present with signs of increased intracranial pressure (IICP), and furosemide should be given to patients who are suspected to have fluid overload.
3. Anticonvulsant medication should be used to control seizures.
4. No data from controlled studies are available that support the use of intravenous immunoglobulin. Preliminary cytokine studies and pathologic evidence may justify its use. Until controlled evidence is available, we recommend that such treatment be used only for severe cases and only in the early stages of the disease.
5. Blood pressure, oximeter readings, Glasgow coma scale score, and blood sugar levels should be closely monitored. Patients who present with tachypnea or apnea, hypertension or hypotension, IICP signs, and hyperglycemia should be admitted to the intensive care unit.

Most patients recover with minimal sequelae within days to weeks. Some patients (12 [21%] of 57 patients at the Chang Gung Children’s Hospital during the 1998 epidemic) develop further complications [11].

Stage 3: Cardiopulmonary Failure
We arbitrarily divide stage 3 into 2 substages, on the basis of therapeutic requirements.

Stage 3A: Hypertension. The landmarks of stage 3A are hypertension, cold sweating, hyperglycemia, and frequent myoclonic jerks. Intensive care includes:
1. Continued fluid restriction.
2. Use of vasodilators (such as nitroprusside and milrinone) to control severe hypertension. Use nitroprusside with caution, because blood pressure sometimes drops very quickly, and no evidence has shown a significant increase in systemic vascular resistance.
3. Early intubation to allow positive-pressure mechanical ventilation with increased positive end-expiratory pressure for treatment of pulmonary edema. Use of a high-frequency oscillatory ventilator should be considered if pulmonary edema or hemorrhage persists or if severe hypoxemia develops.
4. When echocardiographic examination suggests that left ventricular systolic function is decreased or when the signs of decreased perfusion appear, the phosphoesterase inhibitor milrinone may be used to improve cardiac contractility and decrease the afterload, even if the patient’s blood pressure is within normal limits.

When blood pressure decreases to less than the normal range for the patient’s age, the patient enters stage 3B of the disease. However, we have observed that the blood pressure of some patients is very unstable and oscillates between stage 3A and stage 3B levels; such patients require very fine adjustment of cardiovascular drugs.

Stage 3B: Hypotension. In stage 3B, pulmonary edema may improve, but neurologic and cardiovascular condition deteriorates.
1. Use of nitroprusside should be discontinued.
2. Use of inotropic agents, such as dopamine and epinephrine, becomes necessary to maintain sufficient perfusion pressure.
3. The use of extracorporeal membrane oxygenation or a left ventricular assist device is still controversial. Because most evidence suggests that cardiopulmonary failure has a central origin, indications for these therapies remain undefined, even if satisfactory blood pressure and cardiac output are not maintained with the strategies already listed.

Stage 4: Convalescence
Stage 4 is characterized by almost-complete recovery of cardiac output function. Most survivors of EV71 infection who experience cardiopulmonary failure (13 [87%] of 15 patients in 2000 and 2001; L.-Y.C., T.-Y.L., and S.-H.H., unpublished data) have moderate to severe neurologic sequelae.
1. Long-term care needs include tracheostomy and referral to respiratory care centers.
2. Sufficient chest care is necessary to avoid recurrent pneumonia.
3. Rehabilitation to treat limb weakness or atrophy, dys-
Figure 1. Phylogenetic analysis of VP1 genes from enterovirus 71 isolated in Taiwan from 1998 through 2001. A phylogenetic tree was constructed, using the neighbor-joining method. The percentage of difference is indicated at the bottom of the figure; genotypes are marked at right. BrCr and MS-1987-7423 sequences are from GenBank (accession nos. U22521 and U22522, respectively).

phagia, diaphragm dysfunction, apnea, or central hypoventilation may be required.

**ONGOING QUESTIONS**

Seroepidemiologic studies carried out before and after the outbreak and clinical experiences during 1998 indicate that EV71 existed in Taiwan for at least 15 years before the 1998 epidemic. Why a common virus caused such a large-scale epidemic with such a high mortality rate remains unknown. We think that viral mutation, virus loads in intrafamilial transmission that are larger than those in the general population, individual host susceptibility, and lack of physician awareness are possible reasons. After the 1998 outbreak, EV71 became an endemic infection in Taiwan, and it may cause severe outbreaks in other parts of the world. We learned much after the outbreak, but we still face many unsolved problems:

1. Understanding of the route of transmission is important to interruption of an outbreak, but the route remains unclear. Both fecal-oral and oral-oral transmission is possible.
2. The precise risk factors for CNS invasion and cardio-
3. Pulmonary decompensation are important to early recognition and management.
4. Basic immunologic and virologic studies are needed to delineate the neurovirulent factors and pathogenesis of this infection.
5. Studies of testing for IgM antibody by ELISA and PCR microchips to make rapid diagnosis possible are ongoing and promising.
6. Understanding of the pathogenic mechanism is important to development of effective management strategies.
7. The antiviral drugs currently available, including some capsid binders, are ineffective for therapy. Studies of antiviral drugs are in progress, and some promising herbal drugs and chemical compounds have good in vitro antiviral effect on EV71. The role of immunomodulation needs further study.
8. After the eradication of poliomyelitis, EV71 will become the most important enterovirus that affects children. Active immunization may be the only effective way to prevent infection in children. Studies of inactivated vaccines, live vaccines, and DNA vaccines are in progress.

**Table 5. Proposed pathogenesis of severe enterovirus 71 infections.**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Syndrome</th>
<th>Underlying cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hand-foot-and-mouth disease/</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>herpangina</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Encephalomyelitis</td>
<td>Direct invasion or viremia</td>
</tr>
<tr>
<td>3</td>
<td>Pulmonary edema and cardiovascular collapse</td>
<td>Neurogenic inflammatory response</td>
</tr>
<tr>
<td>4</td>
<td>Convalescence</td>
<td>—</td>
</tr>
</tbody>
</table>

**References**

5. Gilbert GL, Dickson KE, Waters MJ, Kennett ML, Land SA, Sneddon
Enterovirus 71 Outbreak in Taiwan


