

Long-Term Cognitive and Motor Deficits After Enterovirus 71 Brainstem Encephalitis in Children

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There are more than 60 distinct serotypes of enteroviruses within the family Picornaviridae. Enterovirus 71 (EV71) was first isolated from patients with encephalitis, aseptic meningitis, or myocarditis in California between 1969 and 1972. Several epidemics of EV71 infections occurred in Taiwan since 1998. EV71 usually causes hand-foot-and mouth disease (HFMD) or herpangina, but the infection can progress to a polio-like, acute flaccid paralysis or brainstem encephalitis (BE). BE is the most common neurological complication in children. The highest mortality rate occurs in children who developed pulmonary edema.

This study was designed to determine the long term outcome of children who survived hospitalization for EV71 BE. Attention was focused on cognitive and motor outcomes because the disease is most often localized to the brainstem, pons and midbrain.

The study population consisted of Taiwanese children who were under the age of 12 years when they were hospitalized for EV71 BE. They were prospectively followed at at the Department of Pediatrics and Emergency Medicine of National Cheng Kung University Hospital from 1998 to 2004 and were invited to return for further assessment.

BE (stage II) was defined as an illness characterized by myoclonus, ataxia, nystagmus, oculomotor palsies, and bulbar palsy, in various combinations, with or without confirmation by neuroimaging. ANS dysregulation (stage IIIa) was defined as the occurrence of cold sweats, mottled skin, tachycardia, tachypnea, and hypertension. PE (stage IIIb) was defined as the occurrence of respiratory distress, tachycardia, tachypnea, rales and copious frothy sputum with chest radiological findings of bilateral pulmonary infiltrates without cardiomegaly.

A pediatrician used a standardized questionnaire to obtain information from parents or guardians and healthcare providers. This included information on demographic characteristics, co-morbid illnesses, current medications, memory loss, cognitive function and ability to perform activities of daily living.



The Wechsler Pre-school and Primary Scale of Intelligence-Revised (WPPSI-R) was used for subjects 3 to <6 years of age. The Wechsler Intelligence Scale for Children-Revised (WISC-R) was used for subjects 6 to 16 years of age. The Movement Assessment Battery for Children (M-ABC) test was used to assess general motor performance. M-ABC consists of four age bands suitable for a specific age group. Each age band consists of eight items that measure three aspects of motor ability: manual dexterity, ball skills, and balance. Total scores were expressed as percentile. Children with scores at or below the 5th percentile for their age were identified as having motor difficulties. Scores between 5th and 15th percentile were considered to be borderline. The Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI) was used to assess visual-motor skills. Children with scores at or below 5th percentile for their age were identified as abnormal.

Sixty-three previously healthy children with EV71 BE (49 stage II, 7 stage IIIa, 7 stage IIIb) were followed for 2.8 ± 1.0 years (range: 1.4~4.9 years). The mean age at the time of diagnosis was 2.4 ± 1.4 years (range: 0.3~7.1 years). There were no significant differences in social or demographic characteristics by stage of BE. Neurological examinations were completed in 63 subjects. Cognitive and M-ABC tests were completed in 54 and the VMI test in 53. Three children with stage IIIb disease died during the follow-up period.

The neurological findings during hospitalization and at follow-up are summarized in Table 1. The most frequent neurological abnormalities during hospitalization were abnormal activities of daily living (52.4%), followed by altered consciousness (47.6%), cerebellar dysfunction (17.5%) and cranial nerve palsy (15.9%). Most of these had resolved by the time of follow-up.

Residual cognitive or motor disorders were noted at follow-up in nine of the 63 patients (14.3%) (Table 2). Among the 9 children with residual deficits, 3 (4.8%) had cognitive and 7 (11.1%) had motor defects (mostly cerebellar dysfunction). Two children with stage IIIb disease continued to have severe motor dysfunction and respiratory failure complicated by urinary and fecal incontinence.

This is the first study to evaluate the long-term cognitive and motor sequelae of EV71 brainstem encephalitis. The inflammatory lesions in this disease are usually localized to the posterior two thirds of the medulla oblongata and pons and the anterior two thirds of the spinal cord. There is increasing evidence that subcortical structures, including the basal ganglia, brain stem, and cerebellum are involved in cognitive and behavioral processes in humans. Cerebellar dysfunction is the most common neurological deficit in children with stage II disease. Pulmonary edema with hypoxia is the major cause of death in children with stage IIIb EV71 infection. Failure to provide prompt pulmonary resuscitation with a patent airway may lead to a hypoxic-ischemic encephalopathy superimposed on the direct brain stem insult caused by the virus. Aggressive resuscitation needs to be instituted as soon as possible to prevent global brain damage.

Altered consciousness during the acute illness and the potential to develop cognitive impairment in EV71 BE appears to be multifactorial. The current findings indicate that long term cognitive function is usually preserved in children after EV71 BE. This is based on both objective tests as well as confirmatory reports by parents and guardians.

In conclusion, we found that the long term cognitive function of children with EV71 BE was generally quite good. Nevertheless, residual defects, mostly consisting of cerebellar dysfunction, were still present in 10.2% of children with EV71 BE stage II at about three years following hospitalization. Children with EV71 BE stage IIIb continued to have severe respiratory and motor impairment. Close monitoring of cerebellar dysfunction and early rehabilitation are recommended. Long term follow-up of

this cohort is needed to determine the ultimate prognosis.

Table 1. Abnormal Findings on Neurological Examination of Children with EV71 BE on Admission and at Follow-up

Characteristics	Stage II N=49 (%)	Stage IIIa n=7 (%)	Stage IIIb ^a n=7 (%)	Total N=63 (%)
Altered consciousness				
Admission	18 (36.7)	6 (85.7)	6 (85.7)	30 (47.6)
Follow-up	0	0	0	0
Activities of daily living^b				
Admission	22 (44.9)	5 (71.4)	7 (100)	33 (52.4)
Follow-up	0	0	2 (28.6)	2 (3.2)
Cranial nerve palsy^c				
Admission	2 (4.1)	3 (43.9)	5 (71.4)	10 (15.9)
Follow-up	1 (2.0)	0	2 (28.6)	3 (4.8)
Sensory coordination^d				
Admission	0	0	0	0
Follow up	1 (2.0)	0	2 (28.6)	3 (4.8)
Cerebellar dysfunction^e				
Admission	7 (14.3)	4 (57.1)	0	11 (17.5)
Follow-up	5 (10.2)	0	2 (33.3)	7 (11.1)

^a Three patients expired during the follow up.

^b Abnormal activities of daily living disorders on admission were: stage II - attention, 1; movement, 6; feeding, 15; stage IIIa - feeding, 2; attention, movement, and feeding, 2; attention, movement, respiration and feeding, 1; stage IIIb - respiration, 4. On follow-up, two stage IIIb patients developed additional attention, movement, respiration, feeding, and defecation and urination abnormalities.

^c Cranial nerve (CN) palsies noted on admission were: stage II - CN VII, 1; CN VIII, 1; stage IIIa - CN VII, 2; CN VIII, 1, and stage IIIb - CN VIII, 4. On follow-up one stage II patient developed a new CN II palsy; two stage IIIb patients developed new CN I, V and CN VIII palsies.

^d Abnormal findings of sensory coordination noted on follow-up were: stage II - tendon reflex, 1; stage IIIb - muscle tone, 2.

^e Abnormal findings of cerebellum function noted on admission were: stage II - gait and balance, 7; and stage IIIa - gait and balance, 4. Abnormal findings of cerebellum function noted on follow-up were: stage

II - gait and balance, 5, and stage IIIb - gait and balance, position, and vibration, 2.

Table 2. Residual Cognitive and/or Motor Disorders Detected Among 9 of 63 Children with EV71 BE

Age at onset,y	Gender	Stage	Time Followed,y	Cognitive and motor disorders
1.6	F	II	2.2	WPPSI-R < 2SD
3.4	M	II	1.8	WPPSI-R < 2SD, Cerebellar dysfunction
2.4	F	II	1.8	WPPSI-R < 2SD
1.4	M	II	2.6	M-ABC < 5 th percentile, Cerebellar dysfunction
1.7	M	II	2.6	M-ABC < 5 th percentile, New cranial nerve II palsy, Poor sensory coordination, Cerebellar dysfunction
2.9	M	II	2.6	Cerebellar dysfunction
2.5	M	II	1.7	Cerebellar dysfunction
1.9	M	IIIb	3.8	Abnormal attention, movement, respiration, feeding, defecation and urination, Cranial nerve palsies in I,V and VIII, Poor position and vibratory sensation, Cerebellar dysfunction
0.7	M	IIIb	3.0	Abnormal attention, movement, respiration, feeding, defecation and urination, Cranial nerve palsies in I,V and VIII, Poor position and vibratory sensation ,Cerebellar

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