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Long-term psychiatric outcomes in youth with enterovirus A71 central nervous system involvement

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ABSTRACT

Long-term neurological and neurodevelopmental sequelae are a concerning issue for people with Enterovirus A71 (EV-A71) central nervous system (CNS) infection. Unfortunately, no longitudinal prospective clinical study has systematically investigated the consequences of EV-A71 CNS infection during early life on the later development of other psychiatric disorders. In this naturalistic longitudinal follow-up design, we followed forty-three youth, who got EV-A71 CNS involvement 6–18 years ago and were enrolled in other EV-A71 clinical studies then. Their psychiatric presentation, emotional/behavioral problems, and cognitive issues were examined using a psychiatrist-conducted diagnostic interview, parent- and self-rated questionnaires, and neuropsychological tests, respectively. We compared the prevalence of psychiatric disorders in youth with EV-A71 CNS involvement to a nationally representative cohort. Emotion/behavior and cognition in EV-A71-CNS-infected youth were compared to those in a matched community-based sample of healthy controls and youth with attention-deficit/hyperactivity disorder (ADHD). Compared to a national sample (absolute ADHD prevalence 10.1%), youth with EV-A71 CNS involvement had three times the odds of receiving an ADHD diagnosis (standardized prevalence ratio, 95% CI = 1.8, 4.2; absolute ADHD prevalence 34.9%). No other psychiatric diagnoses were more common in EV-A71-CNS-infected youth. Compared to community-based ADHD youth, EV-A71-CNS-infected youth with psychiatric disorders showed comparable core ADHD symptoms, opposition/defiance, autistic features, and suboptimal sustained attention performance (based on the Conners' Continuous Performance Test), all of which were more severe than healthy controls. EV-A71-CNS-infected youth without psychiatric disorders showed comparable autistic features to EV-A71-CNS-infected youth with psychiatric disorders and ADHD youth. EV-A71 CNS involvement may cause long-term, adverse psychiatric outcomes that develop into an ADHD diagnosis alongside social/communication/emotion problems and autistic features. We recommend earlier identification and intervention of these problems among these children.

1. Introduction

Enterovirus A71 (EV-A71) is one of the most common intestinal viruses that cause hand, foot, and mouth disease in infants and young children (Solomon et al., 2010). It has emerged as a significant pediatric infectious disease (Solomon et al., 2010)—especially in South-East Asia

Abbreviations: EV-A71, enterovirus A71; CNS, central nervous system; ADHD, attention-deficit/hyperactivity disorder; TDC, typically developing control; TNESCMD, Taiwan's National Epidemiological Study of Child Mental Disorders; FSIQ, full-scale intelligence quotient; PIQ, performance intelligence quotient; VIQ, verbal intelligence quotient; K-SADS-E, Kiddie Schedule for Affective Disorders and Schizophrenia-Epidemiological Version; SNAP-IV, Swanson Nolan and Pelham, Version IV Scale; SRS, Social Responsiveness Scale; AQ, Autism Spectrum Quotient; SDQ, Strengths and Difficulties Questionnaire; CCPT, Conners' Continuous Performance Test; ASD, autism spectrum disorder.

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(Sabanathan et al., 2014)—because of a series of outbreaks. For example, in Taiwan, nationwide epidemics occurred in 1998, 2000–2001, 2005, 2008, and 2012 (Chia et al., 2014). In addition to frequent outbreaks, EV-A71 is associated with the severe central nervous system (CNS) involvement and high mortality rates (Chang et al., 1999; Huang and Shih, 2015). Today, long-term neurological and neurodevelopmental sequelae remain a concerning issue for people with EV-A71 CNS involvement (Chang et al., 2019). Such sequelae negatively impact the quality of life and well-being of surviving patients and their families.

Most studies in this area have focused on neurological sequelae such as limb weakness and atrophy, and seizure (Chang et al., 2007, 2019; Huang et al., 2006; Tsou et al., 2008). However, neurodevelopment of emotional and cognitive regulation can also be negatively affected by EV-A71 CNS involvement (Chang et al., 2007, 2019; Gau et al., 2008a). Specifically, our previous studies show that children with severe EV-A71 CNS involvement score lower on intelligence tests than infected children with mild CNS involvement three years after an acute infection (Chang et al., 2007). Furthermore, based on parent-rated psychometric assessments, children with EV-A71 CNS involvement have more severe symptoms of attention-deficit/hyperactivity disorder (ADHD) and internalizing problems five years later when compared to typically developing controls (TDC) (Gau et al., 2008a).

In addition to this dimensional approach placing problematic behaviors on a continuum of severity, earlier literature suggests that childhood exposure to viral CNS infections in general may contribute to the categorical diagnosis (which is relied on diagnostic criteria to determine the presence or absence of abnormal behaviors) of mental disorders (Köhler-Forsberg et al., 2019; Pedersen et al., 2020). Although earlier reports using Taiwan's national health insurance register indicate the association between symptomatic enterovirus infection (including herpangina, hand-foot-mouth disease, enterovirus infection with CNS diseases without specification of strains) and ADHD (Chou et al., 2015; Tseng et al., 2020), no longitudinal, prospective clinical study has systematically investigated the consequence of EV-A71 CNS involvement during early life on the later development of other psychiatric disorders.

This study aims to investigate: (1) if there is an increased risk of any psychiatric disorders associated with EV-A71 CNS involvement during early childhood, and (2) if these infected youth have more significant emotional/behavioral problems. To answer these, we conducted a longitudinal follow-up investigation in a cohort of youth with prior EV-A71 CNS involvement. Compared to previous studies, our cohort has the longest follow-up period (ranging from 6 to 18 years) to date. We examined their psychiatric presentation and emotional/behavioral and cognitive problems using a psychiatrist-conducted diagnostic interview, parent- and self-rated questionnaires, and neuropsychological tests, respectively. We then used two complementary approaches to analyze the data. First, we compared the prevalence of psychiatric disorders in youth with EV-A71 CNS involvement to a nationally representative cohort (Chen et al., 2019). Second, we compared emotional/behavioral and cognitive profiles of EV-A71-infected youth to those of sex- and age-matched TDC and youth with ADHD from a community-based sample. We hypothesized that youth with EV-A71 CNS involvement are more likely to receive an ADHD diagnosis relative to a nationally representative cohort. Additionally, comparable to youth with ADHD in the community, youth who survived EV-A71 CNS infection and have ADHD and/or other psychiatric disorders have more pronounced emotional/behavioral and cognitive problems when compared to TDC. Moreover, youth who survived EV-A71 CNS infection without developing psychiatric disorders have an intermediate level of emotional/behavioral and cognitive problems in-between the TDC and ADHD youth/EV-A71-CNS-infected youth with psychiatric disorders.

2. Methods

2.1. Procedures

The Research Ethics Committee at National Taiwan University Hospital (NTUH), Taiwan, approved this longitudinal follow-up (#201605072RINA), the national survey (#201411056RINA), and the recruitment of community sample (#200903062 R). Youth participants and their parents received a comprehensive explanation of the purpose and procedure of this study. Before the evaluation, written informed consent for all enrollees was obtained from them and their parents.

2.2. Participants

2.2.1. Patients with EV-A71 CNS involvement

The inclusion criterion for the patient cohort of this naturalistic longitudinal follow-up study were youth that were infected with EV-A71 CNS involvement, which confirmed by viral isolation, clinical manifestation, cerebrospinal fluid study, and magnetic resonance image (MRI) findings, and were also previously enrolled in other clinical studies focusing on the various outcome metric after acquiring severe EV-A71 infection (Chang et al., 2007; Gau et al., 2008a). The exclusion criterion was the age at infection older than 7 years old. This age cutoff was decided to enhance the causal inference between the occurrence of psychiatric issues and EV-A71 CNS infection, as many neurodevelopmental disorders, especially ADHD, require the expression of some symptoms at early age. Notably, we only defined this exclusion criteria because we aimed to depict the psychiatric manifestations of these EV-A71 CNS infection survivors in an inclusive and representative sample. Based on the criteria, we sent mail invitations to 132 eligible youth infected 6–18 years ago and waited for responses for one month. We then contacted them via the phone to confirm 46 youth were willing to participate in the study. Three responded participants were further excluded because they were infected after age 7 years. Eventually, 43 (32%) youth (aged 6–20 years, 11.0 $\pm$ 4.4 years) with earlier EV-A71 CNS involvement enrolled in this study. There were no significant differences in clinical severity ($p = 0.40$), age at infection ($p = 0.60$), or sex ($p = 0.45$) between the 43 patients who were assessed and the 89 patients who were not enrolled. The severity of CNS involvement was classified as mild, severe, or cardiopulmonary failure after CNS involvement (severity scores 1–3, respectively) (Chang et al., 2019). Aseptic meningitis or myoclonic jerk was classified as mild CNS involvement, while encephalitis, encephalomyelitis, or polio-like syndrome was classified as severe CNS involvement. Notably, children with any levels of CNS involvement (even classified as the "mild" severity) were considered having severe EV-A71 infection (Chang et al., 2019). Since the current naturalistic design was not explicitly considered during the design phase of the previous outcome studies (Chang et al., 2007; Gau et al., 2008a), we did not preset the sample size and statistical power.

2.2.2. Nationally representative sample

We compared the prevalence of psychiatric disorders in the follow-up cohort to a nationally representative sample of 4816 youth. These youth, aged 8–14 years (11.3 $\pm$ 1.8 years), were recruited in a national survey from 2015 to 2017 (Taiwan's National Epidemiological Study of Child Mental Disorders, TNESCMD) using stratified cluster sampling from 45 elementary schools and 24 junior high schools across Taiwan (Chen et al., 2019; Lin et al., 2021).

2.2.3. Community-based sample

We compared emotional/behavioral profiles and cognition in patients who survived EV-A71 CNS infection to a sex- and age-matched community-based sample of youth with ADHD ($N = 45$) and TDC ($N = 46$) (Tung et al., 2021). Participants with ADHD were clinically diagnosed and recruited from NTUH. TDC were recruited from the same

neighborhoods participants with ADHD. Participants of this community-based sample were excluded if they had: (1) major medical issues; (2) a history of major psychiatric disorders; (3) depression/anxiety symptoms and suicidal ideations; (4) any psychotropic agents, except medications for ADHD; or (5) a full-scale IQ (FSIQ) < 80 as estimated by the Wechsler Intelligence Scale (Wechsler, 1991, 1997). The community-based sample recruitment was detailed elsewhere (Tung et al., 2021). Notably, considering that the present sample of youth with earlier EV-A71 CNS involvement also received the MRI assessments, we first screened the participants in the NTUH cohort with the MRI data identical to the present scanning sequences, then randomly selected the community samples to one-on-one match the sex and age of EV-A71-CNS-infected cohort. All EV-A71-CNS-infected youth and the community samples of ADHD and TDC received multimodal MRI assessments, including T1-magnetization prepared rapid gradient echo (MPRAGE) structural image (Chang et al., 2021), multi-echo resting-state functional MRI (Hearne et al., 2021), and diffusion spectrum image (DSI) (Tung et al., 2021), in a 3-T Siemens Tim Trio scanners. The information about sequences are detailed elsewhere (Chang et al., 2021; Hearne et al., 2021; Tung et al., 2021).

2.3. Measures

2.3.1. The Mandarin version of the Kiddie-schedule for affective disorders and schizophrenia-epidemiological version (K-SADS-E) for DSM-5

The Mandarin version of the K-SADS-E for DSM-5 (Chen et al., 2017) is a semi-structured clinical interview to systematically assess the presentation of 39 mental disorders in Taiwanese children and adolescents (Chen et al., 2017; Gau et al., 2005). It was first translated and developed following the DSM-IV-TR in 2002 (Gau et al., 2005) and was modified for the DSM-5 in 2015 (Chen et al., 2017). The Mandarin version of the K-SADS-E for DSM-5 has good inter-rater reliability and convergent/divergent validity (Chen et al., 2017). An experienced child psychiatrist (H.-Y.L.) conducted the K-SADS-E for all EV-A71-CNS-infected youth. We also asked their parents if any psychiatric symptoms were present before EV-A71 infection and if parents or siblings of participants have any psychiatric disorders. All TNESCMD cohort and community-based sample participants also received K-SADS-E interviews (Chen et al., 2017; Tung et al., 2021).

2.3.2. Subjective behavioral measures

We assessed symptoms of inattention, behavioral regulation, and social/communication/emotional problems in EV-A71-CNS-infected youth and in the community-based cohort using parent-rated questionnaires, including the Chinese version of Swanson Nolan and Pelham, Version IV Scale (SNAP-IV) (Gau et al., 2008b), Social Responsiveness Scale (SRS) (Gau et al., 2013), and Autism Spectrum Quotient (AQ) (Lau et al., 2013).

The Chinese SNAP-IV is a 26-item scale that measures core ADHD symptoms and opposition/defiance (Bussing et al., 2008). Sums of raw scores in inattention, hyperactivity/impulsivity, and opposition/defiance domains were used in the analysis.

The SRS was developed to quantify autistic traits and associated social/communication/emotion symptoms (Constantino et al., 2003). The Chinese SRS was developed and translated with permission from Dr. John Constantino and Western Psychological Services. We used total raw SRS scores to estimate participants' social/communication/emotion issues. Although the SRS manual provides T-scores for clinical use, the raw score is commonly used in research to estimate mild impairment in social functioning (Constantino et al., 2003; De la Marche et al., 2012; Lyall et al., 2014; Reiersen et al., 2007; Virkud et al., 2009).

The Chinese AQ (Lau et al., 2013) is a 35-item self- or parent-reported questionnaire quantifying autistic traits in intellectually able people. It was derived from the original 50-item version(Baron-Cohen et al., 2001). All these three Chinese-version measures have excellent psychometric properties (Gau et al., 2008b, 2013; Lau et al., 2013).

In addition to parent-rated questionnaires, participants completed the self-rated Strengths and Difficulties Questionnaire (SDQ) (Liu et al., 2013) to estimate their emotional and behavioral problems. The SDQ is a 25-item questionnaire assessing a broad area of emotions and behaviors of youth (Goodman, 1999). Total scores from 4 subscales (Conduct, Hyperactive, Peer problems, and Emotion) (Liu et al., 2013) were used.

Higher scores in all questionnaires used herein depict more severe symptoms.

2.3.3. Cognitive measures

Clinical psychologists assessed each youth of the EV-A71-CNS-infected and community-based samples using the Wechsler Intelligence Scale-III for Children (if < 16 years) (Wechsler, 1991) or Adults (if ≥ 16 years) (Wechsler, 1997). This scale provides scores for Verbal IQ (VIQ), Performance IQ (PIQ), and FSIQ.

Youth also received the Conners' Continuous Performance Test (CCPT) (Conners and Staff., 2000), which is a 14-min, computerized, go/no-go task requiring participants to tap on the spacebar when any character ('target'), except *X* ('non-target'), is shown on the screen. The standard format of the CCPT includes 360 trials divided into 6 blocks with 3 sub-blocks each. The outcome measures herein were T-scores of omission (failing to respond to a target), commission errors (responding to a non-target), and response variability for assessing participants' sustained attention, impulsivity, and vigilance, respectively. Youth with ADHD generally perform poorly on these metrics (Munkvold et al., 2014). We asked participants who took ADHD medications to abstain for at least 24 h before the cognitive assessment.

2.4. Statistical analysis

2.4.1. Comparisons of prevalence of mental disorders with the national cohort

Initially, we used standardization to adjust for differences in age and sex distributions between EV-A71-CNS-infected youth and youth in the TNESCMD cohort. Participants with EV-A71 CNS infection were classified into two age groups: children and adolescents (cut-off = 12 years). We then calculated the lifetime prevalence of psychiatric disorders. Finally, we used the standardized prevalence ratio and 95% confidence interval to describe the magnitude of prevalence discrepancy between the EV-A71-CNS-infected and TNESCMD cohorts. A standardized prevalence ratio >1 suggested that EV-A71-CNS-infected youth were more likely to have this psychiatric disorder relative to the representative Taiwanese youth cohort.

2.4.2. Comparisons of emotional/behavioral problems and cognition with a community-based sample

We compared emotional/behavioral problems (i.e., ADHD symptoms by the SNAP-IV; social/communication/emotion by the SRS; autistic traits by the AQ; summarized emotional/behavioral problems by the SCQ) and cognitive function (i.e., Wechsler's IQ profiles; attention and inhibitory control by the CCPT) among EV-A71-CNS-infected youth with psychiatric disorders, EV-A71-CNS-infected youth without psychiatric disorders, youth with ADHD only, and TDC. A chi-square test was used for categorical variables. The Shapiro-Wilk test was used to examine normality of continuous variables. Inattention, hyperactivity/impulsivity, and opposition/defiance scores in the SNAP-IV, alongside commission and omission errors on the CCPT, deviated significantly from a normal distribution. We thus used the Kruskal–Wallis test for group comparisons of these variables and a one-way ANOVA to compare group differences in the remaining variables. When there was a statistical significance in ANOVA or Kruskal–Wallis test—suggesting notable differences between groups—we conducted post-hoc comparisons to determine pairwise differences. We used Scheffé's method for ANOVA and Dunn-Bonferroni procedure for Kruskal–Wallis test to control for multiple tests in post-hoc comparisons.

3. Results

3.1. Prevalence of mental disorders

The clinical features of EV-A71-CNS-infected youth are listed in Table 1. STable 1 shows basic features and the results of K-SADS-E. Table 2 shows the prevalence of psychiatric disorders in youth who survived EV-A71 CNS infection. 22 out of 43 youth in the EV-A71-CNS-infected follow-up sample had at least one psychiatric disorder based on the K-SADS-E. Based on the cognitive assessment using the Wechsler Intelligence Scale, we did not observe EV-A71-CNS-infected youth had any intellectual disabilities. Among them (STable 1), 7 had ADHD only, 8 had ADHD plus other psychiatric disorders, and 7 had psychiatric disorders other than ADHD only. Except for an adolescent diagnosed with autism spectrum disorder (ASD), none of the youth displayed any noticeable associated symptoms before they were infected with EV-A71. Parental reports revealed that only two infected children had a family member with psychiatric disorders.

Compared to the national sample (absolute ADHD prevalence 10.1%), youth with EV-A71 CNS involvement had three times the odds of an ADHD diagnosis (standardized prevalence ratio, 95% CI = 1.8, 4.2; absolute ADHD prevalence 34.9%). No other psychiatric diagnoses were more common in EV-A71-CNS-infected youth.

We undertook a supplementary analysis to investigate if characteristics at infection would drive the later development of psychiatric disorders. We found no significant differences in sex, the age of infection, or the severity of infection between those with and without a psychiatric diagnosis (all 95% CIs include the null value 1).

3.2. Emotional/behavioral and cognition issues

Table 3 shows that there were significant ANOVA/Kruskal–Wallis in all emotional/behavioral problems. Specifically, post-hoc tests revealed that compared to community-based youth with ADHD, EV-A71-CNS-infected youth with psychiatric disorders showed comparable levels of core ADHD symptoms, opposition/defiance, and autistic features, all of which were more severe than TDC. EV-A71-CNS-infected youth without psychiatric disorders also showed comparable levels of autistic features to EV-A71-CNS-infected youth with psychiatric disorders and youth with ADHD. However, EV-A71-CNS-infected youth without psychiatric disorders did not differ from the other three groups on inattention, hyperactivity/impulsivity, and opposition/defiance symptoms.

Regarding cognition (Table 4), there were significant ANOVA/Kruskal–Wallis in FSIQ, omission and response variability (reaction time standard deviation). Post-hoc tests revealed that EV-A71-CNS-infected youth, regardless of the presence or absence of current psychiatric disorders, had comparable omission errors on the CCPT relative to community-based youth with ADHD, which were higher (i.e., poorer sustained attention performance) than TDC. There were no differences in VIQ, PIQ, and commission errors among EV-A71-CNS-infected youth, youth with ADHD, and TDC.

4. Discussion

This work is the first follow-up study to describe the long-term psychiatric outcomes in youth who had EV-A71 CNS infection 6–18 years ago. We contrast their prevalence of psychiatric disorders with a nationally representative youth cohort (Chen et al., 2019) and their behavioral/emotional and cognitive issues with a community-based sample comprising youth with ADHD and TDC. We demonstrate that EV-A71 CNS infection links with an ADHD diagnosis, impaired cognitive performance in sustained attention, and increased social/emotional problems with the caveats of a small sample size and a lack of blinding in the context of naturalistic study design. Nonetheless, these limitations reflect the value of this study given difficulties in conducting this kind of longitudinal clinical study in real life.

Advancing our earlier findings (Gau et al., 2008a), the present study finds that youth with EV-A71 CNS involvement have a higher prevalence of ADHD diagnosis compared to a nationally representative youth cohort. This suggests that after around 11 years (mean) following the infection, youth with EV-A71 CNS involvement have a markedly increased risk of receiving a ADHD diagnosis, rather than just having elevated symptoms without confirmation of diagnostic status (Gau et al., 2008a). This result is also consistent with earlier, indirect evidence based on national health insurance claim data (Chou et al., 2015; Tseng et al., 2020).

Beyond ADHD, no other psychiatric disorders are more common in youth with EV-A71 CNS involvement. Nevertheless, we find that infected youth who later develop ADHD and/or other psychiatric disorders show comparable behavior/emotion and cognition profiles to a community sample of youth with ADHD. This result suggests that the long-term psychiatric outcome of EV-A71 CNS involvement could be very similar to the presentation of idiopathic ADHD.

We found that EV-A71-infected youth with psychiatric disorders showed similar social/communication/emotion problems to youth with ADHD, and the extent of the issues was more remarkable when compared to TDC. This finding is compatible with the finding that people with ADHD commonly have higher autistic traits and associated problems (Astle et al., 2021; Reiersen et al., 2007). Surprisingly, we found that youth with EV-A71 CNS involvement who did not develop any psychiatric disorders also demonstrated pronounced autistic features, alongside poor sustained attention performance, which has never been reported. The present distributions of SRS scores in TDC are in agreement with the existing literature (Constantino et al., 2003; Lyall

Table 1
Description of enrolled cases previously infected with EV-A71.

	Mild CNS involvement[a] (n = 25)	Severe CNS involvement[b] (n = 14)	Cardiopulmonary failure after CNS involvement (n = 4)	Total (N = 43)
Demography				
Sex (male/female)	15/10	10/4	3/1	28/15
Age of onset[c], years (range)	2.5 ± 1.7 (0.5–5.9)	2.3 ± 2.2 (0.2–7.5)	1.2 ± 1.1 (0.5–2.8)	2.3 ± 1.8
Age at follow-up, years (range)	10.1 ± 4.0 (6.1–20.4)	11.6 ± 5.0 (6.1–20.5)	14.2 ± 4.1 (10.7–18.2)	11.0 ± 4.4
Interval between onset and follow-up	7.6 ± 4.0 (5.6–18.1)	9.3 ± 5.3 (5.5–18.1)	13.0 ± 4.9 (7.9–17.7)	8.7 ± 4.7
Outcome				
Recovery	25 (100%)	11 (79%)	2 (50%)	38 (88%)
Focal limb weakness and atrophy	0	3 (21%)[d]	2 (50%)	5 (12%)
Central hypoventilation with ventilator support (removed)	0	0	1 (25%)	1 (2.3%)

Abbreviation: EV-A71 = enterovirus A71, CNS = central nervous system.
[a] Mild CNS involvement was defined as aseptic meningitis and/or myoclonic jerk.
[b] Severe CNS involvement indicated encephalitis (n = 8), polio-like syndrome (n = 3) or encephalomyelitis (n = 3).
[c] Age of onset was defined as the age of their EV-A71 CNS infection onset.
[d] Sequelae of focal limb weakness and atrophy were found in 2 of 11 (18%) encephalitis or encephalomyelitis cases and 1 of 3 (33%) polio-like cases.

Table 2
Standardized prevalence ratios of psychiatric diagnosis (Youth with previously infected with EV-A71 vs. a national cohort).

	Youth previously infected with EV-A71				TNESCMD Weighted Prevalence					Standardized prevalence ratio[a]
	Male		Female		Male		Female		Total (n = 4816)	
DSM-5 Diagnosis	Children (n = 22)	Adolescents (n = 5)	Children (n = 10)	Adolescents (n = 6)	Children (n = 1359)	Adolescents (n = 1161)	Children (n = 1290)	Adolescents (n = 1006)		
ADHD	10 (45.5%)	1 (20%)	2 (20%)	2 (33.3%)	15.4%	15.9%	5.0%	5.2%	10.1%	3.00 (1.81–4.19) **
ODD	3 (13.6%)	1 (20%)	0	0	2.7%	3.4%	1.0%	1.4%	2.0%	4.19 (0.41–7.98)
Anxiety disorders	3 (13.6%)	2 (40%)	1 (10%)	2 (33.3%)	10.0%	9.2%	13.5%	14.9%	15.2%	1.62 (0.65–2.60)
ASD	2 (9.1%)	0	0	0	1.6%	0.7%	0.5%	0.2%	1.0%	4.57 (0.00–10.62)
Tic disorder	2 (9.1%)	2 (40%)	0	0	4.9%	2.9%	1.3%	0.8%	2.7%	2.83 (0.27–5.40)
OCD	0	1 (20%)	0	1 (16.7%)	0.5%	2.0%	0.6%	2.6%	1.2%	4.79 (0.00–10.78)
MDD	0	1 (20%)	0	0	0.5%	0.9%	1.0%	4.2%	1.4%	2.00 (0–5.50)
Dissociative disorders	0	0	0	1 (16.7%)	0.1%	0.8%	0.8%	0.3%	0.5%	6.00 (0.00–16.74)

Abbreviation: TNESCMD = Taiwan's National Epidemiological Study of Child Mental Disorders; ADHD = attention-deficit/hyperactivity disorder; ODD = oppositional defiant disorder; ASD = autism spectrum disorder; OCD = obsessive compulsive disorder; MDD = major depressive disorder.
$^{**}P < 0.01$.
[a] Standardized prevalence ratio was adjusted for sex and age groups (children and adolescents).

Table 3
Comparisons of emotional and behavioral problems among youth previously infected with EV-A71 CNS involvement with and without any current psychiatric disorders, a community sample of youth with attention-deficit/hyperactivity disorder (ADHD)-alone and typically developing controls (TDC).

	EV-A71 without Psychiatric Dx (N = 21)	EV-A71 with Psychiatric Dx (N = 22)	ADHD (N = 45)	TDC (N = 46)	Statistics	Post-hoc comparison[c]
Sex (M/F)	11/10	17/5	29/16	28/18	$X^2 = 3.07$	-
Age[a]	10.1 ± 4.5	11.8 ± 4.3	12.3 ± 3.4	12.4 ± 3.0	F = 2.06	-
SNAP-IV Inatt[b]	7.0 [6.0]	12.5 [9.0]	16.0 [7.0]	4.0 [7.0]	H = 23.1***	3, 2 > 4
SNAP-IV Hyper[b]	4.0 [5.0]	5.5 [8.0]	7.0 [9.0]	2.0 [4.0]	H = 22.8***	3, 2 > 4
SNAP-IV Oppo[b]	6.0 [5.0]	7.0 [6.8]	7.0 [11.0]	3.0 [6.0]	H = 17.79***	2, 3 > 4
SRS Total[a]	46.0 ± 11.5	54.1 ± 18.2	46.2 ± 13.9	32.2 ± 19.4	F = 9.51***	2, 3, 1 > 4
AQ Total[a]	85.4 ± 10.5	86.9 ± 9.3	83.4 ± 12.1	72.9 ± 13.4	F = 9.29***	2, 1, 3 > 4
SDQ Total[a]	12.4 ± 3.5	13.3 ± 3.8	16.8 ± 5.2	9.9 ± 4.9	F = 10.23***	3 > 4

$^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.
Abbreviation: M = male; F = female; Dx = diagnoses; SNAP-IV = the parent-rated Chinese version of Swanson Nolan and Pelham, Version IV Scale; Inatt = inattention; Hyper = hyperactivity/impulsivity; Oppo = opposition/defiance; SRS = the parent-rated Chinese version of Social Responsiveness Scale; AQ = the parent-rated Chinese version of Autism Spectrum Quotient; SDQ = the self-rated Strengths and Difficulties Questionnaire.
[a] Group comparisons were conducted using ANOVA. The data is presented as Mean ± Standard deviation. Post-hoc analysis was conducted using Scheffé's method for ANOVA.
[b] Group comparisons were conducted using the Kruskal–Wallis test. The data is presented as Median [Inter-quartile range] because they were not normally distributed. Post-hoc analysis was conducted using Dunn-Bonferroni procedure for the Kruskal–Wallis test.
[c] 1 = EV-A71 without psychiatric disorders; 2 = EV-A71 with psychiatric disorder; 3 = ADHD-alone; 4 = TDC.

et al., 2014), illustrating the representativeness of this sample. This similarity also applies to the AQ (Bishop et al., 2004; Okyar and Görker, 2020; Panagiotidi et al., 2019). Although the mildly elevated mean SRS scores (ranging 45–55) do not meet clinical cutoffs for a ASD diagnosis, the range is still comparable to that observed in people with ADHD (Reiersen et al., 2007) or first-degree relatives of people with ASD, i.e., broad autism phenotype (De la Marche et al., 2012; Lyall et al., 2014; Virkud et al., 2009), who have gradually become a focus of clinical attention. These elevated scores are suggested to be largely attributable to autistic traits, rather than general impairment in social functioning (Reiersen et al., 2007). The new findings of elevated autistic traits in EV-71-CNS-infected youth may relate to earlier epidemiological data, which suggest that viral infections during prenatal periods (Shuid et al., 2021) or early childhood (Lopez-Aranda et al., 2021) may mediate the risk of developing ASD. Further, preclinical data also imply infection-induced immune activation relates to aberrant social behaviors in rats (Lopez-Aranda et al., 2021; Turano et al., 2021). Nonetheless, we acknowledge autistic traits are not always related to a ASD diagnosis (Lord and Bishop, 2021). Taken together, our findings suggest that caregivers, school staff, and medical service providers around youth with EV-A71 CNS involvement need to be aware of the potential development of social/emotion problems and autistic traits, regardless of whether they develop psychiatric disorders later in life. This implication is vital as individuals with better social bonding live healthier lives both mentally and physically (Kappeler et al., 2015).

Consistent with earlier studies (Köhler-Forsberg et al., 2019; Pedersen et al., 2020), the present results suggest a link between viral infection and development of mental health issues. Enteroviral (Gau et al., 2008b) and cytomegaloviral (Zhou et al., 2015) infections are theoretically linked to ADHD etiology, despite scarce empirical evidence hitherto. Some enterovirus such as EV-A71, coxsackievirus B, and poliovirus are neurotropic and neurovirulent (Huang and Shih, 2015). Neuroradiological lesion findings in patients with enterovirus infection and CNS involvement suggest that EV-A71 may affect diffuse brain structures, including the striatum (Cabrera Filho et al., 2021; Liang et al., 2021), cerebellum (Liang et al., 2021), and white matter in frontal and parietal cortices (Nakamura et al., 2020). Alterations in these brain areas are commonly involved in ADHD pathophysiology (Faraone et al., 2015).

Table 4
Comparisons of cognition among youth previously infected with EV-A71 CNS involvement with and without any current psychiatric disorders, a community sample of youth with attention-deficit/hyperactivity disorder (ADHD)-alone and typically developing controls (TDC).

	EV-A71 without Psychiatric Dx (N = 21)	EV-A71 with Psychiatric Dx (N = 22)	ADHD (N = 45)	TDC (N = 46)	Statistics	Post-hoc comparison[c]
VIQ[a]	111.0 ± 7.1	105.6 ± 11.3	105.8 ± 11.6	108.1 ± 12.5	F = 1.19	–
PIQ[a]	111.8 ± 10.0	103.1 ± 9.3	103.8 ± 13.2	106.0 ± 14.0	F = 2.29	–
FSIQ[a]	112.1 ± 7.5	104.8 ± 9.1	104.1 ± 12.1	107.4 ± 12.7	F = 2.71*	-[d]
CCPT Omission[b]	46.5 [10.7]	45.5 [6.4]	45.2 [7.7]	42.6 [3.0]	H = 21.12***	3, 2, 1 > 4
CCPT Commission[b]	49.5 [10.1]	51.8 [11.2]	51.0 [14.4]	47.0 [16.2]	H = 4.51	–
CCPT RTSD[a]	49.7 ± 10.7	49.5 ± 13.2	52.2 ± 9.4	42.4 ± 9.0	F = 7.09***	3 > 4

Abbreviation: Dx = diagnoses; VIQ = verbal intelligence quotient; PIQ = performance intelligence quotient; FSIQ = full-scale intelligence quotient; CCPT = Conners' Continuous Performance Test; RTSD = standard deviation of reaction time distributions.
*$P < 0.05$, ***$P < 0.001$.
[a] Group comparisons were conducted using ANOVA. The data is presented as Mean ± Standard deviation. Post-hoc analysis was conducted using Scheffé's method for ANOVA.
[b] Group comparisons were conducted using the Kruskal–Wallis test. The data is presented as Median [Inter-quartile range] because they were not normally distributed. Post-hoc analysis was conducted using Dunn-Bonferroni procedure for the Kruskal–Wallis test.
[c] 1 = EV-A71 without psychiatric disorders; 2 = EV-A71 with psychiatric disorder; 3 = ADHD-alone; 4 = TDC.
[d] No significant difference was found after adjustment of multiple comparisons.

However, the tropism of poliovirus is different from EV-A71, potentially leading to the distinct pattern that polio survivors may have an increased risk of developing milder psychiatric diseases, including personality disorder, substance abuse, and transient maladaptation (Nielsen et al., 2007). Moreover, this virus-specific association with the distinct late manifestations of neuropsychiatric problems after infection is further evidenced in data from survivors of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; COVID-19) infection, who shows an increased risk of deficits in memory, executive function alongside attention, and depression/anxiety symptoms (Ali Awan et al., 2021; De Berardis, 2020). Multi-level investigations surrounding mechanisms are warranted in the future.

This study has many strengths, despite possibilities of unnoticed/undiagnosed issues in family members and recall bias. For example, we considered parental accounts of family history and the absence of relevant behavior/emotion issues before the infection. Moreover, we only included participants who got infected before age 7, reducing the bias that some psychiatric disorders may develop spontaneously and coincidentally with the time of being infected. With these rigorous designs that reduce unmeasured genetic and familial confounding factors, these findings provide more direct evidence to suggest that EV-A71 CNS infection may be one of the etiologies for ADHD. Nonetheless, the current design fails to fully elucidate whether the link of EV-A71 CNS infection and ADHD/autistic traits is driven by the biological characteristics of EV infection, psychological and/or social distress that occurs whenever young children survive a life-threatening disease early in life, or a combination of both factors. Further, the current small sample size lacks a power to stratify the EVA71 CNS survivors to test the effect of the infection severity and/or duration of symptoms on the psychiatric and cognitive sequelae. Future studies can leverage a control of the study that compares an EV-A71-CNS-infected cohort with children that experience hospitalization or other viral infection early in life. At the same time, EV-A71-infected children without CNS involvement can be another control group in the future investigation to see whether there is a connection between CNS invasion and development of ADHD.

5. Conclusions

EV-A71 CNS involvement may cause long-term, adverse psychiatric outcomes that develop into an ADHD diagnosis alongside social/communication/emotion problems and autistic features. We recommend earlier identification and intervention of these complications among these children. This essential action could help offset the consequent school, family, and personal dysfunctions from these neurodevelopmental issues. More research is needed to investigate why EV-A71 CNS involvement specifically contributes to the development of neurodevelopmental disorders rather than other psychopathology.

Conflict of interest disclosures (includes financial disclosures)

All authors have declared that they have no potential conflict of interest or financial interests, which may arise from authorship.

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Clinical trial registration

N/A.

Contributors' statement page

Dr. Hsiang-Yuan Lin conceptualized and designed the study, collected data, interpreted the results drafted the initial manuscript, and reviewed and revised the manuscript. Dr. Yi-Lung Chen carried out the initial analyses, interpreted the results, and reviewed and revised the manuscript. M.Sc. Pei-Hsuan Chou collected data, reviewed and revised the manuscript. Dr. Susan Shur-Fen Gau designed the data collection instruments, provided the national epidemiological data and community-based ADHD and control data, supervised the project, and reviewed and revised the manuscript. Dr. Luan-Yin Chang conceptualized and designed the study, collected data, interpreted the results,

supervised the project, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Appendix A. Supplementary data

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