

NEUROLOGIC COMPLICATIONS IN CHILDREN WITH ENTEROVIRUS 71 INFECTION

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ABSTRACT

Background Enterovirus 71 infection causes hand-foot-and-mouth disease in young children, which is characterized by several days of fever and vomiting, ulcerative lesions in the oral mucosa, and vesicles on the backs of the hands and feet. The initial illness resolves but is sometimes followed by aseptic meningitis, encephalomyelitis, or even acute flaccid paralysis similar to paralytic poliomyelitis.

Methods We describe the neurologic complications associated with the enterovirus 71 epidemic that occurred in Taiwan in 1998. At three major hospitals we identified 41 children with culture-confirmed enterovirus 71 infection and acute neurologic manifestations. Magnetic resonance imaging (MRI) was performed in 4 patients with acute flaccid paralysis and 24 with rhombencephalitis.

Results The mean age of the patients was 2.5 years (range, 3 months to 8.2 years). Twenty-eight patients had hand-foot-and-mouth disease (68 percent), and six had herpangina (15 percent). The other seven patients had no skin or mucosal lesions. Three neurologic syndromes were identified: aseptic meningitis (in 3 patients); brain-stem encephalitis, or rhombencephalitis (in 37); and acute flaccid paralysis (in 4), which followed rhombencephalitis in 3 patients. In 20 patients with rhombencephalitis, the syndrome was characterized by myoclonic jerks and tremor, ataxia, or both (grade I disease). Ten patients had myoclonus and cranial-nerve involvement (grade II disease). In seven patients the brain-stem infection produced transient myoclonus followed by the rapid onset of respiratory distress, cyanosis, poor peripheral perfusion, shock, coma, loss of the doll's eye reflex, and apnea (grade III disease); five of these patients died within 12 hours after admission. In 17 of the 24 patients with rhombencephalitis who underwent MRI, T₂-weighted scans showed high-intensity lesions in the brain stem, most commonly in the pontine tegmentum. At follow-up, two of the patients with acute flaccid paralysis had residual limb weakness, and five of the patients with rhombencephalitis had persistent neurologic deficits, including myoclonus (in one child), cranial-nerve deficits (in two), and ventilator-dependent apnea (in two).

Conclusions In the 1998 enterovirus 71 epidemic in Taiwan, the chief neurologic complication was rhombencephalitis, which had a fatality rate of 14 percent. The most common initial symptoms were myoclonic jerks, and MRI usually showed evidence of brain-stem involvement. (N Engl J Med 1999;341:936-42.)

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ENTEROVIRAL meningoencephalitis generally has a good prognosis,¹ except when the cause is enterovirus 71, in which case there is a substantial mortality rate.^{2,3} Since it was identified in 1969,⁴ enterovirus 71 has caused epidemics in several parts of the world.²⁻¹⁵ It is one of the two causes of hand-foot-and-mouth disease, which has a prevalence pattern typical of enteroviral disease, with peaks in the summer and fall. Young children are most commonly affected. The infection is characterized by several days of fever and vomiting; ulcerative lesions of the buccal mucosa, tongue, palate, and gums; and lesions of the hands and feet, which are usually vesicular and occur on the dorsal surfaces, but they may also occur on the palms and soles. Although the initial viral illness is self-limited, it is sometimes followed by aseptic meningitis, meningoencephalitis, or even an acute flaccid paralysis that is indistinguishable from that caused by poliomyelitis.

In 1998, an epidemic of hand-foot-and-mouth disease due to enterovirus 71 affected thousands of children in Taiwan. Of the 320 children who were hospitalized with acute neurologic disease in the Taiwan epidemic, at least 55 died.² This is the third such outbreak of enterovirus 71 infection in which there was rapid deterioration leading to death in young children; the first occurred in Bulgaria in 1975,¹⁵ and the second in Malaysia in 1997.² The Bulgarian outbreak was characterized by a rapid onset of medullary involvement of the central nervous system. The clinical presentations in the Malaysian epidemic were less well described than those in the Bulgarian outbreak but appeared to be similar to those in Taiwan: fever and hand-foot-and-mouth disease were followed by rapid clinical deterioration.^{2,14,16} We characterized the presentation and outcome of 41 children in the Taiwan epidemic who had neurologic involvement and determined the characteristics of brain-stem encephalitis (or rhombencephalitis) due to enterovirus 71 infection.

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METHODS

Patients

From April to November 1998, 41 patients with acute neurologic manifestations were admitted to one of three major Taiwanese hospitals (Chang Gung Children's Hospital in Kaohsiung, National Cheng Kung University Medical Center in Tainan, or Tri-Service General Hospital in Taipei). All 41 had culture-confirmed enterovirus 71 infection. The diagnosis of enterovirus 71 infection was established by isolation of the virus from one or more throat swabs, stool specimens, cerebrospinal fluid, or other tissue fluids that were collected from each patient on the day of admission.

Symptoms

Prodromal symptoms were defined as systemic symptoms that occurred before the onset of neurologic manifestations. The extent of neurologic involvement was prospectively categorized according to the presence of aseptic meningitis, acute flaccid paralysis, and rhombencephalitis. Aseptic meningitis was diagnosed on the basis of the presence in cerebrospinal fluid of more than 10 white cells per cubic millimeter, negative results on bacterial culture, and signs of fever, vomiting, headache, and stiffness of the neck. Acute flaccid paralysis was characterized by the acute onset of flaccid muscle weakness and lack of reflexes. The diagnosis of rhombencephalitis was based on the presence in cerebrospinal fluid of more than 10 white cells per cubic millimeter; signs of ataxia, tremor, myoclonic jerks, oculomotor problems, or bulbar palsy; or evidence of brain-stem involvement on magnetic resonance imaging (MRI).

Isolation of Virus

Specimens for viral isolation were collected in transport medium and inoculated onto monolayers of A549 cells, green-monkey-kidney cells, and Vero cells within 24 hours. After the replacement of maintenance medium, the cell cultures were incubated at 37°C and inspected daily for a minimum of 14 days for evidence of a viral cytopathic effect.¹⁷ Isolates that produced typical enteroviral cytopathic effects but that could not be typed with the use of type-specific antiserum pools (American Type Culture Collection, Rockville, Md.) were typed by an immunofluorescence assay with enterovirus 71 monoclonal antibodies 3323 and 3324 (Chemicon International, Temecula, Calif.). Because monoclonal antibody 3323 cross-reacts with coxsackievirus A16 and monoclonal antibody 3324 does not, isolates that stained for both monoclonal antibodies were identified as enterovirus 71. The identification of these isolates was confirmed by a neutralization test with polyclonal antibodies against enterovirus 71.

Magnetic Resonance Imaging

MRI was performed with a 1.5-T unit in 4 patients with acute flaccid paralysis and 24 patients with rhombencephalitis. Twenty-six patients underwent MRI within five days after the onset of neurologic symptoms. Two patients underwent MRI two months after the onset of symptoms because the occurrence of cardiopulmonary collapse and prolonged apnea made earlier MRI impossible. The sequences consisted of spin-echo T₁-weighted axial images (repetition time, 500 to 600 msec; echo time, 15 to 40 msec; number of signals acquired, 1 or 2) with a thickness of 5 mm and T₂-weighted axial images (repetition time, 2800 to 3000 msec; echo time, 90 to 120 msec; number of signals acquired, 1) with a thickness of 5 mm. Enhanced T₁-weighted images of axial, coronal, and sagittal planes were obtained with the intravenous injection of 0.1 mmol of gadopentetate dimeglumine per kilogram of body weight. Depending on the scanners available, both fast spin-echo T₂-weighted images (repetition time, 4000 msec; echo time, 90 msec; number of signals acquired, 3) and gradient-echo T₂-weighted images (repetition time, 808 msec; echo time, 15 msec; angle, 20 degrees; number of signals acquired, 3) were used to study the spinal cord.

An autopsy was performed in one patient who died of fulminant neurogenic shock and pulmonary hemorrhage within one day after admission. All surviving patients underwent a follow-up neurologic examination a mean of 5.7 months after the onset of disease.

RESULTS

Characteristics of the Isolates

During the eight-month period, 126 isolates of enterovirus 71 were collected at the three hospitals, 48 of which were from the 41 patients with acute neurologic symptoms. The 48 isolates were obtained from throat swabs in 27 cases (66 percent), stool specimens in 18 cases (44 percent), cerebrospinal fluid in 1 case (2 percent), gastric fluid in 1 case (2 percent), and a tracheal aspirate in 1 case (2 percent).

Prodrome

The mean age at the onset of disease was 2.5 years (range, 3 months to 8.2 years). The highest incidence was among children who were one to two years of age. Twenty-four patients (59 percent) were two years of age or younger, and 37 (90 percent) were five years of age or younger.

The disease had a biphasic course: a prodrome of hand-foot-and-mouth disease or herpangina, vomiting, and fever lasted an average of 3.2 days, followed by neurologic manifestations. Other symptoms included nausea, poor feeding, and malaise. Twenty-eight patients (68 percent) had hand-foot-and-mouth disease, and six (15 percent) had herpangina. The other seven patients had no skin or mucosal lesions.

Neurologic Syndromes

Neurologic disorders began two to five days after the onset of skin or mucosal lesions or fever. Three neurologic syndromes were identified on the basis of the extent of neurologic involvement: aseptic meningitis (3 patients [7 percent]), acute flaccid paralysis (4 patients [10 percent]), and rhombencephalitis (37 patients [90 percent]) (Table 1). Three of the patients with acute flaccid paralysis had myoclonus and tremor before the onset of paralysis. The mean (\pm SD) white-cell counts in cerebrospinal fluid were 33 ± 15 per cubic millimeter among the patients with aseptic meningitis, 151 ± 174 cells per cubic millimeter among those with acute flaccid paralysis, and 194 ± 185 cells per cubic millimeter among those with rhombencephalitis. There was no significant difference in white-cell counts or levels of glucose, protein, and lactate in cerebrospinal fluid among the three groups.

Aseptic Meningitis

All three patients with aseptic meningitis presented with headache, vomiting, fever, and stiffness of the neck. One patient had hand-foot-and-mouth disease, and one had herpangina. The third patient had no skin or mucosal lesions. All three recovered with-

TABLE 1. ACUTE NEUROLOGIC SYNDROMES IN 41 CHILDREN WITH CULTURE-CONFIRMED ENTEROVIRUS 71 INFECTION.

NEUROLOGIC SYNDROME	NO. OF CHILDREN (%)	OUTCOME		
		RECOVERY	SEQUELAE	DEATH
Aseptic meningitis	3 (7)	3	0	0
Rhombencephalitis	37 (90)*	27	5	5
Grade I (myoclonus with tremor, ataxia, or both)	20*	19	1	0
Grade II (myoclonus with cranial-nerve involvement)	10	8	2	0
Grade III (rapid cardiopulmonary failure)	7	0	2	5
Acute flaccid paralysis	4 (10)*	2	2	0

*Three patients with myoclonus and tremor subsequently had acute flaccid paralysis.

in five days after admission. None had neurologic sequelae at follow-up.

Acute Flaccid Paralysis

Four patients had acute flaccid paralysis: one had paralysis of the right arm, and three had paralysis of the legs (unilateral in two patients and bilateral in one). Two patients had hand-foot-and-mouth disease, and one had herpangina. The fourth patient had no skin or mucosal lesions. Transient atonic neurogenic bladder was found in one patient. None of the patients had a disturbance in their ability to sense pain or heat or cold; none had bulbar involvement. Transient signs of rhombencephalitis, including myoclonus, tremor, and ataxia, were found in three patients before the onset of paralysis. Virologic and serologic tests for all three types of poliovirus were negative.

Three of the four patients had abnormal findings on MRI. One patient had enhanced lesions of the left anterior horn and ventral roots on the same side on T₁-weighted images at the level of L2 to L4. Another patient had similar unilateral lesions in the anterior horn at the level of C3 to C7. The remaining patient, who had paralysis of both legs, had bilateral lesions of high signal intensity in the anterior horns at the level of T10 to L5 on T₂-weighted images. Follow-up evaluation revealed complete recovery in two patients and persistent mild weakness and atrophy of the affected limbs in the other two.

Rhombencephalitis

Among the 37 patients with rhombencephalitis, 27 had hand-foot-and-mouth disease and 5 had herpangina. The other five patients had no skin or mucosal lesions. Myoclonus, which ranged in severity from mild myoclonic jerks during sleep to very frequent myoclonus during sleep and waking hours, was present in 32 patients (86 percent), and tremor,

ataxia, or both were present in 23 (62 percent). The severity of rhombencephalitis also varied. Twenty patients had grade I rhombencephalitis (54 percent), defined as generalized myoclonic jerks with tremor, ataxia, or both. Ten patients had grade II rhombencephalitis (27 percent), defined as myoclonus with cranial-nerve involvement, including ocular disturbances in nine patients (nystagmus, strabismus, or gaze paresis) and bulbar palsy in one (dysphagia, dysarthria, dysphonia, and facial weakness). Seven patients had grade III rhombencephalitis (19 percent), defined as transient myoclonus followed by the rapid onset of respiratory distress, cyanosis, poor peripheral perfusion, shock, coma, loss of the doll's eye reflex, and apnea. All seven patients with grade III rhombencephalitis required mechanical ventilation and cardiopulmonary support immediately after admission because of fulminant neurogenic pulmonary edema and apnea, and five died within 12 hours after admission despite cardiopulmonary support.

Except for those with grade III rhombencephalitis, none of the patients with rhombencephalitis had serious disturbances in the level of consciousness or seizures. Hyporeflexia or areflexia was found in 10 patients with grade I rhombencephalitis and 2 patients with grade II disease. Transient visual hallucinations occurred in four patients: two with grade I and two with grade II rhombencephalitis. Transient urinary retention occurred in three patients: one with grade I and two with grade II rhombencephalitis. Hyperventilation or Cheyne-Stokes respiration developed in nine patients. The incidence of abnormal respiration increased with increasing severity of rhombencephalitis: it was present in three patients with grade II disease (30 percent) and six patients with grade III disease (86 percent).

Electroencephalographic examination revealed that two patients with grade I rhombencephalitis (10 percent) and three with grade II rhombencephalitis (30 percent) had intermittent slow waves bilaterally in central and parietal areas. A chest x-ray film revealed no lung abnormalities in patients with grade I or grade II disease, whereas all patients with grade III rhombencephalitis had radiologic abnormalities, including diffuse pulmonary edema in six and pneumonic infiltration in one. The white-cell counts, glucose level, and protein level in cerebrospinal fluid were similar among the patients with grade I, II, and III rhombencephalitis. The mean cerebrospinal fluid lactate level was significantly higher in patients with grade III disease (12.2 ± 12.6 mmol per liter) than in those with grade I disease (2.1 ± 0.8 mmol per liter, $P < 0.001$) or grade II disease (2.2 ± 0.6 mmol per liter, $P < 0.001$).

Seventeen of the 24 patients with rhombencephalitis who underwent MRI (71 percent) had lesions of high signal intensity in the brain stem on T₂-weighted images. None had supratentorial cerebral

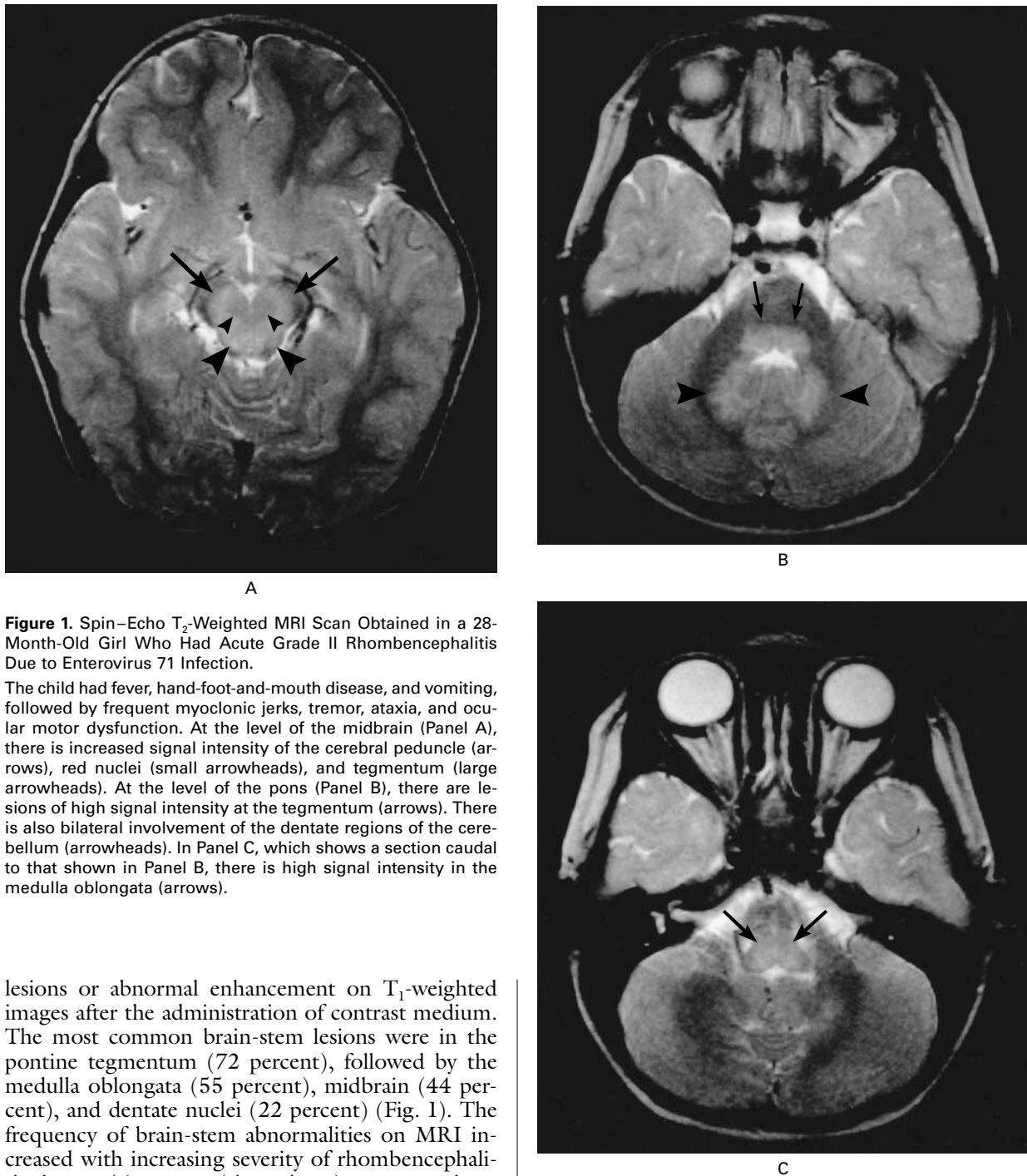


Figure 1. Spin-Echo T_2 -Weighted MRI Scan Obtained in a 28-Month-Old Girl Who Had Acute Grade II Rhombencephalitis Due to Enterovirus 71 Infection.

The child had fever, hand-foot-and-mouth disease, and vomiting, followed by frequent myoclonic jerks, tremor, ataxia, and ocular motor dysfunction. At the level of the midbrain (Panel A), there is increased signal intensity of the cerebral peduncle (arrows), red nuclei (small arrowheads), and tegmentum (large arrowheads). At the level of the pons (Panel B), there are lesions of high signal intensity at the tegmentum (arrows). There is also bilateral involvement of the dentate regions of the cerebellum (arrowheads). In Panel C, which shows a section caudal to that shown in Panel B, there is high signal intensity in the medulla oblongata (arrows).

lesions or abnormal enhancement on T_1 -weighted images after the administration of contrast medium. The most common brain-stem lesions were in the pontine tegmentum (72 percent), followed by the medulla oblongata (55 percent), midbrain (44 percent), and dentate nuclei (22 percent) (Fig. 1). The frequency of brain-stem abnormalities on MRI increased with increasing severity of rhombencephalitis: it was 46 percent (six patients) among patients with grade I disease and 100 percent among those with grade II disease (nine patients) or grade III disease (two patients). Except for the patient who had bulbar palsy and grade II rhombencephalitis, no obvious difference was found in the extent of MRI brain-stem lesions between patients with grade I disease and those with grade II disease. The patient with bulbar involvement and grade II rhombencephalitis had brain-stem lesions extending to the

basis pontis. MRI in two patients with chronic grade III rhombencephalitis revealed brain-stem atrophy and cavitation that extended from the tegmentum of the lower brain stem to the anterior horn region of the upper cervical cord (Fig. 2).

Five of the patients with rhombencephalitis died (14 percent), and all had grade III disease. An au-

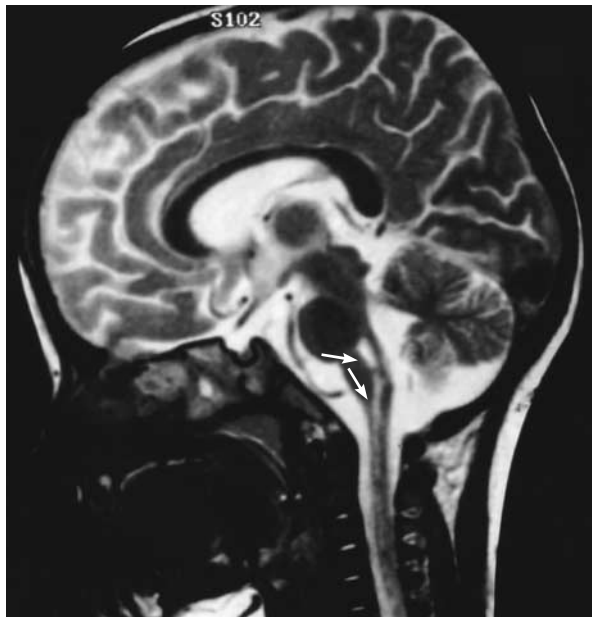


Figure 2. Midsagittal Spin-Echo T₂-Weighted MRI Scan Obtained in a Two-Year-Old Boy Two Months after the Onset of Grade III Rhombencephalitis Due to Enterovirus 71 Infection.

The child required a ventilator because of prolonged central apnea. There was atrophy of the brain stem and longitudinal lesions of high signal intensity, suggesting cavitation (arrows), from the tegmentum of the lower brain stem to the anterior horn region of the upper cervical cord.

Autopsy in one patient revealed extensive encephalomyelitis involving the brain-stem tegmentum at the level of the midbrain, pons, and medulla oblongata and all anterior horns. In the medulla oblongata, the involvement included the dorsal nucleus of the vagus, tractus solitarius and nucleus, olivary nucleus, inferior olivary nucleus, and reticular formation. Enterovirus 71 was isolated from the thalamus, basal ganglia, pons, medulla oblongata, and spinal cord.

At follow-up examinations, five patients (14 percent) had neurologic sequelae. Nineteen of the 20 patients with grade I rhombencephalitis recovered completely; 1 (5 percent) had persistent and marked myoclonus when awake. Two patients with grade II rhombencephalitis (20 percent) had neurologic sequelae. One patient had unilateral abducent-nerve palsy. The other had facial diplegia, ataxia, dysarthria, and internuclear ophthalmoplegia. Both surviving patients with grade III rhombencephalitis had normal levels of consciousness but required a ventilator because of prolonged central apnea.

DISCUSSION

Aseptic meningitis was the most common manifestation of enterovirus 71 infection in outbreaks that occurred before 1975. Serious central nervous system complications were uncommon in the New York,

Swedish, Japanese, and Australian outbreaks.⁵⁻⁹ In the 1975 Bulgarian epidemic, 77 percent of the patients had aseptic meningitis, 7.4 percent had a poliomyelitis-like syndrome, and 9.6 percent had bulbar meningoencephalitis, but none had hand-foot-and-mouth disease.¹⁵ In the 1988-1990 Brazilian outbreak, among patients with acute neurologic involvement, 58 percent had flaccid paralysis, 8 percent had cerebellitis, and none had hand-foot-and-mouth disease or died.¹³ Cerebellar encephalitis was the chief neurologic complication diagnosed on the basis of clinical manifestations in the 1973 Japanese epidemic, though no fatalities were mentioned.⁶ Our study confirms that the chief neurologic syndrome in patients involved in the recent Taiwanese epidemic of enterovirus 71 infection was rhombencephalitis. Autopsy results from four Malaysian patients support the finding of brain-stem involvement.¹⁴ In contrast to the earlier epidemics of enterovirus 71 infection, the Malaysian and Taiwanese epidemics were characterized by rhombencephalitis. This change may indicate the reemergence of virulent strains of enterovirus 71 with serious neurologic effects or the emergence of a new strain.

In general, enterovirus 71 rhombencephalitis seems to be a benign neurologic syndrome, but it can be severe, even deadly. Myoclonic jerks with tremor, ataxia, or both in patients with grade I rhombencephalitis represent one end of the clinical spectrum, with a transient, focal pathological process involving mainly the pontine tegmentum. At the other end of the spectrum is grade III rhombencephalitis, a potentially fatal disorder, complicated by acute cardiopulmonary failure and extensive brain-stem damage. Since the dorsal pontine tegmentum was the most commonly affected area in our patients, it is possible that enterovirus 71 may initially involve the pontine tegmentum, with subsequent rostral and caudal progression.

Rhombencephalitis is a rare disorder that was first reported in 1951.¹⁸ The infectious agents that may cause rhombencephalitis include bacteria (i.e., *Listeria monocytogenes*, *Mycoplasma pneumoniae*, and *Borrelia burgdorferi*) and viruses (i.e., herpes simplex virus, Epstein-Barr virus, influenza A, adenovirus, echovirus, the flavivirus that causes Japanese encephalitis, poliovirus, cytomegalovirus, and varicella-zoster virus),^{1,19-21} with fatal cases associated with infection with Epstein-Barr virus and chickenpox.^{22,23} Enterovirus 71, though now viewed as one of the chief causes of acute flaccid paralysis after the worldwide effort to eradicate poliomyelitis, has not been seen as an important cause of rhombencephalitis. Although many types of viral brain-stem encephalitis are characteristically sporadic, self-limited, and reversible,¹ enterovirus 71 rhombencephalitis is potentially epidemic and fatal.

The brain-stem lesions that we found on MRI ac-

counted for the neurologic manifestations in our patients with rhombencephalitis. Pathologic changes in the mesencephalic reticular formation or upper pontine tegmentum can produce myoclonus.²⁴⁻²⁶ Findings of truncal ataxia and intention tremor provide evidence of lesions in the rhombencephalon. The ocular disturbances in our patients may have been due to lesions in the midbrain and pons. Visual hallucinations can occur in patients with lesions of the midbrain or pontine tegmentum.^{25,27} Transient urinary retention can be caused by lesions in the pontine micturition center,²⁸ and hyperventilation or Cheyne-Stokes respiration can result from lesions in the diencephalon or midbrain.

The lesions that we found on MRI in our patients with rhombencephalitis, especially those with grade III disease, may have resulted from the direct invasion of the brain stem by enterovirus 71.^{14,16} The virus was cultured from cerebrospinal fluid in one surviving patient with grade III rhombencephalitis and from the spinal cord and brain stem of the patient who underwent autopsy. The main pathological feature was widespread inflammation in the central gray matter of the spinal cord and the entire medulla oblongata. Direct destructive processes causing cavitation in the brain-stem tegmentum were found on MRI in the two patients who survived grade III rhombencephalitis. Thus, extensive destruction of the vital vasomotor and respiratory centers located in the lower brain stem appears to be responsible for the rapid neurogenic pulmonary edema and vasomotor collapse in patients with grade III disease.^{14,29}

Poliomyelitis-like paralysis can be caused by coxsackievirus A (serotypes 4, 7, 9, and 10) and B (serotypes 2, 4, and 5).¹ Paralysis caused by enterovirus 71 infection is indistinguishable from that caused by poliomyelitis but differs from transverse myelitis, since none of our patients with paralysis had any sensory impairment. In our patients with acute flaccid paralysis, the high-intensity lesions on T₂-weighted MRI were located in the anterior horns of the spinal cord, suggesting the presence of edema or necrosis of the spinal cord. These MRI findings are similar to those in patients with poliomyelitis or the poliomyelitis-like syndrome³⁰⁻³² but differ from those in patients with transverse myelitis, which typically involve both gray and white matter and are characterized predominantly by abnormal signal intensity of the entire spinal cord.³³

Our study included only patients who were hospitalized for acute neurologic diseases related to enterovirus 71 infection. Some patients with enterovirus 71 infection may have had aseptic meningitis that was not severe enough to require hospitalization. Enterovirus 71 and poliovirus infections are very similar in terms of their seasonality, preference for young children, biphasic clinical presentation, and brain-stem and spinal cord involvement. However, 90 percent

of the children with neurologic diseases related to enterovirus 71 infection in the Taiwanese epidemic had rhombencephalitis, which is symptomatically distinct from the predominantly acute flaccid paralysis caused by poliovirus. The presence of myoclonus, cerebellar and oculomotor signs, and hand-foot-and-mouth disease or herpangina clearly distinguishes enterovirus 71 rhombencephalitis from bulbar poliomyelitis.

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