Cognitive development of children with Kawasaki Disease and the parenting stress of their caregivers

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Abstract

Background

Kawasaki disease (KD) is an acute form of febrile vasculitis that occurs in early childhood. The multi-systemic vasculitis common in KD patients may influence blood perfusion in the brain, and thus caregivers of KD children may feel stress with regard to caring for them. Intravenous immunoglobulin (IVIG) infusion is the standard treatment for acute KD, and the most serious complication of KD is coronary artery aneurysms (CAL). This study aimed to investigate the relationships between KD heterogeneity and the risk of patients' cognitive impairment or caregivers' parenting stress.

Methods

This cross-sectional study consisted of 176 patients with KD (mean age: 5.5 years, 60.8% male) and 85 healthy children (mean age: 6.4 years, 54.1% male). Based on the children's age, each KD patient and control subject was administered an assessment using the Mullen Scales of Early Learning or the Wechsler Intelligence Scale, and parenting function of their caregivers was assessed using the Parenting Stress Index-Short Form (PSI).

Results

We observed no significant differences in any developmental index, cognitive function, or parenting stress between KD patients and controls. Among the KD children, IVIG administration nor CAL was associated with children's cognitive scores. However, the caregivers of patients who had CAL suffered from greater PSI total scores than those of patients without CAL ($p = 0.019$). Furthermore, the caregivers who had education levels of a master's degree or above showed less parenting stress than those who had an education level of college ($p = 0.010$) or lower ($p = 0.021$).

Conclusion

No significant differences in developmental index, cognitive function or parenting stress between KD patients and controls. In KD patients, neither IVIG response nor CAL appear to have a relationship with development milestones or cognitive function. However, caregivers' education is associated to parenting stress, and caregivers of KD patients who developed CAL may feel stress about the unpredictable sequela caused by CAL for their children. Such caregivers may require support to fulfill their parenting roles.

Background

Kawasaki disease (KD) manifests with acute fever, mainly affects children under the age of 5 years old, and involves multi-systemic vasculitis of unknown etiology [1, 2]. Although it occurs around the world, KD

incidence rates are especially high in East Asia, particularly Japan, Korea, and Taiwan [3, 4]. The primary clinical characteristics of KD consist of prolonged fever, diffuse mucosal inflammation, bilateral non-purulent conjunctivitis, non-suppurative cervical lymphadenopathy, indurative angioedema of the hands and feet, and polymorphous skin rashes [5–7]. Intravenous immunoglobulin (IVIG) infusion has been established as the standard treatment for acute KD [8], but 10–20% of patients still show resistance to IVIG therapy and are at high risk for coronary artery complications [9], of which, the formation of coronary artery lesions (CAL) is the most serious [10]. Current studies suggest that 20–24% of KD children, even when treated with IVIG, still suffer from CAL [11, 12].

In addition to the harm caused to the coronary arteries, KD is also characterized by multi-systemic vasculitis and may thus affect blood perfusion and cause inflammatory changes in the brain [13, 14]. Central nervous system (CNS) symptoms, such as lethargy, cranial nerve palsy, and prolonged partial seizures, occur in 1–30% of KD patients [15–18]. Fortunately, current studies have consistently demonstrated that patients with KD are not associated with cognitive impairment sequelae [19–21]. However, different responses to IVIG treatment and the development of coronary aneurysms may be related to a discrepancy in patients' immunological profiles or genetic background [22]. Therefore, the relationships between heterogeneity of KD and the risk of cognitive impairments warrant further investigation.

On study revealed that children with KD suffered acute and prominent impairment in health-related quality of life, and the impairments even exceeded that of children newly diagnosed with cancer [23]. Furthermore, patients with KD, as well as their caregivers, may consistently worry about patients' potential risk of cardiac event-related death [24]. With a lack of support and adequate knowledge available at the societal level, patients' caregivers may experience stress from coping with their children's needs and fulfilling their parenting roles. Due to the uncertainty of the long-term KD prognosis, the parents of children with coronary artery complications suffered from persistent anxiety even years after the acute phase of the illness [25]. The psychosocial burden of parents is associated with intensity of medical experience and family's psychosocial limitations [26]. However, the evidence with regarding to parenting stress among caregivers of KD children is still scarce.

To fill this research gap, we performed a clinical survey to explore whether children with KD and healthy controls exhibited different cognitive profiles and whether their caregivers had differential parenting stress. We used linear regression to examine the factors correlated to patients' cognitive profiles and caregivers' parenting stress among children with KD.

Methods

Participants

We recruited a total of 176 patients with KD from the Department of Pediatrics from June 2016 to July 2018, Kaohsiung Chang Gung Memorial Hospital, Taiwan or communities near the hospital. A senior

clinician diagnosed patients with KD in accordance with the recommended universal KD criteria published by the American Heart Association (AHA) [27]. The diagnostic criteria of KD includes fever that lasts longer than five days, as well as four of the following five symptoms: diffuse mucosal inflammation with strawberry tongue and fissure lips, bilateral non-purulent conjunctivitis, indurative angioedema of the hands and feet, dysmorphic skin rashes, and unilateral cervical lymphadenopathy, as stated in our previous reports [28]. Once their symptoms were remitted, KD patients were administered a developmental or cognitive assessment in either outpatient department or in the ward.

Because most of our KD patients were recruited from the outpatient department, we recruited 85 healthy children from communities around Kaohsiung Chang Gung Memorial Hospital or children suffering from upper respiratory tract infection (URI) whose symptoms were currently in remission as a control group. We excluded any patients with other immunological diseases (asthma, allergic rhinitis, atopic dermatitis, or allergic conjunctivitis) or major physical illnesses (such as genetic, metabolic, or infectious conditions).

CAL Assessment

All participants were provided with a structured questionnaire in order to collect demographic data, such as age, gender, and age of onset. We recorded body temperature every 6 h during the febrile stage. The CAL was defined as a luminal diameter of more than 3.0 mm in a child under the age of 5 years old or more than 4.0 mm in those aged 5 years and older, when the internal diameter of a segment is 1.5 times or greater than that of an adjacent segment, or when the luminal contour is clearly irregular or has a Z score > 2.5 SD [29, 30]. We estimated the Z score of the proximal right coronary artery, left main coronary artery, and proximal left anterior descending artery, as well as the maximum Z score of coronary arteries both at baseline and weeks 6–8 with 2D echocardiography. The body weight and height used to calculate Z scores were obtained from the Taiwan Society of Pediatric Cardiology website (http://www.tspc.org.tw/service/z_score.asp). The IVIG resistance was defined as persistent or recrudescent fever for at least 48 h but no more than 7 days after completing the first IVIG treatment [31].

Neurocognitive Assessments

Each KD patient and control subject was administered a developmental or cognitive assessment carried out by an experienced child psychologist in a room designed to reduce testing condition variables. Subjects under the age of 4 years old were assessed using the Mullen Scales of Early Learning (MSEL); subjects between the ages of 4 and 7 years old were examined using the Wechsler Preschool and Primary Scale of Intelligence-Fourth Edition (WPPSI-IV); and subjects older than 7 years old were tested using the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV).

The MSEL, a standardized developmental assessment for newborns through children 68 months of age, offers an overall index of cognitive ability and developmental delay [32]. It consists of five sub-scales: Gross Motor (only for children younger than 33 months), Visual Reception, Fine Motor, Expressive Language, and Receptive Language. After scoring each item, the crude scores of each of the five scales are transformed into normalized age-specific scores, referred to as T scores. The T scores of all except

the Gross Motor scale are added together and converted into the Early Learning Composite (ELC) score. The MSEL has been applied in Taiwan's toddler samples [21, 33].

The WPPSI-IV is an individually administered, standardized tool for evaluating intelligence in children between the ages of 2 years 6 months and 7 years 7 months [34]. The test takes about 30–45 minutes for children between the ages of 2 years 6 months and 3 years 11 months and provides a Full-Scale Intelligence Quotient (FSIQ), Verbal Comprehension Index (VCI), Visual Spatial Index (VSI), and Working Memory Index (WMI). For children between the ages of 4 years and 7 years 7 months, it takes about 45–60 minutes and provides a FSIQ, VCI, VSI, Fluid Reasoning Index (FRI), WMI, and Processing Speed Index (PSI) [35]. The WPPSI-IV has been used in clinical study in Taiwan [21, 36].

The WISC-IV is an individually administered and norm-referenced tool developed to measure the intelligence of children aged from 6 to 16 [37]. The WISC-IV includes 10 core and 5 supplemental subtests. The core subtests create four factor indexes, including the VCI, the Perceptual Reasoning Index (PRI), the WMI, and the PSI. Meanwhile, the 10 core subtests form the FSIQ. Each factor index, as well as the FSIQ, has a population mean of 100 and a standard deviation of 15. The WISC-IV has been applied for Taiwanese school-aged children in several clinical studies [38, 39].

Parenting Stress

Caregivers' characteristics, including age, gender, and education levels, were recorded, and their parenting function was assessed using the Parenting Stress Index-Short Form (PSI-SF). The PSI-SF, a widely adopted self-administered questionnaire for evaluating parenting stress, includes 36 items (rated on a 5-point Likert scale) and stems directly from the full-length 120-item Parenting Stress Index (PSI) test [40]. The PSI-SF provides scores in the following subscales: (a) Parental Distress, (b) Parent-Child Dysfunctional Interaction, and (c) Difficult Child. The three sub-scores are added together to yield a total parenting stress score [41]. Studies have reported that the Chinese version of the PSI-SF is a reliable assessment tool for identifying parenting stress with a need for intervention in clinical practices [42–44].

Statistical Analysis

All data processing and statistical analyses were performed using the Statistical Package for Social Science (SPSS) software, Version 14.0 (SPSS, Chicago, IL, USA). Two-tailed p values < 0.05 were considered statistically significant.

We used the chi-square test to compare differences in categorical variables between patients with KD and those without KD. An independent t-test was adopted to compare continuous variables between the two groups. We performed a multiple linear regression to observe the factors related to cognitive function among the KD patients and set the dependent variable as a cognitive score. The cognitive scores of patients who were assessed using the MSEL were set as the ELC scores, and the cognitive scores of those assessed with the WPPSI or WISC-IV were set as the FSIQ. The independent variables were the characteristics of the children and caregivers. Furthermore, multiple linear regression was adopted to determine the factors associated with parental stress among the KD patients. The dependent variable

was set as the total PSI score, and the independent variables were the characteristics of the children and caregivers.

Results

The clinical cohort consisted of 176 patients with KD (mean age: 5.5 years, 60.8% male) and 85 healthy children (mean age: 6.4 years, 54.1% male) (Table 1). The healthy children were older than patients with KD ($p = 0.035$), and the caregivers in the control group had higher education levels than those in the KD group ($p = 0.018$). Apart from this, no significant differences in gender or caregivers' characteristics between KD children and controls. No significant differences in development scores measured using the MSEL or cognitive scores measured using the WPPSI or WISC-IV were observed between the children with KD and the healthy controls. When comparing the caregivers of patients with KD to those of the controls, none of the PSI subscales showed a significant difference.

Table 1
Characteristics of children with Kawasaki disease (KD) and healthy controls

	KD (n = 176)	Controls (n = 85)	Statistic [a]	P-value
Children's characteristics				
Age (months)	66.5 ± 39.0	77.3 ± 38.0	-2.114	0.035*
Age of KD onset (months)	21.6 ± 17.7	-	N/A	N/A
Sex			1.054	0.305
Male	107 (60.8)	46 (54.1)		
Female	69 (39.2)	39 (45.9)		
Intravenous immunoglobulin			N/A	N/A
Non	7 (4.0)	-		
Once	156 (88.6)	-		
Twice	13 (7.4)	-		
Coronary artery aneurysms			N/A	N/A
With	74 (42.0)	-		
Without	102 (58.0)	-		
Mullen Scales of Early Learning				
Gross Motor [b]	52.0 ± 13.1	52.7 ± 12.0	-0.160	0.873
Visual Reception	54.0 ± 13.8	53.1 ± 17.2	0.234	0.816
Fine Motor	50.2 ± 13.4	50.1 ± 11.6	0.054	0.957
Receptive Language	57.0 ± 11.5	51.2 ± 10.7	1.975	0.052
Expressive Language	51.7 ± 13.2	50.5 ± 11.2	0.340	0.734
Composite scores	106.2 ± 19.4	105.0 ± 19.2	0.251	0.802
WPPSI				
Full Scale Intelligence Quotient	103.7 ± 10.4	107.6 ± 11.7	-1.577	0.118
Verbal Comprehension Index	105.2 ± 10.7	107.1 ± 14.3	-0.603	0.550

Note: Data are expressed as mean ± SD or n (%); [a] Statistical values are expressed as t-value or χ^2. [b] Gross Motor is only for children younger than 33 months old. [c]NTD represents new Taiwan dollars (1 U.S. dollar = 31.1 NTD). There were 28 missing values (19 patients with ADHD and 9 controls). *p < 0.05

	KD (n = 176)	Controls (n = 85)	Statistic [a]	P-value
Visual Spatial Index	98.8 ± 14.9	101.5 ± 10.9	-0.985	0.328
Fluid Reasoning Index	107.0 ± 12.0	107.0 ± 13.9	0.006	0.995
Working Memory Index	99.0 ± 12.4	100.3 ± 15.3	-0.430	0.668
Processing Speed Index	103.3 ± 12.5	106.9 ± 12.7	-1.247	0.216
WISC-IV				
Full Scale Intelligence Quotient	109.1 ± 11.1	109.7 ± 17.4	-0.175	0.862
Verbal Comprehension Index	108.2 ± 13.4	111.3 ± 16.3	-0.983	0.328
Perceptual Reasoning Index	106.1 ± 14.8	106.4 ± 17.2	-0.077	0.939
Working Memory Index	110.3 ± 13.1	111.4 ± 15.3	-0.348	0.729
Processing Speed Index	103.0 ± 14.3	98.4 ± 15.1	1.490	0.140
Caregivers' characteristics				
Age (years)	37.6 ± 4.8	38.2 ± 5.0	-0.889	0.375
Sex			1.096	0.295
Male	26 (14.9)	17 (20.0)		
Female	149 (85.1)	68 (80.0)		
Education Levels			8.080	0.018*
High school or lower	81 (46.8)	29 (34.1)		
College	77 (44.5)	39 (45.9)		
Master or above	15 (8.7)	17 (20.0)		
Family expenditure (per month)[c]			0.515	0.773
<50,000 NTD	94 (59.9)	42 (55.3)		
50,000-100,000 NTD	46 (29.3)	24 (31.6)		
>100,000 NTD	17 (10.8)	10 (13.2)		
PSI/SF				

Note: Data are expressed as mean ± SD or n (%); [a] Statistical values are expressed as t-value or χ^2. [b] Gross Motor is only for children younger than 33 months old. [c]NTD represents new Taiwan dollars (1 U.S. dollar = 31.1 NTD). There were 28 missing values (19 patients with ADHD and 9 controls). *p< 0.05

	KD (n = 176)	Controls (n = 85)	Statistic [a]	P-value
Defensive Responding	18.0 ± 5.2	18.0 ± 5.3	-0.025	0.980
Parental Distress	30.2 ± 8.2	30.0 ± 9.0	0.308	0.758
Parent-Child Dysfunctional Interaction	23.1 ± 7.0	24.4 ± 8.3	-1.257	0.210
Difficult Child	27.4 ± 8.1	29.0 ± 8.6	-1.434	0.153
Total Score	80.7 ± 20.4	83.1 ± 21.9	-0.846	0.399

Note: Data are expressed as mean ± SD or n (%); [a] Statistical values are expressed as t-value or χ^2. [b] Gross Motor is only for children younger than 33 months old. [c]NTD represents new Taiwan dollars (1 U.S. dollar = 31.1 NTD). There were 28 missing values (19 patients with ADHD and 9 controls). *$p < 0.05$

Of the children with KD, the mean age of KD onset was 21.6 months; 4% of them never received IVIG treatment, and 88.6% and 7.4% received IVIG treatment once and twice, respectively; 58% of them had no CAL and 42% of them had CAL. Table 2 shows the relationship between children's and caregivers' characteristics and the cognitive score among KD children. We found that neither IVIG administration nor CAL was associated with KD children's cognitive score. The characteristics of children and caregivers were also not correlated with cognitive score.

Table 2
Characteristics of children with Kawasaki disease (KD) and their caregivers regarding KD children's cognition development

	B (95% CI)	*P*-value
Children's characteristics		
Age (months)	0.07 (-0.01, 0.15)	0.067
Age of KD onset (months)	-0.01 (-0.16, 0.13)	0.846
Sex		
Male	1.38 (-3.43, 6.19)	0.572
Female	1	
Intravenous immunoglobulin		
Non	3.01 (-10.86, 16.88)	0.669
Once	1.43 (-7.25, 10.11)	0.746
Twice	1	
Coronary artery aneurysms		
Without	1.32 (-3.42, 6.07)	0.583
With	1	
Caregivers' characteristics		
Age (years)	-0.07 (-0.66, 0.52)	0.824
Sex		
Male	-5.23 (-11.97, 1.52)	0.128
Female	1	
Education Levels		
High school or lower	-3.73 (-12.25, 4.78)	0.388
College	-1.13 (-9.60, 7.35)	0.794
Master or above	1	

Note: The dependent variable in the multiple linear regression model is a cognitive score (Early Learning Composite Score of the MSEL or the Full-Scale Intelligence Quotient of the WPPSI or WISC-IV). Data are expressed as B-value, 95% Confidence Interval and *p*-value using multiple linear regression model.

Regarding the factors related to the total scores of PSI (Table 3), caregivers of KD patients who had CAL suffered from greater parenting stress than the caregivers of patients without CAL ($p = 0.019$). Furthermore, the caregivers who had education levels of a master's degree or above showed less parenting stress than those who had an education level of college ($p = 0.010$) or lower ($p = 0.021$).

Table 3
Characteristics of children with Kawasaki disease (KD) and their caregivers regarding parenting stress of the children's caregivers

	B (95% CI)	P-value
Children's characteristics		
Age (months)	0.01 (-0.09, 0.11)	0.834
Age of KD onset (months)	-0.18 (-0.37, 0.01)	0.066
Sex		
Male	0.37 (-5.89, 6.63)	0.907
Female	1	
Intravenous immunoglobulin		
Non	1.46 (-16.60, 19.51)	0.874
Once	-5.92 (-17.22, 5.39)	0.303
Twice	1	
Coronary artery aneurysms		
Without	-7.41 (-13.59, -1.23)	0.019*
With	1	
Caregivers' characteristics		
Age (years)	-0.11 (-0.88, 0.66)	0.784
Sex		
Male	-0.57 (-9.35, 8.21)	0.898
Female	1	
Education Levels		
High school or lower	13.11 (2.03, 24.20)	0.021*
College	14.55 (3.52, 25.58)	0.010*
Master or above	1	

Note: The dependent variable in the multiple linear regression model is the total score of the Parenting Stress Index. Data are expressed as B-value, 95% Confidence Interval and *p*-value using multiple linear regression model. *$p < 0.05$

Discussion

This study demonstrates the potential effect of KD heterogeneity on cognitive development and parenting stress. Our data revealed that no significant differences in developmental index, cognitive function or parenting stress between KD patients and controls. Both IVIG administration and CAL development were not associated with KD children's cognitive profiles. In addition, the profiles of parenting stress in caregivers of KD patients were examined in this study. We found that caregivers' education is associated to parenting stress, and the caregivers of patients who had CAL suffered from greater parenting stress than those of patients without CAL.

In our study sample, 4% never received IVIG, and 88.6% and 7.4% received IVIG treatment, once and twice, respectively. Although IVIG has been established as a standard treatment for KD [8], 4% of patients still never received such intervention, and 7.4% received IVIG treatment twice due to treatment resistance at the first administration. Since the study sample included patients referred from local hospitals of remote areas, some of the patients may have missed the opportunity to be correctly diagnosed and receive IVIG at the critical period. Notably, 10–20% of patients show resistance to IVIG therapy and are at risk for complications [9]. Our KD population consisted of 42% patients who exhibited CAL, a higher proportion of CAL than has been reported in the current literature [10]. Current studies suggest that approximately 20% of KD patients suffer from CAL [45]. This discrepancy may be due to Kaohsiung Chang Gung Memorial Hospital being the main medical center in Southern Taiwan and patients recruited for this study possibly having a higher severity or greater comorbidities than those in general hospitals.

The results of the current study show that KD is not related to cognitive impairment sequelae, which was generally consistent with the previous literature [19–21]. Because IVIG reduces vasculitis that presumably underlies any cognitive impairment, we assumed that KD patients who had a poor response to IVIG or had developed CAL may be related to a higher severity of systemic vasculitis [13, 14]. However, we found that neither IVIG administration nor CAL development was associated with cognitive performance. In our study population, most KD patients (96%) received IVIG treatment. The case numbers of children who didn't receive IVIG (only 4%) and treatment resistance (7.4%) were too small and it is difficult to make a sufficient comparison. Therefore, a future study with larger sample size is required to verify whether IVIG administration is associated with cognitive outcomes or not. Notably, a nationwide survey in Taiwan previously demonstrated that epilepsy and developmental delay were factors associated with cognitive impairments [21]. Whether physical comorbidities other than KD have a greater influence on cognitive function than KD itself or the disease characteristics of KD warrants further research.

We provide more scientific evidence related to parental stress or mental health of caregivers of KD patients and keeping in mind that situation implies more health service. It is noteworthy that patients' caregivers were not assessed during patients' acute phase of KD. The clinical meaning of our findings is that parenting stress of caregivers in KD children during follow-up was comparable those of control children. Nevertheless, our data revealed that caregivers of patients who had CAL suffered from greater parenting stress than the caregivers of patients who did not have CAL. A previous study from Canada revealed a similar finding with ours. The parents of children with coronary artery complications may suffered from a greater anxiety level [25]. The psychological distress is associated with family

characteristics, such as family income and maternal education [26]. Children with persistent CAL may develop complications [11], so caregivers may worry, feel stressed, and experience helplessness with regard to facing the uncertainty of their children's risk of myocardial infarction and the possibility of sudden death. This finding suggests that the parental stress or mental health of caregivers of patients with CAL require particular assistance. Furthermore, caregivers with an education level of a master's degree or above showed lower parenting stress than those who had education levels of college or lower. This finding may imply that caregivers with high education levels had greater internal or external resources to handle the patients' physical illness [26]. Alternatively, caregivers with lower education levels may require support or help to fulfill their parenting roles.

This study has certain limitations. First, due to small case numbers of KD patient without IVIG or treatment resistance, it is difficult to make a strong conclusion about cognitive impairment. Second, this is a cross-sectional study, with a mean interval between KD onset and assessment for cognition and parenting stress of 40.5 months (ranged from 1 to 159 months). Therefore, the measurement for parenting stress was highly dependent on parental recall. The parenting stress reported herein did not necessarily represent the state of patients' caregivers who take care of patients during the acute onset of KD. Third, CAL was only recorded as a categorical variable (with or without), but the influence of CAL severity on cognition or parenting stress was not assessed in this study. Moreover, we did not record any physical comorbidity besides KD. Whether other comorbidities (i.e., developmental delay or epilepsy) actually influence or moderate children's cognitive development warrants further investigation. Fourth, the KD group and control group were not perfectly matched in age and caregivers' characteristics, and those differences may have influenced the results of this study. Finally, all participants were recruited from a single site, whether this finding can be generalized into other patient populations warrants further investigation.

Conclusion

No significant differences in developmental index, cognitive function or parenting stress between KD patients and controls. In KD patients, neither IVIG treatment nor CAL was associated with the cognitive profiles of KD patients. This result is good news for caregivers and patients with KD, reassuring them that their IVIG response or CAL development will have no effect on their development milestones or cognitive function. However, caregivers of KD patients' who had CAL may feel stress about unpredictable sequela caused by CAL for their children. These caregivers may require support or help to fulfill their parenting roles.

Abbreviations

KD, Kawasaki disease; IVIG, Intravenous immunoglobulin; CAL, coronary artery aneurysms; MSEL, Mullen Scales of Early Learning; WPPSI-IV, the Wechsler Preschool and Primary Scale of Intelligence-Fourth Edition; WISC-IV, the Wechsler Intelligence Scale for Children-Fourth Edition; PSI-SF, Parenting Stress Index-Short Form

Declarations

Availability of data and materials

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher on request.

Ethics approval and consent to participate

Chang Gung Memorial Hospital's Internal Review Board approved this study (IRB No.102-3930B), and we obtained the written informed consent from the parents or guardians of all participating children.

Competing interests

The authors hereby declare that they have no conflicts of interest to disclose in relation to this article.

Consent for publication

Written consent was obtained from all children who participated in the study and their parents for publication.

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Authors' contributions

Liang-Jen Wang and Ling-Sai Chang conceptualized and designed the study and drafted the initial manuscript. Zi-Yu Tsai recruited and assessed the patients. Ho-Chang Kuo designed the study, recruited the patients, and approved the final manuscript to be submitted.

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