ORIGINAL ARTICLE

Neurodevelopment and Cognition in Children after Enterovirus 71 Infection

Luan-Yin Chang, M.D., Ph.D., Li-Min Huang, M.D., Ph.D., Susan Shur-Fen Gau, M.D., Ph.D., Yu-Yu Wu, M.D., Shao-Hsuan Hsia, M.D., Tsui-Yen Fan, B.S., Kuang-Lin Lin, M.D., Yhu-Chering Huang, M.D., Ph.D., Chun-Yi Lu, M.D., and Tzou-Yien Lin, M.D.

ABSTRACT

BACKGROUND

Enterovirus 71 is a common cause of hand, foot, and mouth disease and encephalitis in Asia and elsewhere. The long-term neurologic and psychiatric effects of this viral infection on the central nervous system (CNS) are not well understood.

METHODS

We conducted long-term follow-up of 142 children after enterovirus 71 infection with CNS involvement — 61 who had aseptic meningitis, 53 who had severe CNS involvement, and 28 who had cardiopulmonary failure after CNS involvement. At a median follow-up of 2.9 years (range, 1.0 to 7.4) after infection, the children received physical and neurologic examinations. We administered the Denver Developmental Screening Test (DDST II) to children 6 years of age or younger and the Wechsler intelligence test to children 4 years of age or older.

RESULTS

Nine of the 16 patients with a poliomyelitis-like syndrome (56%) and 1 of the 5 patients with encephalomyelitis (20%) had sequelae involving limb weakness and atrophy. Eighteen of the 28 patients with cardiopulmonary failure after CNS involvement (64%) had limb weakness and atrophy, 17 (61%) required tube feeding, and 16 (57%) required ventilator support. Among patients who underwent DDST II assessment, delayed neurodevelopment was found in only 1 of 20 patients (5%) with severe CNS involvement and in 21 of 28 patients (75%) with cardiopulmonary failure ($P<0.001$ for the overall comparison). Children with cardiopulmonary failure after CNS involvement scored lower on intelligence tests than did children with CNS involvement alone ($P=0.003$).

CONCLUSIONS

Enterovirus 71 infection with CNS involvement and cardiopulmonary failure may be associated with neurologic sequelae, delayed neurodevelopment, and reduced cognitive functioning. Children with CNS involvement without cardiopulmonary failure did well on neurodevelopment tests. (ClinicalTrials.gov number, NCT00172393.)

From the Departments of Pediatrics (L.-Y.C., L.-M.H., T.-Y.F., C.-Y.L.) and Psychiatry (S.S.-F.G.), National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei; and the Departments of Child Psychiatry (Y.-Y.W.) and Pediatrics (S.-H.H., K.-L.L., Y.-C.H., T.-Y.L.), Chang Gung Children's Hospital, Chang Gung University, Taoyuan — both in Taiwan. Address reprint requests to Dr. Chang at the Department of Pediatrics, National Taiwan University Hospital, College of Medicine, National Taiwan University, No. 7, Chung-Shan South Rd., Taipei, Taiwan, or at ly7077@tpts6.seed.net.tw.

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Enterovirus 71 (EV71) is a cause of hand, foot, and mouth disease and encephalitis. In Bulgaria in 1975, Hungary in 1978, and Malaysia in 1997, large outbreaks of EV71 infection resulted in dozens of deaths.[1-3] In Taiwan, the most severe EV71 epidemic to date occurred in 1998.[4] During that epidemic, almost all patients with cardiopulmonary failure died.[4,5] In 2000, Taiwan developed a disease-management program to improve the survival rate of patients with the infection.[6,7] Although that program led to a reduction of acute mortality,[7] concern about long-term sequelae remains.

Neurodevelopment and cognitive function may be affected by viral encephalitis or by bacterial meningitis. In a meta-analysis involving 1602 children with bacterial meningitis, 16.4% of the survivors had major adverse outcomes, such as deafness, intellectual disability, epilepsy, and physical impairment.[8] In another study of children with meningitis caused by *Haemophilus influenzae* type b, poor school performance and more behavioral disturbances were found.[9] Neurologic sequelae were found in one third to one half of patients in two studies of herpes encephalitis[10,11] and in about one third of the survivors of Japanese encephalitis.[12,13] It has been reported that the more severe the brain injury (as in cases of bacterial meningitis), the greater the effect on cognitive function and behavioral manifestations.[14,15]

One of the most important causes of viral encephalitis is the enterovirus, and EV71 is especially important in Asia. Even though the survival rate from EV71 infection with central nervous system (CNS) involvement has improved in Taiwan, the effect of the virus on the subsequent neurodevelopment and cognitive function of the survivors is not known (unlike the effects of other forms of viral encephalitis). We conducted this study to assess the long-term neurologic sequelae, neurodevelopment, and cognitive function of children who had EV71 infection with CNS involvement.

METHODS

PATIENTS AND CLINICAL SEVERITY

The institutional review board of the National Taiwan University Hospital approved the study. We prospectively identified all pediatric patients with EV71 infection who had been treated at Chang Gung Children's Hospital and at the National Taiwan University Hospital between 1998 and 2003. The patients were clinically confirmed to have had laboratory-confirmed EV71 infection and one of the following: hand, foot, and mouth disease; herpangina; or febrile illness. The presence of EV71 infection was confirmed on the basis of positive viral isolation of EV71, positive EV71 IgM, or an increase by a factor of 4 in EV71 neutralizing antibody serotiters between a serum sample taken at the acute stage of infection and one taken at the convalescent stage.

In total, we found 621 patients who had EV71 infection (534 at the Chang Gung Children's Hospital and 87 at the National Taiwan University Hospital). Of these, 232 patients (37.4%) had CNS involvement. The clinical severity of the condition of patients with CNS involvement was classified according to the level of severity: group 1, mild CNS involvement (i.e., aseptic meningitis); group 2, severe CNS involvement (including encephalitis, a poliomyelitis-like syndrome, and encephalomyelitis); and group 3, cardiopulmonary failure after CNS involvement. Patients who were assigned to group 1 had headaches, irritability, and cerebrospinal fluid (CSF) pleocytosis ($>5\times10^6$ leukocytes per liter) but no altered level of consciousness or focal signs. Patients who were assigned to group 2 had encephalitis with an altered level of consciousness plus CSF pleocytosis, a poliomyelitis-like syndrome with acute limb weakness and decreased reflex and muscle strength, or encephalomyelitis with the occurrence of both encephalitis and a poliomyelitis-like syndrome. Patients who were assigned to group 3 had had cardiopulmonary failure 2 to 36 hours (median, 12 hours) after manifestations of EV71 infection with CNS involvement; these children all required the use of inotropic agents, endotracheal intubation, and ventilator support, and they had cardiopulmonary failure due to medullary damage without evidence of independent pneumonia, myocarditis, or bacterial sepsis.

Of the 232 children with CNS involvement, 25 (10.8%) died of cardiopulmonary failure and brainstem encephalitis during the acute phase, and 14 (6.0%) died from deep coma or aspiration pneumonia during the convalescent stage, which was defined as more than 1 month after the onset of disease. Of the remaining 193 patients with CNS involvement, 22 declined to be assessed and 29 could not be located. Therefore, a total of 142 patients (73.6%) were prospectively enrolled in our study and were assessed between January 2003 and

December 2005 after written informed consent was obtained from their parents. There were no significant differences in clinical severity (P=0.22), age at onset (P=0.33), and sex (P=0.35) among the 142 patients who were assessed and the 51 who were not.

CLINICAL AND NEUROLOGIC ASSESSMENT

All the children underwent physical and neurologic examination by a pediatrician or a pediatric neurologist during an outpatient visit or during their stay in chronic respiratory centers. Their physical handicap or neurologic sequelae, need for ventilator support, and need for tube feeding were recorded.

Patients with EV71 infection who were 6 years of age or younger during our evaluation were assessed with the Denver Developmental Screening Test (DDST II), which measured development in four categories: gross motor, fine motor, language, and personal–social.[16] Each test item was scored as either pass or fail. For each category in the overall assessment, patients were considered to be developmentally delayed if they failed two or more test items that 75 to 90% of children of their age could pass or if they failed one or more test items that more than 90% of children younger than their age could pass. Otherwise, the development of the children was considered to be normal.

ASSESSMENT OF COGNITIVE FUNCTION

The profile on the Wechsler Intelligence Scale for Children, third edition (WISC-III), was individually assessed by a child psychologist for all children 4 years of age or older, except for three of

Table 1. Clinical and Neurologic Outcomes of 142 Patients after EV71 Infection with CNS Involvement.*

Variable	Group 1 (N=61)	Group 2 (N=53)	Group 3 (N=28)	P Value†
Demographic characteristics				
Male sex — no.	45	28	15	0.04
Age at onset — yr				<0.001
Median	2.0	2.3	0.7	
Range	0.1–7.7	0.2–13.5	0.2–4.3	
Age at assessment — yr				<0.001
Median	4.7	6.7	3.1	
Range	1.3–12.4	2.2–20.8	1.5–5.9	
Outcome				
Recovery — no. (%)	61 (100)	42 (79)	7 (25)	<0.001
Focal limb weakness and atrophy — no. (%)	0	10 (19)‡	18 (64)	
Dysphagia with tube feeding — no. (%)	0	0	17 (61)	
Central hypoventilation with ventilator support — no. (%)	0	0	16 (57)	
Facial nerve palsy — no. (%)	0	1 (2)§	7 (25)	
Seizure — no. (%)	0	0	4 (14)	
Hypoxia-related psychomotor retardation — no. (%)	0	0	5 (18)	

* Group 1 comprises patients with mild CNS involvement (aseptic meningitis); group 2 patients with severe CNS involvement: encephalitis (32 patients), a poliomyelitis-like syndrome (16 patients), or encephalomyelitis (5 patients); and group 3 patients with cardiopulmonary failure after CNS involvement.

† P values for the overall comparisons were calculated with the Kruskal–Wallis test for continuous variables or Fisher's exact test for categorical variables.

‡ Sequelae of focal limb weakness and atrophy were found in 1 of 5 patients with encephalomyelitis (20%) and in 9 of 16 patients with a poliomyelitis-like syndrome (56%).

§ Facial nerve palsy was seen in 1 of 32 patients with encephalitis (3%).

the children who had tracheostomies and could not talk. The WISC-III is composed of 13 subtests to test children's cognitive ability; the subtests are grouped into two scores: the performance IQ and the verbal IQ.[17] Four factorially derived composite subscales have been created: information, similarities, vocabulary, and comprehension for verbal comprehension; picture completion, picture arrangement, block design, and object assembly for perceptual organization; arithmetic and digit span for freedom from distractibility; and coding and symbol search for process speed.[17] Each of the IQ scores and four composite subscales yields a standard score with a mean of 100 and a standard deviation (SD) of 15. Borderline intelligence or below was defined as an IQ of less than 85.

STATISTICAL ANALYSIS

Fisher's exact test was used for analysis of categorical data, and Student's t-test and analysis of variance were used for continuous variables with normal distributions. Either the Mann–Whitney rank-sum test or the Kruskal–Wallis test was used for continuous variables without a normal distribution. If a significant difference was found by analysis of variance, pairwise comparison was performed with the use of the Scheffé method. Five separate multiple regression analyses were performed with the use of predictors identified in univariate analyses for the five separate cognitive outcomes (verbal IQ, performance IQ, full-scale IQ, verbal comprehension, and perceptual organization). All reported P values are two-sided; those under 0.05 are considered to be statistically significant. Statistical operations were performed with the use of the SAS Statistical Package, version 9.1 (SAS Institute).

RESULTS

CLINICAL AND NEUROLOGIC OUTCOMES

Of the 142 patients (85 boys and 57 girls) who had EV71 and CNS involvement, the median age at disease onset was 1.8 years (range, 0.1 to 13.5), the median age at the time of assessment was 5.0 years (range, 1.3 to 20.8), and the median interval from disease onset to assessment was 2.9 years (range, 1.0 to 7.4). There was no significant difference in the age distribution between boys and girls. The educational level of the parents was not found to be related to the clinical severity of the children's disease (P=0.45 for education of the father, and P=0.68 for education of the mother). Demographic data and clinical and neurologic outcomes were analyzed according to the clinical severity of the CNS involvement (Table 1). Group 3 was found to have had a significantly lower age at onset and age at the time of assessment (P<0.001). Some difference between boys and girls was found among the three groups (P=0.04).

All the patients with mild CNS involvement (aseptic meningitis) recovered completely. Of the 53 patients with severe CNS involvement (encephalitis, a poliomyelitis-like syndrome, and encephalomyelitis), 1 of the 32 patients with encephalitis (3%) had mild left facial nerve palsy, and 9 of the 16 patients with a poliomyelitis-like syndrome (56%) and 1 of the 5 patients with encephalomyelitis (20%) had unilateral limb weakness and atrophy.

Of the 28 patients who had cardiopulmonary failure after CNS involvement, 21 (75%) had sequelae, including 18 with limb weakness and atrophy (64%), 7 with facial nerve palsy (25%), 17 with dysphagia necessitating tube feeding (61%), 16 with central hypoventilation necessitating ventilator support (57%), 4 with seizure (14%), and 5 with seizure and psychomotor retardation from hypoxia (18%). Nineteen patients with sequelae had abnormal findings on magnetic resonance imaging, including high-intensity lesions in the tegmentum of the brain stem or high-intensity lesions in the spinal cord on the T_2-weighted image. Among patients who had cardiopulmonary failure after CNS involvement, the percentage with

Table 2. Neurodevelopment of 91 Patients after EV71 Infection with CNS Involvement.*

Type of Delay	Group 1 (N=43)	Group 2 (N=20)	Group 3 (N=28)	P Value†
		number (percent)		
Any delay	0	1 (5)	21 (75)	<0.001
Gross motor delay	0	1 (5)	19 (68)	
Fine motor delay	0	0	16 (57)	
Language delay	0	0	18 (64)	
Personal–social delay	0	1 (5)	15 (54)	

* Group 1 comprises patients with mild CNS involvement, group 2 patients with severe CNS involvement, and group 3 patients with cardiopulmonary failure after CNS involvement. The original denominators in group 1, group 2, and group 3 were 61, 53, and 28, respectively. Only 91 children who were 6 years of age or younger at the time of our study underwent assessment with the Denver Developmental Screening Test.

† The P value for the overall comparison was calculated with Fisher's exact test.

sequelae was significantly higher than that among patients with CNS involvement alone (P<0.001).

NEURODEVELOPMENTAL OUTCOME

Of the 142 patients who had EV71 infection, 91 were 6 years of age or younger at the time of our study and were assessed with the use of DDST II. Neurodevelopment of all 43 patients with aseptic meningitis was normal; only 1 patient who had severe CNS involvement without cardiopulmonary failure had a delay in the gross motor and personal–social categories (Table 2). Of the 28 patients who had cardiopulmonary failure after CNS involvement, 21 (75%) were found to have delayed neurodevelopment: 4 patients had one of four categories of delay, 2 had delay in two categories, and the other 15 had delay in all four categories. The clinical severity of the CNS involvement was significantly associated with the children's neurodevelopment (P<0.001).

COGNITIVE FUNCTION

The cognitive functions of 90 of the patients with EV71 infection who were 4 years of age or older were assessed with the use of the WISC-III (Table 3). In addition, three children in this age group could not be assessed because they had undergone tracheostomy and could not speak. Of the 90 patients who were assessed, 39 who were between the ages of 4 and 6 years were assessed with the use of both the DDST II and IQ tests. Of the 39 patients who underwent these tests, 1 in group 3 who had delayed development (according to the DDST II score) had a full-scale IQ of 47; the other 38 patients with normal scores on the DDST II had a mean (±SD) full-scale IQ of 98±13, with a median full-scale IQ of 97 (range, 67 to 118).

Clinical severity, the age at disease onset, and the educational levels of the parents were significantly associated with IQ scores in the univariate analysis. For example, the mean full-scale IQ of

Table 3. Cognitive Function of 90 Patients after EV71 Infection with CNS Involvement.*

Variable	No. of Patients	Verbal IQ	Patients with Verbal IQ <85	Performance IQ	Patients with Performance IQ <85	Full-Scale IQ	Patients with Full-Scale IQ <85
			no. (%)		*no. (%)*		*no. (%)*
Clinical severity†							
Group 1	38	99±12	5 (13)	100±14	5 (13)	99±12	5 (13)
Group 2	44	102±12	3 (7)	98±13	8 (18)	100±12	5 (11)
Group 3	8	86±22	4 (50)	82±15	4 (50)	83±19	4 (50)
P value		0.01	0.01	0.004	0.06	0.003	0.04
Age at onset							
<2 yr	34	94±12	7 (21)	93±14	11 (32)	93±12	11 (32)
≥2 yr	56	102±13	5 (9)	100±14	6 (11)	101±13	3 (5)
P value		0.006	0.20	0.02	0.02	0.005	0.002
Maternal educational level							
High school or less	57	96±13	9 (16)	96±13	10 (18)	96±13	10 (18)
College or more	33	104±13	3 (9)	100±15	7 (21)	102±13	4 (12)
P value		0.01	0.52	0.29	0.78	0.04	0.56
Paternal educational level							
High school or less	54	96±13	8 (15)	96±15	11 (20)	96±13	10 (19)
College or more	36	104±13	4 (11)	99±13	6 (17)	102±13	4 (11)
P value		0.003	0.76	0.34	0.79	0.02	0.39

* Plus–minus values are means ±SD. The original denominators in group 1, group 2, and group 3 were 61, 53, and 28, respectively, but only 90 children who were 4 years of age or older underwent assessment of IQ with the Wechsler Intelligence Scale for Children, third edition. Each of the IQ scores and four composite subscales yields a standard score of 100±15. Borderline intelligence or below was defined as an IQ of less than 85. P values were calculated with analysis of variance, Student's t-test, or Fisher's exact test.

† Group 1 comprises patients with mild CNS involvement, group 2 patients with severe CNS involvement, and group 3 patients with cardiopulmonary failure after CNS involvement.

patients with cardiopulmonary failure after CNS involvement was significantly lower than that of the other patients (P<0.05 for the comparisons between group 1 and group 3 and between group 2 and group 3). Children who were less than 2 years of age at disease onset had lower full-scale IQs and were more likely to have a full-scale IQ of less than 85 than were children whose age at onset was 2 or more years. Moreover, patients whose parents had gone to college or had postgraduate training had higher full-scale IQs than did patients whose parents had lower educational levels. Sex was not associated with IQs (P=0.98 for verbal IQ, P=0.95 for performance IQ, and P=0.89 for full-scale IQ).

Table 4 shows the results of four composite subscales for the 48 children who were 6 years of age or older at the time of the assessment and who had CNS involvement alone, without cardiopulmonary failure. The subscales that assessed processing speed and freedom from distractibility were not associated with the clinical severity of disease, the age at onset, sex, or the educational level of the parents. Verbal comprehension was significantly associated with the age at onset (P<0.001), the educational level of the father (P=0.01), and the educational level of the mother (P=0.04), and perceptual organization was significantly associated with the age at onset (P=0.04).

Table 5 presents the regression coefficients for five predictors identified by univariate analysis in the five separate multivariate models with the use of multiple regression analyses. Clinical severity was associated with IQ. There was a signifi

Table 4. Scores on Four Composite Subscales of the WISC-III in 48 Patients after EV71 Infection with Mild or Severe CNS Involvement but without Cardiopulmonary Failure.*

Variable	No. of Patients	Verbal Comprehension	Perceptual Organization	Freedom from Distractibility	Processing Speed
Clinical severity†					
Group 1	19	99±13	100±11	102±10	102±15
Group 2	29	102±12	99±13	106±17	99±18
P value		0.40	0.84	0.28	0.58
Age at onset					
<2 yr	10	90±9	92±10	101±13	97±15
≥2 yr	38	104±12	101±12	106±15	101±17
P value		<0.001	0.04	0.34	0.48
Sex					
Male	33	100±12	97±10	104±13	98±15
Female	15	103±14	104±14	107±18	106±18
P value		0.40	0.08	0.48	0.09
Maternal educational level					
High school or less	30	98±10	97±10	104±16	100±15
College or more	18	106±15	103±14	106±13	100±19
P value		0.04	0.08	0.67	0.92
Paternal educational level					
High school or less	26	97±10	97±11	103±15	99±14
College or more	22	106±13	101±13	107±14	102±19
P value		0.01	0.22	0.42	0.52

* Plus–minus values are means ±SD. The original denominator of patients in group 1 was 61, and the original denominator in group 2 was 53, but only 48 patients in both groups who were 6 years of age or older underwent assessment for the four composite subscales. Because only one patient in group 3 underwent the complete subscale assessment, group 3 was not factored into the analysis. Each of the IQ scores and four composite subscales on the Wechsler Intelligence Scale for Children, third edition (WISC-III), yields a standard score of 100±15. P values for the overall comparison were calculated with Student's t-test.

† Group 1 comprises patients with mild CNS involvement, and group 2 patients with severe CNS involvement.

Table 5. Multivariate Analysis of Factors Associated with IQ, Verbal Comprehension, and Perceptual Organization in Patients after EV71 Infection with CNS Involvement.*

Variable	Verbal IQ (N=90)		Performance IQ (N=90)		Full-Scale IQ (N=90)		Verbal Comprehension (N=48)		Perceptual Organization (N=48)	
	β	P Value	β	P Value	β	P Value	β	P Value	β	P Value
Clinical severity (with group 1 as reference group)†										
Group 2	2.6	0.34	−1.6	0.60	0.5	0.86	3.8	0.28	−1.9	0.60
Group 3	−11.4	0.03	−17.0	0.003	−15.5	0.003	ND	ND	ND	ND
Age at onset <2 yr vs. ≥2 yr	−5.4	0.06	−4.3	0.16	−5.2	0.06	−11.8	0.009	−8.2	0.07
Male sex vs. female sex	−0.5	0.85	−2.4	0.43	−1.8	0.51	1.0	0.80	−5.8	0.14
Maternal educational level of college or more vs. high school or less	2.4	0.50	1.8	0.65	2.3	0.51	3.7	0.42	6.3	0.18
Paternal educational level of college or more vs. high school or less	6.5	0.07	1.6	0.68	4.7	0.18	3.6	0.45	−3.8	0.43

* The original denominator of patients was 142, but only the 90 children who were 4 years of age or older underwent assessment of IQ with the Wechsler Intelligence Scale for Children, third edition, and only 48 patients in group 1 and group 2 who were 6 years of age or older underwent assessment with the composite subscales of verbal comprehension and perceptual organization. Adjusted P values were derived by multiple regression. β denotes the regression coefficient in the multivariate model, and ND not done.

† Group 1 comprises patients with mild CNS involvement, group 2 patients with severe CNS involvement, and group 3 patients with cardiopulmonary failure after CNS involvement.

cant association between the age at onset and the assessment of verbal comprehension (P=0.009); the association between the age at onset and the assessment of perceptual organization did not reach statistical significance (P=0.07).

At the time of our study, 47 of the 142 patients were attending school. Of those children, six (13%), including two in group 1 and four in group 2, had received the diagnosis of attention-deficit–hyperactivity disorder (ADHD) requiring medication; one of the six children with ADHD also had aggressive behavior, and another three (6%), all in group 3, required special education services at school.

DISCUSSION

Our study assessed long-term neurologic sequelae, neurodevelopment, and cognitive function in patients who had EV71 infection with CNS involvement. We found that patients who had EV71 infection with CNS involvement had an increased likelihood of long-term neurologic sequelae, as well as delayed neurodevelopment, as a function of the clinical severity of the CNS involvement. Of the children assessed who had severe CNS involvement but who did not have cardiopulmonary failure, only 1 of 20 (5%) had delayed neurodevelopment. We also found cognitive function to be associated with the clinical severity of the illness and the patient's age at the onset of infection.

The cause of long-term neurologic sequelae is related to neuron damage. This complication could have been caused by a direct EV71 invasion or, in some cases, by hypoxia. The findings on imaging studies of our patients who had EV71 infection were compatible with the neuroanatomic lesions of their sequelae, similar to previous reports.[18,19] EV71 viral antigen has been seen in neurons with immunocytochemical staining.[20,21] Therefore, direct EV71 invasion and subsequent neuron damage could be said to be the main cause of the sequelae. These clinical characteristics raise important questions about the biology of the virus and its mode of spread.[22] Further investigation into its virulence and its mode of transmission is mandatory to help control EV71 infection.

There have been few studies to date on cognitive function after viral encephalitis. Therefore, our study may provide information that can be used to assess long-term prognosis of viral CNS infection. Patients with the most severe illness

— those with severe CNS involvement plus cardiopulmonary failure — scored significantly lower on IQ evaluations than did patients with less severe illness, a difference that may have been due to both direct viral CNS effects and the indirect anoxic and ischemic effects on the CNS. However, we cannot exclude the possibility that the inability to attend school accounted for the patients' poor testing results. Patients who had CNS involvement alone did well in the assessment of neurodevelopment, but children who were infected before the age of 2 years had lower scores on verbal comprehension than did children who were infected at older ages (Table 4 and Table 5). It is possible that neuron damage may be more profound when the CNS of younger children is infected by EV71. This possibility may be applied to CNS infection with other enteroviruses as well. The possibility that younger children who had CNS infection caused by other enteroviruses have reduced cognitive function also deserves further exploration.

Because psychiatric problems after EV71 infection may be noticed only when children start going to school, there may be higher rates of learning and behavioral problems at school age. For example, some of the patients we studied were found to have ADHD, resulting in behavioral problems and the need for medication or special educational services at school. Most children who had cardiopulmonary failure after CNS involvement were not yet old enough to attend school. Many severe learning and behavioral problems may be observed only after children start school. Careful follow-up is thus warranted. Our results suggest that children who have had EV71 infection with CNS involvement may benefit from early evaluation for psychiatric problems and early intervention.

In conclusion, EV71 infection with CNS involvement and cardiopulmonary failure may be associated with long-term neurologic sequelae, delayed neurodevelopment, and reduced cognitive function — conditions that may cause further learning and behavioral problems once children attend school. Patients who had EV71 infection with CNS involvement alone without cardiopulmonary failure did well on neurodevelopment testing but had reduced scores on verbal comprehension if they were under the age of 2 years at the onset of the infection. Early evaluation and intervention for psychiatric and cognitive problems may prove beneficial for children after EV71 infection with CNS involvement and cardiopulmonary failure and for children who are infected at a very young age.

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