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Pediatrics published online Jul 7, 2008;
DOI: 10.1542/peds.2007-3799

ARTICLE

Attention-Deficit/Hyperactivity–Related Symptoms Among Children With Enterovirus 71 Infection of the Central Nervous System

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The authors have indicated they have no financial relationships relevant to this article to disclose.

What's Known on This Subject

Neurodevelopment and cognitive function can be affected by CNS infections such as tuberculosis meningitis, herpes simplex encephalitis, Japanese encephalitis, and several bacterial meningitis infections including *Haemophilus* type b meningitis.

What This Study Adds

EV71 CNS infection may affect long-term regulation of attention and emotion and cause hyperactivity-impulsivity in children.

ABSTRACT

BACKGROUND. No study has investigated the association between enterovirus 71 central nervous system infection and symptoms related to attention-deficit/hyperactivity disorder. In this study we evaluated attention-deficit/hyperactivity disorder–related symptoms and internalizing problems as long-term sequelae resulting from enterovirus 71 central nervous system infection in children.

METHODS. We enrolled 86 children 4 to 16 years old with virus-culture–confirmed enterovirus 71 infection and central nervous system involvement diagnosed 3 to 7 years before the study and 172 control subjects, matched for age, gender, and parents' education levels. Their mothers and teachers were asked to report on possible attention-deficit/hyperactivity disorder–related symptoms, and their mothers were asked to report on possible internalizing problems. All of the children previously infected with enterovirus 71 received intelligence tests.

RESULTS. Forty-two (49%) of the children previously infected with enterovirus 71 had had viral meningitis; 35 (41%) had severe central nervous system involvement, such as encephalitis, poliomyelitis-like syndrome, or encephalomyelitis; and 9 (10%) had cardiopulmonary failure and central nervous system involvement. The children previously infected with enterovirus 71 had higher scores than matched control subjects on teacher- and mother-rated scales of inattention, hyperactivity-impulsivity, oppositional symptoms, and attention-deficit/hyperactivity disorder index. The rate of elevated attention-deficit/hyperactivity disorder–related symptoms among children with enterovirus 71 central nervous system infection was 20%, whereas that rate among matched control subjects was only 3%. They also had more internalizing problems. Their verbal and performance IQs, as well as verbal comprehension indices, were significantly inversely correlated with symptoms of inattention, hyperactivity-impulsivity, and attention-deficit/hyperactivity disorder index scores.

CONCLUSIONS. Enterovirus 71 central nervous system infection may affect long-term regulation of attention and emotion and cause hyperactivity-impulsivity in children. *Pediatrics* 2008;122:e000

www.pediatrics.org/cgi/doi/10.1542/peds.2007-3799

doi:10.1542/peds.2007-3799

This trial has been registered at www.clinicaltrials.gov (identifier NCT00172393).

Key Words
enterovirus 71, central nervous system, attention deficit, intelligence, children

Abbreviations
EV71— enterovirus 71
CNS— central nervous system
ADHD—attention-deficit/hyperactivity disorder
CSF— cerebrospinal fluid
WISC-III—Wechsler Intelligence Scale for Children-Third Edition
CPRS-R:S—Conners' Parent Rating Scale-Revised: Short Form
CTRS-R:S—Conners' Teacher Rating Scale-Revised: Short Form
SDQ—Strengths and Difficulties Questionnaire
ICC—intraclass correlation
PIQ—performance IQ
VIQ—verbal IQ
VCI—verbal comprehension index
POI—perceptual organization
FDI—freedom-from-distractibility index
PSI—process speed index
CI— confidence interval

Accepted for publication Mar 27, 2008

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THERE WERE LARGE outbreaks of enterovirus 71 (EV71) infection resulting in dozens of deaths in Bulgaria in 1975,[1] Hungary in 1978,[2] and Malaysia in 1997[3] and in the largest and most severe EV71 epidemic to date in Taiwan in 1998.[4] During the 1998 Taiwan EV71 epidemic, almost all of the patients with cardiopulmonary failure died.[4,5] In 2000, to improve survival, we developed a disease management program that was adjusted depending on stage of EV71 infection.[6,7] Although this program reduced acute mortality, long-term sequelae, particularly cognitive and mental problems, have remained a great concern.

Neurodevelopment and cognitive function can be affected by central nervous system (CNS) infections, such as tuberculosis meningitis,[8] herpes simplex encephalitis,[9,10] Japanese encephalitis,[11,12] and several bacterial meningitis,

including Haemophilus type b meningitis.[13–16] Until our follow-up study of 142 children who had survived EV71 CNS infections in 2007, no study had focused on long-term sequelae in this population.[17]

Children with CNS infection may also suffer from inattention, hyperactivity, and impulsivity when the prefrontal lobe and its connection to striatum, the parietal lobe, cerebellum, and other circuits are involved[18] and from emotional problems when the function of brain areas such as amygdala and nucleus accumbens is affected.[19] The likelihood of developing attention deficit is also thought to be increased in children with acquired hearing loss after bacterial meningitis or congenital rubella.[20]

Although there is strong evidence suggesting that genetic factors play a significant role in the development of attention-deficit/hyperactivity disorder (ADHD),[21] biological adversity, such as trauma, metabolic derangement, toxin exposure, and CNS infection, may also cause ADHD in some children.[8,22] However, few studies have systemically and prospectively examined the consequence of CNS infection on the controls of attention, activity, and impulsivity.[8,14,15] Wait et al[8] have reported increased rates of ADHD among 21 children who had survived tuberculosis meningitis. However, to the best of our knowledge, no longitudinal study has specifically investigated ADHD-related symptoms and emotional problems as sequelae of EV71 CNS infection. To do this, we prospectively followed up a cohort of children with EV71 CNS infection to assess their ADHD symptoms and other emotional/behavioral problems, compared the prevalence of elevated ADHD-related symptoms in children previously affected by EV71 CNS infection with that of matched control children, and correlated the intellectual factors with ADHD-related symptoms.

METHODS

Participants

Patient Enrollment and Clinical Severity of EV71 CNS Infections

From 1998 to 2003, we identified all of the patients with EV71 at Chang Gung Children's Hospital and National Taiwan University Hospital on the basis of clinical diagnoses of hand, foot, and mouth disease, herpangina, or febrile illness. EV71 infection was confirmed by positive viral isolation of EV71, and/or positive EV71 immunoglobulin M, and/or a fourfold rise in EV71 neutralizing antibody serotiters between acute and convalescent sera.

During this study period, 621 patients with EV71 were identified, 534 at Chang Gung Children's Hospital and 87 at National Taiwan University Hospital. A total of 232 had CNS involvement. They were categorized into 3 groups: (1) case subjects with mild CNS involvement, that is, aseptic meningitis; (2) case subjects with severe CNS involvement, such as encephalitis, poliomyelitis-like syndrome, or encephalomyelitis; and (3) case subjects with cardiopulmonary failure after CNS involvement. Aseptic meningitis was defined as having headache, irritability, and cerebrospinal fluid (CSF) pleocytosis ($>5 \times 10^6$ leukocytes per L) without an altered level of consciousness or focal signs. Encephalitis was defined as having an altered level of consciousness plus CSF pleocytosis, poliomyelitis-like syndrome as having acute limb weakness and decreased reflex and muscle strength, and encephalomyelitis as having the occurrence of both encephalitis and poliomyelitis-like syndrome. Cardiopulmonary failure was defined as pulmonary edema and/or hemorrhage with decreased ejection fraction of the left ventricle, necessitating inotropic agent support as assessed by echocardiography.

Thirty-nine (16.8%) of these 232 patients died as a result of cardiopulmonary failure induced by brainstem encephalitis during acute illness or either aspiration pneumonia or sepsis during the convalescent stage. Of the remaining 193 patients with CNS involvement (172 at Chang Gung Children's Hospital and 21 at National Taiwan University Hospital), 22 refused the assessment and 29 could not be located, leaving 142 to be enrolled for the assessment of neurodevelopment and cognition, including the Wechsler Intelligence Scale for Children-Third Edition (WISC-III).[17] A total of 107 (aged ≥4) of the 142 patients with CNS involvement were eligible for the assessment of intelligence and emotional or behavioral problems. Of these 107 children, 21 refused the assessment of ADHD-related symptoms, whereas 86 (80.4%) consented to this study and completed the assessments. There were no significant differences in clinical severity or demographics between the 86 patients whom we assessed for ADHD-related symptoms and the 21 patients whom we did not assess ($P = .19$ for clinical severity, $P = .13$ for age of onset, and $P = .98$ for gender). The mean ± SD interval between the assessment of neurodevelopment/cognition and assessment of ADHD-related symptoms was 1.23 ± 0.85 years (range: 0.00–2.64 years).

Community-Based Controls

Each case subject was matched with 2 neighborhood or school control subjects for age, gender, school performance, and parental educational levels. Children with any history of developmental delay or use of special educational services and children with superior academic performance were excluded from the control group. The final sample consisted of 86 case subject 4 to 16 years old (51 boys and 35 girls) and 172 matched control subject (Table 1).

Measures

Chinese Version of the Conners' Parent Rating Scale-Revised: Short Form and Conners' Teacher Rating Scale-Revised: Short Form

The Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S), a 27-item parent-reported rating scale, consists of 3 factor-derived subscales (those with the highest loadings on the CPRS-R: long form) and the ADHD index.[23,24] The 3 subscales are inattention/cognitive problems (6 items), hyperactivity/impulsivity (6 items), and oppositional (6 items). The ADHD index (12 items) is used to assess children and adolescents at risk for ADHD on the basis of diagnostic criteria of the *Diagnostic*

TABLE 1 **Sample Description**

Variable	EV71 Case Subject ($N = 86$)
Gender, *n* (%)	
Boy	51 (59)
Girl	35 (41)
Age range, y	4.17 to 16.08
Mean ± SD	7.11 ± 2.54
Age at EV71 infection, range, y	0.10 to 12.68
Mean ± SD, y	2.52 ± 2.12
Duration after EV71 infection, range, y	0.42 to 7.45
Mean ± SD, y	4.58 ± 1.56
Father's education level, *n* (%)	
Junior high or less	18 (21)
Senior high	32 (38)
College or higher	34 (40)
Mother's education level, *n* (%)	
Junior high or less	15 (18)
Senior high	36 (43)
College or higher	33 (39)
Birth order, *n* (%)	
Single child	8 (9)
First child	24 (28)
Youngest child	44 (52)
Middle child	9 (11)
IQ, mean ± SD	
Full-scale IQ	99.35 ± 13.25
VIQ	100.38 ± 13.18
PIQ	98.52 ± 14.34

and Statistical Manual of Mental Disorders, Fourth Edition, rather than factor analysis.[23] Likewise, the Conners' Teacher Rating Scale-Revised: Short Form (CTRS-R:S), a 28-item teacher-reported rating scale, also consists of 3 subscales and the ADHD index (12 items). The 3 subscales are oppositional (5 items), inattention/cognitive problems (5 items), and hyperactivity/impulsivity (7 items), as well as the ADHD index (12 items).[23,25] Each item on both scales is rated on a 4-point Likert scale (0 for never or seldom, 1 for occasionally, 2 for often or quite a bit, and 3 for very often or very frequently).[23]

The Chinese versions of the CPRS-R:S and CTRS-R:S have been found to be reliable and valid instruments for measuring ADHD-related symptoms in Taiwan.[26] This study used cutoff values of 20 and 17 for the ADHD index of the Chinese CPRS-R:S and CTRS-R:S, respectively, to define a case subject as potentially having ADHD.[26] A *t* score >70 (2 SDs greater than mean score) was also used to define a case subject as potentially having ADHD.

Strengths and Difficulties Questionnaire

The Strengths and Difficulties Questionnaire (SDQ), a 25-item behavioral screening questionnaire, is designed to assess a broader area of various behaviors in children and adolescents. Each item is rated on a 3-point scale (0, not true; 1, somewhat true; 3, certainly true).[27] The parent form of the Chinese SDQ includes 4 subscales: conduct problem, inattention/hyperactivity, prosocial, and internalizing.[28] It has been found to have good test-retest reliability (intraclass correlations [ICCs]) and internal consistency (Cronbach's α) for the prosocial subscale (ICC = 0.90; α = .74) and the internalizing subscale (ICC = 0.85; α = .88), which were used in this study.

Wechsler Intelligence Scale for Children-Third Edition

In this study, a child psychologist assessed each child individually by using the WISC-III.[29] The WISC-III is composed of 13 subtests to assess cognitive ability by performance IQ (PIQ) and verbal IQ (VIQ). Four factorially derived composite subscales have been created: (1) verbal comprehension index (VCI) (information, similarities, vocabulary, and comprehension); (2) perceptual organization index (POI) (picture completion, picture arrangement, block design, and object assembly); (3) freedom-from-distractibility index (FDI; arithmetic and digit span); and (4) process speed index (PSI) (coding and symbol search).[30]

Laboratory Data

All of the patient laboratory data were collected during patient hospitalization for treatment of EV71 infection and included glucose, protein, lactate, and white blood cell count (including neutrophils, lymphocytes, and monocytes) in the CSF. We also used estimations of the severity of CNS involvement and findings from electroencephalogram, CNS computed tomography, and CNS MRI during hospitalization and follow-up.

Procedures

The institutional review board of National Taiwan University Hospital approved this clinical study. The child subjects and their parents and teachers received a comprehensive explanation of the purpose and procedure of this study, as well as reassurance of confidentiality. They were informed that participation in this study was completely voluntary and that nonparticipation would not influence their treatment. Written informed consent for all of the enrollees was obtained from their parents. Their parents answered the Chinese CPRS-R:S and SDQ either at the clinic or at home, and their teachers answered the CTRS-R:S at school.

Statistical Analysis

Alpha value was preselected at the level of $P < .05$. The descriptive results were displayed as frequency and percentage for categorical variables; for continuous variables, results were displayed as mean and SD. To conduct a matched case-control analysis for the continuous variables, we used the linear multilevel model to compare the mean scores and *t* scores of subscales of the CPRS-R:S, CTRS-R:S, and SDQ between the case and control groups. The *t* score was defined by multiplying the *z* score by 10 and adding 50 with a mean of 50 and an SD of 10 [*t* score = (*z* score × 10) + 50]. The effect sizes (standardized difference between 2 means) were further computed using Cohen's *d*.[31] We defined small, medium, and large effect sizes as Cohen's *d* 0.25 to 0.5, 0.5 to 0.75, and >0.75, respectively. We used conditional logistic regression to compare the prevalence rate

TABLE 2 **Comparison of ADHD Symptoms Between Children With EV71 CNS Infection and Control Subjects**

Variable	Case ($N = 86$)		Control ($N = 172$)		Statistics		Cohen's *d*
	Mean (SD)	*t* Score (SD)	Mean (SD)	*t* Score (SD)	F Value	*P*	
CPRS-R:S							
Inattention-cognitive problems	4.84 (4.01)	54.63 (12.49)	3.22 (2.50)	49.48 (7.86)	15.93	<.001	0.49
Hyperactivity-impulsivity	5.13 (4.95)	54.51 (13.86)	3.61 (3.36)	50.22 (9.15)	10.58	.001	0.36
Oppositional	5.06 (3.38)	54.60 (12.81)	4.24 (2.45)	51.48 (9.30)	4.92	.028	0.28
ADHD index	11.65 (7.59)	53.73 (11.84)	8.75 (5.21)	49.16 (8.13)	13.71	<.001	0.45
Sum score	24.45 (16.05)	54.63 (12.44)	18.37 (10.19)	49.89 (7.94)	14.99	<.001	0.45
CTRS-R:S							
Inattention-cognitive problems	2.99 (2.90)	54.35 (9.66)	1.53 (2.62)	49.53 (8.10)	14.60	<.001	0.53
Hyperactivity-impulsivity	3.52 (4.13)	55.46 (13.26)	1.45 (2.41)	49.09 (7.78)	27.16	<.001	0.61
Oppositional	1.63 (2.45)	55.66 (15.05)	0.74 (1.86)	50.41 (12.01)	9.61	.002	0.41
ADHD index	8.98 (7.71)	57.54 (12.38)	4.06 (4.42)	49.85 (7.36)	42.13	<.001	0.78
Sum score	16.51 (14.75)	57.15 (12.47)	7.52 (8.45)	49.88 (7.33)	37.89	<.001	0.75
SDQ							
Prosocial behaviors	11.42 (3.25)	51.93 (11.32)	10.82 (2.94)	49.83 (10.17)	2.28	.133	0.19
Internalizing symptoms	4.12 (2.94)	54.30 (12.13)	3.18 (2.31)	50.41 (9.61)	8.93	.003	0.36

of children with elevated ADHD-related symptoms and to calculate the odds ratio and 95% confidence interval (CI). Multiple linear regression was used to correlate the cognitive components with the severity of ADHD-related symptoms among affected children. All of the statistical operations were performed by using SAS 9.1 (SAS Institute, Inc, Cary, NC).

RESULTS

Demographics and Clinical and Neurologic Outcomes

Table 1 presents the distribution of cases by gender, age of assessment, age of disease onset, parents' education levels, birth orders, and IQ. The mean full-scale IQ for 86 case subjects was 99.35, indicating that intelligences were within the reference range. Forty-two subjects had mild CNS involvement, 35 had severe CNS involvement, and 9 had cardiopulmonary failure after CNS involvement. With regard to their neurologic outcomes, all of the case subjects with mild CNS involvement (aseptic meningitis) recovered completely, 4 of the case subjects with severe CNS involvement had sequelae of limb weakness/atrophy ($n = 3$) or facial nerve palsy ($n = 1$), and 3 of the case subjects with cardiopulmonary failure after CNS involvement had sequelae of limb weakness/atrophy. There were significant differences in the outcomes among case subjects categorized by 3 levels of severity ($P = .006$).

ADHD-Related and Internalizing Symptoms

The children with EV71 CNS infection were found 4 to 5 years later after initial diagnosis to have significantly higher sum scores and *t* scores on the 4 subscales and total scale of the CPRS-R:S and CTRS-R:S than control subjects. The effect sizes (Cohen's *d*) varied from small (0.28 for the oppositional subscale of the CPRS-R:S) to large (0.78 for the ADHD index of the CTRS-R:S). In addition, the study population of EV71 case subjects with CNS involvement had a higher score on screening for internalizing problems with small effect size (Table 2). There was no difference in prosocial behaviors.

On the basis of our categorical approach, the children with EV71 CNS infection (20%) were more likely than the matched control subjects (3%) to have elevated ADHD-related symptoms, regardless of whether they were assessed by parents or teachers, using cutoff points of 20 for the CPRS-R:S and of 17 for the CPRS-R:S and *t* score >70 for both scales ($P < .001$; Table 3).

Cognitive Function (IQ) and ADHD-Related Symptoms

Table 4 summarizes the regression coefficients and their 95% CIs for the effect of each subscale of the WISC-III on the ADHD-related symptoms measured by the CTRS-R:S. We found that the PIQ, VIQ, FIQ, VCI, FDI, and PSI scores were significantly reversely correlated with the severity of the inattention/cognitive problems. We also found that the PIQ, VIQ, FIQ, VCI, and PSI scores were significantly reversely correlated with the severity of the hyperactivity/impulsivity symptoms and that the VIQ, FIQ, VCI, and PSI scores were reversely correlated with the severity of the ADHD index. However, we found no association between oppositional symptoms and measures of IQ (*P* values ranging from .20 to.97).

We further conducted backward model selection to identify the WISC-III subscales (VCI, POI, FDI, and PSI) that correlated the most with severity of ADHD-related symptoms. We found VCI to be the only variable significantly correlated with severity of attention/cognitive problems ($P = .004$; $R^2 = 22.36\%$), severity of hyperactivity/impulsivity symptoms ($P = .005$; $R^2 = 21.4\%$), and severity of ADHD index scores ($P = .014$; $R^2 = 16.93\%$).

Neither the clinical severity nor laboratory data collected during the hospitalization for EV71 CNS infection predicted ADHD symptoms (all $P > .05$). Moreover, we did not find a significant association between age of EV71 infection and severity of ADHD-related symptoms ($P = .13$–$.88$).

DISCUSSION

This study, the first follow-up study examining the behavioral outcomes in children with EV71 CNS infection,

TABLE 3 **Rates of Elevated ADHD-Related Symptoms Between Children With EV71 CNS Infection and Control Subjects**

Variable	Case, *n* (%)	Control, *n* (%)	Odds Ratio	95% CI	*P*
Cutoff score					
CPRS-R:S (ADHD index >20)	10 (12)	5 (3)	4.66	1.45 to 14.98	<.001
CTRS-R:S (ADHD index >17)	11 (13)	3 (2)	10.29	2.27 to 46.66	.003
Either one	17 (20)	5 (3)	8.15	2.73 to 24.28	<.001
t score of the ADHD index >70					
CPRS-R:S	8 (9)	1 (1)	16.00	2.00 to 127.87	.009
CTRS-R:S	12 (14)	5 (3)	7.07	1.97 to 25.32	.003
Either one	16 (19)	5 (3)	9.72	2.81 to 33.56	<.001

Data are based on the ADHD index of Conners' Rating Scale.

has clearly demonstrated the association between the EV71 CNS infection and increased symptoms of inattention, hyperactivity, oppositional defiance, internalizing problems, and increased likelihood of ADHD diagnosis. Our findings support our hypothesis that children infected with EV71 CNS are more likely to have ADHD-related symptoms regardless of IQ. Literature has clearly documented that increased severity of ADHD symptoms is related to poorer academic performance even in normally intelligent children.[32] Because no study has systemically examined the ADHD symptoms or diagnosis among a large sample of children with CNS infections, 1 possible explanation of the reduced academic achievement noted among the normally intelligent children with *Haemophilus influenzae* type b meningitis might be a result of ADHD-related symptoms.[14–16] Additional systematic follow-up studies and detailed clinical evaluation on different groups of children after CNS infections are needed to confirm whether an increased ADHD symptom is specific to EV71 or common to a variety of microorganisms.

Our finding of increased severity of ADHD symptoms in children with EV71 CNS infection suggests that the infection may involve the prefronto-striatum-subcortical area of the brain or another area related to the core symptoms of ADHD[8,18] and that this involvement may not be identified by anatomic changes detected by the kind of structural brain imaging that we used in this study but by the functional changes using the neuropsychological assessment. This study only used mother and teacher reports of standardized behavioral measures. Additional studies using neuropsychological assessment can be conducted to further confirm our findings of increased ADHD symptoms in these children.

We were surprised that we did not find a correlation between age of EV71 infection, any laboratory data, or the severity of CNS involvement and the severity of ADHD-related symptoms among children with EV71 CNS infection. However, we found that intelligence scales were correlated with the severity of ADHD symptoms rather than oppositional defiant symptoms. Consistent with literature, the FDI is related to symptoms of inattention.[33] Previous studies, however, do not support our finding that the VCI can predict ADHD-related symptoms.[34] Our finding suggests that the ADHD-related symptoms associated with CNS infection may have different behavioral and cognitive manifestations and that EV71 CNS infection may affect a brain area involving both ADHD-related symptoms and verbal comprehension.

We found some evidence of an association between EV71 CNS involvement and increased internalizing symptoms. This finding might be explained by CNS involvement in the brain areas related to emotional regulation,[19] concurrence with anxiety/depression in children with ADHD,[35] or post-CNS infection adjustment problems. Although our evidence is weak, and more detailed evaluation to confirm the results of increased internalizing symptoms is needed, some attention should be paid to the possible increase in anxiety/depressive symptoms in these children.

This study is the first to investigate the risk for ADHD in a prospective follow-up matched case-control study of children after EV71 CNS infection with a large sample

TABLE 4 **Correlation of Cognitive Function With the Teacher-Reported ADHD-Related Symptoms Among Children With EV71 CNS Infection**

Variables	CTRS-R:S								
	Inattention/Cognitive Problem			Hyperactivity-Impulsivity			ADHD Index		
	β	95% CI	*P*	β	95% CI	*P*	β	95% CI	*P*
Full-scale IQ	−.09	−0.143 to −0.037	.001	−.11	−0.179 to −0.041	.002	−.18	−0.324 to −0.041	.012
PIQ	−.06	−0.109 to −0.003	.039	−.07	−0.140 to −0.004	.039	−.10	−0.242 to 0.036	.144
VIQ	−.10	−0.155 to −0.053	<.001	−.12	−0.186 to −0.052	.001	−.21	−0.344 to −0.067	.004
Verbal comprehension	−.11	−0.175 to −0.036	.004	−.13	−0.222 to −0.042	.005	−.25	−0.445 to −0.054	.014
Perceptual organization	−.04	−0.107 to 0.036	.318	−.07	−0.161 to 0.019	.118	−.09	−0.281 to 0.111	.384
FDI	−.08	−0.148 to −0.011	.025	−.06	−0.149 to 0.038	.234	−.12	−0.315 to 0.081	.237
PSI	−.06	−0.117 to 0.005	.071	−.08	−0.157 to −0.003	.043	−.18	−0.340 to −0.014	.034

size and use of standardized measures. However, it has some limitations. First, the average age of onset of EV71 CNS infection is ~2.5 years old, and there is no suitable behavioral measure for ADHD for children at such young ages. Therefore, we were unable to assess ADHD symptoms before the onset of EV71 CNS infection, which also limited our ability to clearly establish a causal link between the CNS infection and ADHD symptoms. However, because there is no literature showing ADHD as a risk factor for EV71 infection, it can be assumed that children with EV71 infection were not selected from the population at risk of ADHD and that EV71 CNS infection predicted increased ADHD-related symptoms, as well as emotional symptoms in this study. Second, we did not do any neuropsychological studies, which could have validated our behavioral-based findings that EV71 CNS infection may cause the functional impairment in the control of attention, motor, and impulse. Third, because we did not collect information on academic performance, we were unable to test whether EV71 CNS infection, such as *H influenzae* type B,[36] negatively impacts on achievement and cognitive dysfunction in normally intelligent children. Future studies should be conducted using a psychiatric interview to confirm the diagnosis of ADHD and its comorbid mental disorders.

Our findings suggest that, although only some of the children with EV71 CNS infection in this study had obvious ADHD symptoms, it would be advisable to assess symptoms of ADHD regardless of the extent of brain involvement or intelligence test scores, because ADHD symptoms may influence school performance, peer relationships, and at-home behaviors.[32,35,37] Early identification of ADHD symptoms may make possible early parental counseling/training and educational intervention and, thus, possibly offset adjustment problems at school and in society and family dysfunction.

CONCLUSIONS

EV71 CNS infection may affect long-term regulation of attention and emotion and cause hyperactivity-impulsivity in children. Early assessment and identification of ADHD symptoms and emotional/behavior problems among these children are recommended, and early intervention may prove beneficial for their future performance.

ACKNOWLEDGMENTS

This work was supported by the National Research Program for Genomic Medicine, National Science Council (Taiwan) grant NSC95-3112-B-002-025.

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Pediatrics published online Jul 7, 2008;
DOI: 10.1542/peds.2007-3799