ORIGINAL ARTICLE

Behavioral Problems and Psychiatric Comorbidities in Children with *SCN1A*-Related Dravet Syndrome

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Objective: To study psychiatric comorbidities and behavioral problems in children with Dravet syndrome related to *SCN1A* using standardized tools and parental questionnaires to describe their specific profiles.

Materials and Methods: The present study was a descriptive cross-sectional study. Twenty-one children were invited to participate in the study and 11 completed the study measures, including a psychiatric interview, a cognitive evaluation, and two parental questionnaires, the Thai version of Child Behavioral Checklist or Thai Youth Checklist (TYC) and the Strengths and Difficulties Questionnaire (SDQ).

Results: The findings showed pathological development in all patients (100%). The intellectual disability (ID) and global developmental delay (GDD) were found in 10 of 11 (90.9%). Six patients (54.5%) had autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD). No statistical significance was found between the type of mutation and ASD or ADHD with odds ratio of 1.5 (95% CI 0.14 to 16.55, p=0.74). Nine of 11 patients (81.8%) had motor coordination disorder.

Conclusion: The present study indicated a high prevalence of ID, ASD, ADHD, and motor coordination disorder. Psychiatric assessment and cognitive evaluation are important and critical steps for all patients with Dravet syndrome.

Keywords: Dravet syndrome; *SCN1A*; Epilepsy syndrome; Psychiatric comorbidities; Behavioral problems

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Dravet syndrome is the most common developmental epileptic encephalopathy (DEE). The prevalence of Dravet syndrome is 1 in 40,000. Almost 65% to 80% of Dravet syndrome cases have *SCN1A* mutations[1-3] including truncation in 48% to 62%, and missense mutation in 38% to 52%. The truncating mutation, such as nonsense, frameshift mutation, or splice site defect, typically tends to have a more severe phenotype than the missense mutation due to more severe disruption of protein function[4-6]. The *SCN1B*, *SCN2A*, *GABRG2*, and *GABRD* genes have also been reported infrequently as causes of Dravet syndrome, with varying phenotypes, but the evidence is not clear[2,7-9]. Almost all patients had an early onset of seizures before age one[10-13], precipitated by fever[14,15]. The seizures tend to be prolonged, clustered, multiple types such as focal, generalized tonic clonic, absence, myoclonic, and atonic seizure, and resistant to antiepileptic medications[10]. Compared to the normal population, this syndrome causes more delayed language and social development[11] along with intellectual disability (ID)[8,12,13,16], while reports of incidences of comorbidities with attention-deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) were scarce. However, there was no evidence of a correlation between the type of mutation and psychiatric comorbidities in patients with Dravet syndrome[13,17-19]. The only study from Ishii et al. reported that the truncating mutation caused ID more severely than others[20]. Studies found that about 24% to 39% of Dravet syndrome patients had ADHD and ASD. Those psychiatric disorders affect behavioral problems specifically aggression, self-stimulation, social, and emotional problems[8,18,19,21].

Psychiatric and behavioral problems are chronic and lifelong, causing suffering and reducing the

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quality of life of patients and their families[22]. Thailand has previously lacked comprehensive data on *SCN1A* gene mutations due to limited genetic testing capabilities. Despite recent advancements in *SCN1A* testing availability, no thorough study has been conducted in the country. This research aimed to address this gap by investigating psychiatric comorbidities and behavioral problems in children with Dravet syndrome associated with *SCN1A* mutations, with the goal of improving clinical practices. Additionally, the authors hypothesize that the presence of ADHD and ASD could serve as indicators of Dravet syndrome severity.

Materials and Methods

Study designs and participants

The present study was a cross-sectional study in the Department of Pediatrics of Siriraj Hospital between December 2020 and February 2022. Despite the extended study duration, only 21 patients met the criteria for enrollment. The inclusion criteria were 1) children aged more than one year to 18 years, 2) patients with a confirmed *SCN1A* mutation on a genetic test, and 3) having no seizures for at least seven days. All subjects had their parents, or legal guardians completed the inform consent documents. They were also informed that they could voluntarily terminate their participation in the study at any time. The study was approved by Siriraj Institutional Review Board (COA no. Si 477/2020).

Measures

Psychiatric assessment:

New psychiatric assessments were conducted on all participants by child and adolescent psychiatrists, with diagnoses based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria. Standardized testing was also administered. All evaluations, including psychiatric interviews, developmental assessments, and questionnaires, were collected prospectively and specifically for the present study. Each child's age was recorded at the time of these assessments.

Developmental and intelligence quotient (IQ) measurements:

All children were examined and investigated by a senior psychologist. All the tests performed were standard developmental and IQ tests chosen individually for each subject. Standard tests included were the Mullen Scale of Early Learning and the Stanford-Binet test.

The Beery-Buktenica Developmental Test of Visual-Motor Integration (Beery VMI):

Beery VMI is the neuropsychological test for visual motor integration, or eye-hand coordination, visual perception, and motor coordination. The test had high interrater and test-retest reliabilities with correlation coefficients of 0.92 and 0.93 respectively[23,24].

The Thai version of the Strengths and Difficulties Questionnaire (SDQ):

This questionnaire for children aged 4 to 16 years was developed by Robert Goodman. In addition, it has been translated into Thai by the Department of Mental Health of the Ministry of Public Health and has been used by Thai parents to evaluate their children's behaviors with 25 items divided into five dimensions, conduct problems, hyperactivity, emotional problems, peer problems, and prosocial behavior. In the present study, only the parent version of SDQ was used, which had high reliability. The Cronbach alpha coefficient of the scale was 0.81. The sum of four problem scores represented a total difficulties score (TDS) with a cut-off indicating "clinical range" at the ninetieth percentile. Therefore, children who have significant emotional/behavioral symptoms to obtain the TDS above the cut-off are at risk of having psychiatric disorder. There is also cut-off for each subscale score to identify cases at risk of having mental disorders relevant to each emotional/behavioral symptom[25].

Thai Youth Checklist (TYC):

This questionnaire for children aged 6 to 18 years had copyright and was adapted from the Child Behavior Checklist (CBCL) by Achenbach et al[26]. This scale had 135 items that interpreted the severity of overall clinical problems. The parent version of TYC had a high test-retest reliability at 0.81 and an inter-interviewer reliability at 0.91. The total scores are categorized into "normal", "problem", and "clinical" ranges. For children aged 6 to 11 years, "problem" ranges are total scores of 49 to 66 for boys, and 48 to 65 for girls, and "clinical" ranges are above 66 for boys, and above 65 for girls. For children aged 12 and older of both genders, scores of 42 to 57 and above 57 are considered "problem" and "clinical" ranges, respectively[27].

Children's Global Assessment Scale (CGAS):

The scale was used to determine the global functioning of children as rated by a physician. Scores range from 1 to 90 or 1 to 100, with high scores indicating better functioning[28].

Clinical Global Impression-Severity (CGI-S):

The CGI is rated on a 7-point scale, with the severity of illness scale using a range of responses from 1 (normal) through to 7 (amongst the most severely ill patients). The assessment will be performed by a physician, compared to the clinician's previous experience with similarly diagnosed patients[29].

Global Family Environment Scale (GFES):

This measurement described the quality of the patient's family psychosocial environment, which focused on negative precipitating factors such as divorce, neglect, and physical abuse. The scale was rated as range: 10-1 to 100-91[30].

A general information questionnaire:

The researchers designed a general information questionnaire to collect information on socio-demographic and disease-related variables, including age, age of onset of Dravet syndrome, educational level, type of mutation of the *SCN1A* gene and abnormal movement.

Statistical analysis

IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA) was used to analyze the data. Descriptive statistics were performed using appropriate methods, such as percentage, mean, and standard deviation, according to the type of data to provide the information that was collected. The difference in demographic factors in psychiatric disorder and severity was calculated using the t-test. Statistical significance was set at p-value of less than 0.05. Chi-square analysis was performed to identify any relationship between the type of *SCN1A* mutation and psychological comorbidity.

Results

Of the 21 possible patients, eleven consented to participate and were scheduled to be examined by a child and adolescent psychiatrist and a psychologist. Nine refused to participate because they lived in rural areas far from the study location or because they were worried about the COVID-19 pandemic and another one died. Eleven patients completed the investigation. Their ages ranged between one and ten years, with an average of 7.29 years (SD 2.62). Of the 11 patients, there were four females and seven males. Six patients (54.5%) had the missense *SCN1A* mutation while five patients (45.5%) had the truncated *SCN1A* mutation. Age onset ranged between one and ten months with a mean of 5.36±2.34) as shown in Table 1. Medical history, encompassing antiepileptic drugs (AEDs) and psychotropic medications, was systematically collected through caregiver interviews and patient medical records. A majority of patients were prescribed a combination of AEDs, including valproic acid, clobazam, topiramate, levetiracetam, and rufinamide. Furthermore, two patients had a history of receiving behavioral medications, specifically methylphenidate and risperidone. A notable finding in this cohort was that six patients (54.5%) presented with co-occurring ASD and ADHD, underscoring the frequent diagnostic overlap between these two neurodevelopmental conditions (Table 2). No statistical significance was found between the type of mutation and ASD or ADHD with an odds ratio of 1.5 (95% CI 0.14 to 16.55, p=0.74) for both diagnoses. Furthermore, the type of mutation was not related to the incidence rate of global developmental delay (GDD) or ID and motor coordination disorder (Table 3).

Table 1. Characteristics of the subjects (n=11)

	Value
Sex; n (%)	
Male	7 (63.6)
Female	4 (36.4)
Age (years); mean±SD	7.29±2.62
Age onset (months); mean±SD	5.36±2.34
Epilepsy in first degree relative; n (%)	1 (9.1)
Microcephaly; n (%)	0 (0.0)
Hypertonia; n (%)	2 (18.2)
Crouch gait; n (%)	4 (36.4)
Total current number of status epilepticus events; mean±SD	2.7±0.95
Type of mutation; n (%)	
Missense	6 (54.5)
Truncating	5 (45.5)

SD=standard deviation

Based on the DSM-5 criteria, all 11 patients had developmental issues. Among the ten patients older than 5 years, nine were diagnosed with ID, with six (66.7%) having severe ID and three (33.3%) having moderate ID. Only one patient had a borderline IQ, scoring 88. Of the patients, nine out of 11 (81.8%) had a motor coordination disorder. Additionally, out of the ten subjects who were able to perform the Beery VMI test, eight scored very low at between 45 and 60, while another was diagnosed based on evident clinical symptoms. Despite the researchers' best efforts to administer the tests, one patient could not complete both the IQ and Beery VMI test due to the severity of their ADHD and ASD. This patient also had clinical signs of a motor coordination disorder (Table 2).

Table 2. Developmental and psychiatric comorbidities in the subjects with Dravet syndrome (n=11)

	Age		Sex	Type of mutation	Current AEDs	IQ	ID/GDD	Beery VMI total score	Motor coordination disorder	ADHD	ASD	CGI-S	CGAS	GFES
	Years	Months												
1	6	11	F	Missense	VPA, TPM	28	Severe	50	Yes	No	No	Moderately ill	21 to 30	81 to 90
2	9	10	M	Missense	VPA	36	Severe	45	Yes	Yes	Yes	Markedly ill	21 to 30	71 to 80
3#	10	4	M	Missense	TPM, CLB	23	Severe	45	Yes	Yes	Yes	Markedly ill	11 to 20	71 to 80
4	8	7	M	Missense	VPA, TPM, CLB	43	Moderate	45	Yes	Yes	Yes	Mildly ill	31 to 40	71 to 80
5	5	1	M	Missense	TPM, CLB, perampanel	49	Moderate	50	Yes	No	No	Moderately ill	21 to 30	71 to 80
6	2	0	M	Missense	VPA, TPM, CLB, perampanel	54	Mild	45	*	No	No	Mildly ill	31 to 40	71 to 80
7	5	2	F	Truncating	VPA, TPM	49	Moderate	60	Yes	No	No	Mildly ill	61 to 70	81 to 90
8	9	6	M	Truncating	VPA, TPM	**	Severe	**	Yes	Yes	Yes	Moderately ill	31 to 40	81 to 90
9+	9	10	M	Truncating	VPA, CLB, LEV, RFM	88	Borderline	71	Yes	Yes	Yes	Mildly ill	61 to 70	81 to 90
10	5	7	F	Truncating	VPA, TPM, CLB	49	Severe	45	Yes	Yes	Yes	Moderately ill	31 to 40	81 to 90
11	7	5	F	Truncating	VPA, TPM, CLB, LEV	36	Severe	**	No	No	No	Moderately ill	31 to 40	81 to 90

F=female; M=male; IQ=intellectual quotient; ID=intellectual disability; GDD=global developmental delay; Beery VMI= Beery-Buktenica Developmental Test of visual motor integration; ADHD=attention-deficit hyperactivity disorder; ASD=autism spectrum disorder; CGAS=Children's Global Assessment Scale; CGI-S=Clinical Global Impression-Severity; GFES=Global Family Environment Scale; AEDs=antiepileptic drugs; LEV=levetiracetam; RFM=rufinamide; TPM=topiramate; VPA=valproic acid; CLB=clobazam

* Can not be concluded due to age, ** Did not comply to perform test, # Patient received both methylphenidate and risperidone during the assessment, + Patient received only methylphenidate during the assessment

Age is described in years and months at the time of completed examinations

Table 3. Correlation between the type of mutation and psychiatric comorbidities

	Type of mutation; n (%)		p-value	Odds ratio	95% CI
	Missense	Truncating			
ADHD	3 (27.3)	3 (27.3)	0.74	1.5	0.14 to 16.55
ASD	3 (27.3)	3 (27.3)	0.74	1.5	0.14 to 16.55
GDD/ID	6 (54.5)	4 (36.4)	0.46	2.5	1.18 to 5.35
Motor coordination disorder	5 (50.0)	4 (30.0)	0.89	1.25	0.06 to 26.87

ADHD=attention-deficit hyperactivity disorder; ASD=autism spectrum disorder; ID=intellectual disability; GDD=global developmental delay; CI=confidence interval

Four patients were rated as mildly ill (36.4%), five of them were rated as moderately ill (45.5%), and two were clinically markedly ill (18.1%). Patients with missense mutation had clinically mild to marked disease, while truncated groups had mild to moderate illness. Five of the eleven subjects were rated on the Children's Global Assessment Scale (CGAS) at 31 to 40, which is interpreted as a major impairment of functioning in several areas. Five of the eleven patients were rated on the Global Family Environment Scale (GFES) at 71 to 80, which meant a slightly unsatisfactory environment, while another six had an adequate family environment, scored at 81 to 90 on GFES (Table 2).

Of the seven subjects older than six years, only six responded to both the TYC and SDQ. Out of these, five (83.3%) had no behavioral problems as rated by TYC, while one scored within the clinical range. Additionally, out of ten subjects older than four years, only eight were rated using SDQ. Of these, two (25%) were on the borderline range, and one (12.5%) had a clinically significant problem. In the element domain of SDQ, three out of eight subjects (37.5%) were at risk for conduct symptom/behavior-related mental disorders, six out of eight (75%) were at risk for ADHD due to hyperactivity/inattention, two out of eight (25%) were at risk for developing peer relationship problems, and five out of eight (62.5%) were at risk for mental having difficulties of prosocial behavior. Notably, none of the subjects had emotional problems (Table 4).

By using the Mann Whitney U test, there was no statistically significant correlation between severity of the disease, behavioral problem score, and total current of status epilepticus and psychiatric disorders (Table 5).

Table 4. Behavioral problems assessed by TYC and SDQ

	Age		Sex	TYC (total score)	SDQ (total difficulties score)	SDQ subscales score				
	Years	Months				Emotional	Conduct	Hyperactivity/inattention	Peer relationship	Prosocial behavior
1	6	11	F	Normal	Abnormal	Normal	Abnormal	Abnormal	Normal	Strength
2	9	10	M	Clinical range	Borderline	Normal	Borderline	Borderline	Normal	Difficulty
3	10	4	M	Normal	Normal	Normal	Normal	Abnormal	Borderline	Difficulty
4	8	7	M	Normal	Borderline	Normal	Borderline	Abnormal	Normal	Difficulty
5	5	1	M	*	**	**	**	**	**	**
6	2	0	M	*	*	*	*	*	*	*
7	5	2	F	*	Normal	Normal	Normal	Normal	Normal	Strength
8	9	6	M	Normal	Normal	Normal	Normal	Normal	Borderline	Difficulty
9	9	10	M	**	**	**	**	**	**	**
10	5	7	F	*	Normal	Normal	Normal	Abnormal	Normal	Difficulty
11	7	5	F	Normal	Normal	Normal	Normal	Abnormal	Normal	Strength

F=female; M=male; SDQ=Thai version of Strengths and Difficulties Questionnaire, TYC=Thai Youth Checklist
* Age younger than 6 years old, ** Did not respond to the questionnaire
Age is described in years and months at the time of completed examinations

Table 5. Correlation between severity of Dravet syndrome and psychiatric comorbidities

	Psychiatric comorbidities					
	ADHD/ASD		GDD/ID		Motor coordination disorder	
	Mean±SD	p-value	Mean±SD	p-value	Mean±SD	p-value
CGI-S (n=11)	4±0.89	0.43	3.9±0.74	0.23	3.89±0.78	0.51
Total event of status epilepticus (n=10)	2.67±1.03	1.00	2.67±1.0	0.72	2.56±0.88	0.14

ADHD=attention-deficit hyperactivity disorder; ASD=autism spectrum disorder; ID=intellectual disability; GDD=global developmental delay; CGI-S=Clinical Global Impression-Severity; SD=standard deviation

After identifying behavioral and psychological comorbidities, the researchers initiated appropriate interventions. Patients diagnosed with ADHD received low-dose methylphenidate, to which they responded well. Those with ASD were given behavioral interventions tailored to their developmental needs, such as social skills training and structured routines. All families received counseling on effective care strategies. While two patients successfully enrolled in regular school programs, most families expressed concerns about school attendance, primarily due to their child's seizure risk and behavioral challenges.

Discussion

The present study represents the first investigation in Thailand focusing on psychiatric comorbidities and behavioral problems in patients with *SCN1A*-related Dravet syndrome. The developmental trajectory of children with Dravet syndrome typically begins with febrile seizures in infancy, followed by the emergence of multiple seizure types and developmental delays within the first two years of life. Psychiatric comorbidities such as ASD and ADHD often emerge during early childhood, further complicating the clinical picture. These neuropsychiatric symptoms not only impact functional outcomes but also pose ongoing challenges in behavior management, social adaptation, and educational access. This highlights the importance of early developmental surveillance and comprehensive neuropsychiatric assessments as part of routine care. However, the recent consensus shows that only 70% of patients have *SCN1A*-related Dravet syndrome[31], and our findings demonstrated pathological development in all, which were similar to previous results that showed 97% of pathological cases of *SCN1A*-related patients[21]. In the present study, more than 50% of the patients had ASD and ADHD comorbidities, which was higher than previous results in other regions that reported 24% to 39%[13,19,32]. Furthermore, there was a high prevalence of ID at 90.9%, with 66.7% of those affected being categorized as severe. This suggests that ID is more severe than previous results from Western regions have indicated, yet it aligns with the recent consensus from experts, which states that almost all patients with Dravet syndrome have a developmental quotient of less than 70[32]. Notably, one patient had an IQ of 88, which prompted further examination of this case.

Motor coordination problems are also common in this group. Thus, it can be suggested that patients with Dravet syndrome require rehabilitation or developmental stimulation.

In the present research, the researchers hypothesized that the ADHD and ASD could be indicators of the severity of Dravet syndrome. Contrary to expectations, the researchers found no correlation between mutation type and the presence of psychiatric comorbidities. Notably, both truncated and missense mutations showed equal associations with ADHD and ASD in the present study. To the researchers' knowledge, no other study has investigated the severity of the phenotype across different mutation types as the researchers have. Yet, the subjectivity of the CGI-S scale suggests that more research in this area is crucial.

The behavioral issues were not as prevalent as psychiatric disorders. Only 22.2% of patients fell into the clinical range based on TYC or SDQ assessments. Interestingly, none of the cases reported emotional problems, while other studies have concluded that internalizing behaviors, such as depression and anxiety, are observed in a minority of preschool children. However, these behaviors become more prevalent with age and are presented in over half of the adult population. Areas of concern include prosocial behavior, hyperactivity, and conduct, which are more frequently observed than internalizing behaviors[32].

The researchers did not find a clear connection between the occurrence of ADHD, ASD, GDD, motor coordination disorder, and total current of status epilepticus with the presence of the *SCN1A* mutation. Interestingly, the significant trend seen with the age at onset and language traits might be linked to early development of language brain networks. Past research has indicated a shared pathway for seizures, ID, and ASD in many genetic conditions[33]. This might be applicable to Dravet syndrome, where a malfunction in the *SCN1A* sodium function might be responsible for not just seizures, but also ID and ASD[34]. Continued research with larger sample sizes is essential to confirm these hypotheses.

Treatment for Dravet syndrome currently relies on targeted medications like sodium valproate and clobazam. Excitingly, clinical trials exploring disease-modifying therapies have resulted in a greater reduction in seizures. The behavioral and psychological comorbidities associated with *SCN1A*-related Dravet syndrome significantly complicate patient care, particularly in resource-limited settings. The present study findings reveal that even when ADHD and ASD are identified early, accessing effective, evidence-based interventions remains a challenge. While low-dose methylphenidate showed clinical benefit in the present study small cohort, further research is crucial to assess its long-term safety and outcomes in Dravet syndrome patients, especially given the theoretical risk of seizure exacerbation. Similarly, despite efforts to initiate behavioral therapy for ASD, many caregivers deferred formal education enrollment due to concerns about school readiness and social stigma. These insights underscore the critical need for multidisciplinary care models and robust caregiver support systems to improve both clinical and functional outcomes for this population.

The present study had limitations. First, despite finding 21 eligible patients, only eleven completed the full assessment due to geographic barriers, COVID-19 concerns, or patient death. This small sample size, coupled with the specific focus solely on *SCN1A*-related Dravet syndrome and the exclusion of other gene mutations, limited both generalizability and statistical power. Second, not all patients could complete every assessment because of behavioral issues, particularly those with severe ADHD and ASD. Third, parental recall for behavioral reports might introduce reporting bias. Finally, the cross-sectional design prevented the researchers from drawing causal inferences or conducting long-term outcome analysis. Future research should aim for larger cohorts and longitudinal follow-up to validate and expand on these findings.

Conclusion

The present study highlights the high prevalence of ID, along with significant rates of ASD, ADHD, and motor coordination disorders. Both psychiatric assessment and cognitive evaluation are crucial. In line with global recommendations, issues related to ASD and developmental delays should be addressed promptly to ensure timely interventions. It is essential to introduce and implement specialized developmental stimulation programs for patients with ASD. Recognizing and diagnosing ASD, ADHD, and ID in patients with Dravet syndrome is a pivotal step, as early, tailored interventions can lead to enhanced outcomes and an improved quality of life.

What is already known about this topic?

Dravet syndrome is a severe developmental and epileptic encephalopathy with *SCN1A* mutations in 65% to 80% of cases. ID, ASD, and ADHD are

commonly reported, but their prevalence varies across studies. Data from South-east Asian populations remains scarce. The relationship between *SCN1A* mutation types and psychiatric outcomes is still uncertain.

What does this study add?

This study is the first to examine psychiatric and behavioral profiles of Thai children with *SCN1A*-related Dravet syndrome. It found higher rates of ASD and ADHD at 54.5%, than previously reported, as well as a high prevalence of motor coordination disorder at 81.8%, emphasizing the need for early intervention. No significant link was found between mutation type and psychiatric conditions. These findings highlight the importance of routine psychiatric screening and tailored interventions to improve quality of life.

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Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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