Enterovirus 71 (EV71) has emerged as a significant cause of brainstem encephalitis and acute flaccid paralysis in Taiwan. It may be complicated by autonomic nervous system dysregulation and pulmonary edema (PE). Cytokines in the central nervous system and systemic inflammatory responses play important roles in the pathogenesis of EV71-associated PE. Pathogenesis-based management with intravenous immunoglobulin and milrinone has been associated with reduced mortality in children with severe EV71 infections.

Human enteroviruses (EVs) include the well-recognized polioviruses, Coxsackie A and B viruses, ECHO viruses, and numbered EVs. As global efforts to eradicate poliovirus-associated poliomyelitis proceed, however, EV71 has emerged as an important neurological threat responsible for recent regional outbreaks in the West Pacific area since 1998, especially in Taiwan.2,3 Approximately 250 children have died in Taiwan as a result of EV71 infections between 1998 and the present, according to the Centers for Disease Control, Taiwan.

Southern Taiwan has experienced several EV71 epidemics: in the 1998 outbreak, 89% of patients were aged younger than 5 years. Hand foot and mouth disease occurred in 79% of the children and central nervous system (CNS) involvement in 35%. The predominant neurological presentations were myoclonic jerks (68%), vomiting (53%), and ataxia (35%).2 Of greatest concern was brainstem encephalitis (BE), which was the cardinal feature of EV71 CNS involvement. A subset of affected children developed acute flaccid paralysis.4 BE presents clinically with various combinations of symptoms including myoclonic jerks, ataxia, tremors, nystagmus, oculomotor and cranial nerve palsies, and can progress to seizures. Some children with BE rapidly develop pulmonary edema (PE) and/or hemorrhage, with subsequent cardiopulmonary collapse and shock. Based on the 1998 EV71 outbreak in Taiwan, several clinical stages of the disease were defined by some medical centers.5 We stratified EV71 BE into three important critical stages according to disease severity: uncomplicated BE, autonomic nervous system (ANS) dysregulation, and PE. We then developed effective ways to manage patients.

We observed that the mean cerebrospinal fluid (CSF) concentration of interleukin (IL)-1β in children with EV71-associated PE was significantly higher than that in children with uncomplicated BE. IL-6 and interferon (IFN)-γ levels were also significantly higher.
in patients with EV71-associated PE and ANS dysregulation than in cases with uncomplicated BE. Significant elevations of plasma IL-10, IL-13, and IFN-γ levels were observed in patients with PE. Patients with PE also had lower numbers of circulating CD4+ T-cells, CD8+ T-cells, and natural killer cells. Both the CNS and systemic inflammatory responses to infection play important, but distinctly different, roles in the pathogenesis of EV71-associated PE.

The mainstay of treatment for EV71 disease is supportive management. We suggest that all patients who demonstrate the neurological symptoms and signs described above should be hospitalized. If the patient has been diagnosed with uncomplicated BE, close monitoring of the myoclonic jerks and vital signs, including body temperature, blood pressure (BP) and heart rate (HR), is mandatory. The target CNS organ in EV71 infection is the brainstem, rather than the cerebrum, and increased intracranial pressure is therefore rarely encountered and the administration of osmotic diuretics is usually unnecessary. If the patient has frequent myoclonic jerks, cold sweating, mottled skin, and/or tachycardia (> 150/min) and/or elevation of BP (>2 standard deviations of age-matched BP), the patient has deteriorated to the stage of BE with ANS dysregulation. All patients at this stage should receive intensive care and their hemodynamics should be monitored. On diagnosis of ANS dysregulation, it is critical that intravenous immunoglobulin (IVIG) infusion be administered as soon as possible. Furthermore, patients presenting with acute flaccid paralysis combined with pleocytosis in the CSF should also receive IVIG treatment, because EV71 can be transmitted to the CNS through retrograde axonal pathways. IVIG 1 g/kg should be initiated for the first day, and if ANS dysregulation does not improve, a second dose should be administered the following day. IVIG treatment can reduce the production of IL-6 and IL-8 during the early phase of EV71-associated ANS dysregulation, and prevent further progression to PE. A better survival rate might have been achieved in previous outbreaks by earlier therapy or larger doses of IVIG. If patients have a HR persistently > 180/min, and high BP, milrinone can be administered simultaneously. Advanced airway management is also important, especially prophylactic intubation and adequate oxygenation; otherwise, hypoxic-ischemic encephalopathy can result in patients with PE, in addition to the direct brainstem insult caused by EV71.

In patients with PE, the fatality rate has been as high as 90%, before the introduction of milrinone. All fatalities occurred within 6–12 hours after admission, if not managed promptly. Pure inotropic agents have been associated with poorer outcomes, while milrinone has both inotropic and vasodilating properties. It is a cyclic nucleotide phosphodiesterase inhibitor subtype III that increases cardiac output, and reduces systemic vascular resistance and pulmonary capillary wedge pressure, without causing excessive increases in myocardial oxygen consumption. The drug is administered intravenously at a dosage range of 0.35–0.55 μg/kg/minute. Therapy is continued for only 72 hours, as long-term use poses the potential risk of arrhythmia. In one study, the milrinone-treated group had reduced mortality in comparison with the non-treated group (36.4% vs. 92.3%), and sympathetic tachycardia was decreased. There was also a significant decrease in IL-13 levels in milrinone-treated patients, compared to controls. Milrinone therapy may provide a useful therapeutic approach for treating life-threatening EV71 infections. In order to further test the efficacy of milrinone, a collaborative study with the Children’s Hospital No.1, Ho Chi Minh City, Vietnam is underway and preliminary results are encouraging.

EV71 reemerged in the Taiwanese community in 2008 with a new genotype, after 2 years’ occultation. Up to the middle of August 2008, 340 severe cases and 10 fatal cases have been reported in Taiwan. Using the pathogenesis-based management program described above, we have successfully treated more than 50 severe cases, including six patients whose infections were complicated by PE, at our institution in 2008. This noninvasive and effective program can reduce the morbidity and mortality due to EV71 infection in children, while we await the development of a vaccine.

References


