

Clinical Spectrum and Comorbidities of Dravet Syndrome in Taiwan

Chia-Hsuan Huang

National Taiwan University Hospital Yunlin Branch, Yunlin County, Taiwan

Pi-Lien Hung

Kaohsiung Chang Gung Memorial Hospital

Pi-Chuan Fan

National Taiwan University Hospital

Kuang-Lin Lin

Chang Gung Children's Hospital and Chang Gung Memorial Hospital

Ting-Rong Hsu

Taipei Veterans General Hospital

I-Jun Chou

Chang Gung Children's Hospital and Chang Gung Memorial Hospital

Che-Sheng Ho

Mackay Memorial Hospital

I-Ching Chou

China Medical University Hospital

Wei-Sheng Lin

Taipei Veterans General Hospital

Inn-Chi Lee

Chung Shan Medical University Hospital

Hueng-Chuen Fan

Tungs' Taichung MetroHarbor Hospital

Shyi-Jou Chen

Tri-Service General Hospital

Jao-Shwann Liang

Far Eastern Memorial Hospital

Yi-Fang Tu

National Cheng Kung University Hospital

Tung-Ming Chang

Changhua Christian Hospital

Lee-Chin Wong

Cathay General Hospital

Kun-Long Hung

Fu Jen Catholic University

Wang-Tso Lee (✉ wangtssolee@ntu.edu.tw)

National Taiwan University Hospital

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Abstract

Dravet syndrome (DS) is a rare and devastating epilepsy syndrome, and it can affect the patients and their caregivers. However, the lack of a reliable and valid measures of caregiver impact and the characteristic pattern in Taiwan. The purpose of this study was to describe the characteristics of patients with DS and caregivers' concerns, and to establish a baseline frequency of characteristics of the disease using a cross-sectional survey in Taiwan. We recruit the caregivers of patients with DS and assessed their condition via online anonymous questionnaire. Seizure frequency decreased with age though not statistically significant. Vaccine may not influence the condition of DS. We highlighted the greatest impact on the domains that affect caregivers' daily life, including additional household tasks, symptoms observation, further medical plan and financial problem. Caregivers may also concern about lack of independence/constant care, seizure control, speech/communication and sibling impacts/long-term care when patents are gone. The current findings highlight the significant life effects of caring for a child with DS in Taiwan, and can be used to raise the attention about the need for these families. The possible pathogenic mechanisms of these comorbidities were also discussed.

Introduction

Dravet syndrome (DS), also known as Severe Myoclonic Epilepsy of Infancy, is a rare and devastating epilepsy syndrome. The prevalence rate was estimated to be approximately 1 in 20,000 to 1 in 40,000 children. [1–3] Associated mutations of the *SCN1A* gene were reported in 75% of cases. The characteristics of DS include frequently prolonged hemi-convulsion, developmental delays, speech impairment, and other comorbidities, including ataxia, circadian rhythm disorder, impaired sleep quality, and autistic-like social-interaction deficits[4]. DS is frequently accompanied with a range of triggering factors, such as fever, infections, hot bath, and photosensitivity. Although DS is usually pharmacoresistent, a trend toward less severe epilepsy and cognitive impairment is usually observed after the age of 5 years.[5]

Although current literature had proven that there is no significant difference in the clinical and cognitive outcomes, in the past many parents may worry about vaccination-related seizures.[6–8] Due to the knowledge gap about frequency of seizures following vaccination, misperception of vaccination side effects and reduced vaccination coverage still exists in many DS families. [8]

This study aims to describe the characteristics of patients with DS and caregivers' concerns, and to establish a baseline frequency of characteristics of the disease using a cross-sectional survey in Taiwan. The data may be used to help researchers and clinicians for further studies, and to more understand this refractory epilepsy and most important issues to patients and their families. The possible pathogenic molecular related to comorbidities were also discussed.

Results

Demographics

We identified 38 patients with DS from our study, all of whom had a confirmed mutation in *SCN1A*. However, only 32 patients knew correct mutations data, consisting of 19 missense mutations in 21 patients, 2 nonsense mutations in 2 patients, 1 splice site mutation in 1 patient, 5 frameshift mutations in 6 patients, and 2 chromosome deletion in 2 patients (Fig. 1). Patients ranged in age from 1 to 28 years (mean \pm SD, 10.5 ± 6.3 years). Sixteen patients are female (Table 1). About their language and ambulation evaluation excluding patient age less than 2 years, 51% can speak a clear and correct sentence and 78% of patients can ambulate without assistance.

Table 1
Demographics data in 38 patients.

Patient data N (%)			
Age		Seizure Pattern	
Infants (0–1 y)	1 (2.6%)	Generalized tonic-clonic	25/38 (66%)
Preschool(2-5y)	7(18.4%)	Absence	14/38 (37%)
Middle childhood (6-11y)	18(47.3%)	Focal	11/38 (29%)
Adolescence(12-17y)	7(18.4%)	Myoclonus	6/37 (16%)
Adult (≥ 18Y)	5(13.1%)	Epileptic spasm	1/38 (3%)
Mean age: 10.5 ± 6.3 years			
Female	16 (42%)		
Male	21(58%)		
SCN1A mutation	38(100%)		
First diagnosed age (months)	Mean:9.5 ± 16.1 (Median:6)		

Seizure evaluation

The mean ages of epilepsy onset were about 9.5 \pm 16.1 months (median 6 months). The generalized tonic-clonic seizures, absence seizures and focal seizures were the most common at first time, and occurred in 66%, 37% and 29%, respectively (Table 1). These seizures were often induced by fever (54%) (Fig. 2a), and caregivers reported that fever, infection, sun exposure, warm bath, after exercise and positive mood were the most common triggering factors that induced seizure attack (Fig. 2b). All of each may be > 50%. Besides, vaccination accounted for 32 %, which may trigger seizure attack in DS patients. Photosensitivity and pattern sensitivity were also triggering factors for seizure, and might occur across different age group and might not disappear when age increases.

Frequency of seizure attacks was mostly between weekly and monthly occurrence, accounting for 53% of the patients (Fig. 2c). There was no great difference in age distribution, including infants in 1/1(100%), preschool (2-5y) in 4/7 (57%), middle childhood (6-11y) in 10/18 (56%), adolescence (12-17y) in 4/7 (57%), and adults ($\geq 18y$) in 1/5 (20%). On the other hand, we also noticed that seizure frequency tended to decrease over time although no significant difference was found ($P = 0.329$).

Vaccine evaluation

When we compared between vaccination-proximate and vaccination-distant groups, there was no statistical difference between the two groups (Table 2). Only vaccination in seizure triggering factors had been frequently observed in vaccination-proximate group ($P = 0.038$). No significant difference was present in the language, ambulation, seizure characteristics (first seizure onset, seizure triggering factors except vaccine, seizure pattern, and seizure frequency), and number of anti-epileptic drugs (AEDs) in use.

Table 2

Comparison of seizure characteristics and seizure control between 35 patients with Dravet syndrome in the vaccination-distant and vaccination-proximate groups

	Vaccination-Distant (N = 23)	Vaccination-Proximate (N = 12)	
SCN1A mutation	35 (100%)	12(100%)	-
Seizure onset age (months)	7.7 ± 6.1	14.2 ± 27.9	P = 0.668
Language			P = 0.06
No words	2/22 (9%)	1/12 (8%)	
Single words	2/22 (9%)	6/12 (50%)	
Short sentences	3/22 (14%)	1/12 (8%)	
Correct sentences	15/22 (68%)	4/12 (33%)	
Ambulation			P = 0.641
Need assistance	3/22 (14%)	3/12 (25%)	
Without assistance	19/22 (86%)	9/12 (75%)	
Seizure triggering factors			
Sun exposure	14/21 (67%)	6/11 (55%)	P = 0.703
Hot bath	15/22 (68%)	8/12 (67%)	P = 1.000
Fever	23/23 (100%)	12/12 (100%)	-
Vaccine	5/22 (23%)	6/9 (67%)	P = 0.038
Positive mood	13/23 (57%)	5/11 (46%)	P = 0.717
After exercise	14/23 (61%)	5/11 (46%)	P = 0.475
Numbers of AEDs in use	3.0 ± 1.0	3.5 ± 1.1	P = 0.195
Seizure pattern			
GTC	15/23(65%)	7/12 (58%)	P = 0.726
Focal	6/23 (26%)	3/12(25%)	P = 1.000
Absence	9/23 (39%)	4/12 (33%)	P = 1.000
Myoclonus	5/23 (22%)	1/11 (9%)	P = 0.638
Infantile spasms	0/23 (0%)	1/12(8%)	P = 0.343
Seizure frequency			P = 0.832
Controlled	3/23 (13%)	2/12(17%)	
Uncontrolled	8/23 (35%)	3/12(25%)	
Intractable	12/23 (52%)	7/12(58%)	
* Current seizure control at last follow-up: "controlled" seizure indicates that the patient has less than no seizures in the past 6 months; "uncontrolled" for patients with more than one and less than six times per months seizures in the past 6 months ; "intractable" for one or more seizures each month in the past 6 months.			

Comorbidity evaluation

All questionnaires were reported by 100% of caregivers (Table 3). With the exception of nocturnal seizures, there was little variation in sleep issues among patient age groups.

Both bradycardia and tachycardia were reported in 9% and 3%, respectively. Only one patient had arrhythmia history, and 3 of 36 patients reported abnormalities or changes in the heart structure.

Behavioral and psychiatric issues were commonly reported in the survey, and attention deficit disorder or attention deficit hyperactivity disorder were most complained (61%). Other psychiatric symptoms such as difficulty with impulse control and autistic-like traits were also noticed in 39% and 31%, respectively. 42% had ever went to pediatric psychiatric clinic for evaluation. Anxiety and psychosis accounted for one-third of DS patients.

As for musculoskeletal issues, hypotonia (50%) was relatively common in the patients' early childhood. Broken bones (24%) and scoliosis (19%) had increased with age in our data, which were more prevalent from the population of middle childhood to adult, compared with that of infant to preschool.

Constipation (47%) was another common issue. About one-third of DS patients had appetite disturbance and frequent/chronic urinary tract infection.

Drowsiness, cognition problem and unsteady gait were most common drug side effect, and occurred in 46, 47 and 49%, respectively. The unsteady gait may also arise from the disease entity of DS.

Table 3
Frequencies of the most commonly reported issues.

Issue Reported	n/N (%)	Issue Reported	n/N (%)	Issue Reported	n/N (%)	Issue Reported	n/N (%)
Sleep Issues		Psychiatric Issues		Hematologic Issues		Orthopedic/Movement	
Sleep disturbances	11/38 (29%)	Autistic-like traits	11/36(31%)	Thromopenia	3/36 (8%)	Hypotonia	17/34(50%)
Nocturnal seizures	18/35 (51%)	Impulse control	15/38(39%)	Vitamin D deficiency	2/34 (6%)	Hypertonia	3/34 (9%)
Irregular sleep schedule	6/38 (16%)	ADD or ADHD	23/38 (61%)	Iron deficiency/Anemia	1/35 (3%)	Broken bones	9/38 (24%)
Premature awakening	7/37 (19%)	Anxiety	8/37 (22%)	Significant hair loss	6/36 (17%)	Scoliosis	7/37 (19%)
Sleep apnea	3/37 (8%)	Psychosis	6/31 (19%)	Neutropenia	2/36 (6%)	Hip dysplasia	3/35 (9%)
Cardiac Issues		Depression	1/35 (2%)	Bowel Issues		Urinary tract issues	
Tachycardia	3/35 (9%)	Pediatric psychiatry	16/38(42%)	Slow digestion	5/38 (13%)	Frequent UTIs	11/38(29%)
Bradycardia	1/35 (3%)	Drug side effect		Appetite disturbance	11/38 (29%)	Nephrocalcinosis	1/38 (3%)
Arrhythmia	1/36 (3%)	Drowsiness	17/37 (46%)	Constipation	18/38(47%)		
Abnormalities of heart structure	3/36 (8%)	Cognition problem	16/34 (47%)	GERD	6/37(16%)		
		Unsteady gait	17/35 (49%)	Diarrhea	4/38 (11%)		

Medications survey

The sixth most common daily medications tried at any time by patients were clobazam (68%), valproic acid (66%), levetiracetam (55%), topiramate (29%), stiripentol (26%), and clonazepam (18%). Use of contraindicated medications was also reported, including lamotrigine in 11%, carbamazepine in 3%, and oxcarbazepine in 24%. The survey did not distinguish between medications used prediagnosis and those used postdiagnosis.

In most patients, multiple AEDs were needed, and 78% of patients may need more than 3 drugs for seizure control. 100% (12/12) of responders with children age 12 years or older reported having the use of more than 3 antiepileptic drugs. Only 5% (2/38) of patients

used 1 drug for seizure control and 16% (6/38) of patients needed 2 drugs for seizure control.

Caregiver issues and family dynamics (supplementary tables)

Nearly half of caregivers (47%) reported having suffered from depressed mood via questionnaire, but we did not record whether they had received further help or not. When evaluating the caregiver burden scale in each domain, approximately three quarters of caregivers reported moderate or greater difficulty in doing additional household tasks (79%), watching and reporting symptoms (77%), and seeking further medical plans (76%). The rest of the items of the questionnaire were financial problem (66%), medical or nursing treatments (66%), medication use (63%), patient care (58%) and mobility problem (50%). When being asked to rank their top three concerns in an open response, caregivers highlighted the lack of independence (61%), seizure control (58%), speech and communication challenges (50%), and sibling impacts for long-term caring for patients with DS (50%).

Discussion

In this cross-section cohort, we collected data about patients with DS from caregivers in Taiwan, which add to our understanding about the impact of DS patients' condition and DS on caregivers' concerns. It is important to avoid specific seizure trigger factors in DS. In our study, we found that the most significant trigger factor as shown in other studies is hyperthermia. Therefore, the patients should avoid the predisposing factors of hyperthermia, such as overexcitement, overexertion, sun exposure, and warm bath [9]. The family members should also be educated to seek for medical assistance whenever facing hyperthermia. We also noticed that photosensitivity and pattern sensitivity were trigger factors of seizure, similar to that of Villas et. al. reported in 2017 [10].

In our study, we found that vaccine-related seizures were reported in 12 (34%) of 35 patients at our cohort. This was consistent with previous studies showing that one third of patients with DS developed seizures after vaccination [7, 8, 11] (Table 4). Because there was no statistically significant difference between language, ambulation or seizure characteristics for those with and without vaccine-related seizures, the vaccination should not be withheld in patient with DS, and all clinicians should provide families with proper information before administering vaccination.

Table 4
Comparison of literature review in vaccination-related seizures in Dravet syndrome

Study	Present Study	Wong et al. <i>Pediatr Neurol</i> 2016	Tro-Baumann et al. <i>Epilepsia</i> .2011	McIntosh et al. <i>Lancet Neurol</i> .2010
Country	Taiwan	Hong Kong	Germany and Austria	Austria
Numbers	38	54	70	40
Ethnic Origin	100% Chinese	98% Chinese	Unspecified	Unspecified
Percentage of Vaccination-Related Seizures	34%	31.5%	27%	30%
Significance of <i>SCN1A</i> mutations	Patient recruitment consists of 100% patients with DS with <i>SCN1A</i> mutation	The presence of <i>SCN1A</i> mutation found in the vaccination-proximate (94.1%) compared with the vaccination-distant (78.4%) group ($P = 0.244$, no significant difference)	Patient recruitment consists of 100% patients with DS with <i>SCN1A</i> mutation	Patient recruitment consists of 100% patients with DS with <i>SCN1A</i> mutation
Major Findings	No statistically significant difference between language, ambulation or seizure characteristics.	Vaccination-proximate patients are more likely to develop status epilepticus and absence seizure as subsequent seizure types across the life span in DS when compared with the vaccination-distant group, but no difference in the clinical outcome and subsequent seizure development	58% of patients with vaccination-related seizures represented the first clinical manifestation	No differences in intellectual outcome, subsequent seizure type, <i>SCN1A</i> mutation type

In previous literatures, seizure frequency may decrease with age, which was independent of their *SCN1A* mutation type [12–15]. We also found a tendency of decreasing seizure frequency with age, although this did not reach statistical significance. In other study, in adolescence and adult groups with DS, fever sensitivity persisted but had less influence [14].

According to previous studies in Dravet mouse model, seizure susceptibility in DS is caused by reducing the sodium currents and electrical excitability of GABAergic interneurons, which lower the seizure threshold [16, 17]. Therefore, the first-line treatments for DS include valproic acid and clobazam, and the second-line treatment may include stiripentol, topiramate and the ketogenic diet [18]. As shown in Table 5, valproate was the most commonly used AEDs. Clobazem, topiramate, and stiripentol were also used frequently. In contrast, levetiracetam was the third common AED treatment in Taiwan.

Table 5
Review of real-world evidence on medicine utilization of patients with Dravet syndrome in publish data

Study	Present study	Schubert-Bast et al. Epilepsy Behav 2019	Villas et al. Epilepsy Behav 2017	Lagae et al. Dev Med Child Neurol 2018	Aras et al. Epilepsy Behav 2015
Year of survey	2019/2020	2017/18	2016	2016	2014
Country	Taiwan	Germany	Worldwide	Worldwide	Europe-wide
Numbers	38	93	256	584	274
Age (years)	Mean:10.6	Mean:10.1	Median:7–10	Mean:10.6	Median:4–8
Most used AEDs	1. Clobazam (68%) 2. Valproic acid (66%) 3. Levetiracetam (55%) 4. Topiramate (29%) 5. Stiripentol(26%) 6. Clonazepam (18%)	1. Valproate (66%) 2. Bromide(44%) 3. Clobazam(41%) 4. Stiripentol(35%) 5. Topiramate(15%)	1. Valproate (89%) 2. Clobazam (79%) 3. Topiramate (75%) 4. Lamotrigine (44%) 5. Stiripentol (94%)	1. Valproate (76%) 2. Clobazam (53%) 3. Stiripentol (47%) 4. Topiramate (34%) 5. Bromide(10%)	1. Valproate (86%) 2. Clobazam (55%) 3. Topiramate (44%) 4. Stiripentol (42%) 5. Levetiracetam (22%)

About the side effect of AEDs, drowsiness, cognition problem, and unsteady gait were most common in our study. In contrast, hematologic side effects, such as thrombocytopenia, neutropenia, or anemia, did not reach significance in our study. Nephrocalcinosis caused by topiramate accounted for 3% of the patients, which was similar to other studies [10]. Appetite disturbance and constipation were also noted in our patients, which might be due to AEDs or DS itself.

The characteristic symptoms of DS in our study include nocturnal seizures, hypotonia, drowsiness, cognition problem, unsteady gait, constipation, and psychiatric issues like ADD or ADHD problem, corresponding to previous literatures [10, 19]. In our study, caregivers’ reports of nocturnal seizure were 51%, the same as one previous study [20], and was less compared with another study, which reported 77% of nocturnal seizure [10]. It indicated that nocturnal seizures are a major concern for most caregivers. Awareness and attention between DS with *SCN1A* mutations and heart rate/rhythm and abnormalities are increasing in recent years. Cardiac dysfunction leading to sudden death may be a major concern for caregivers [21]. Although cardiac arrhythmia was noted in some of our patients, no one was found to have sudden death due to cardiac problem.

There was limited discussion about the possible pathogenic mechanisms leading to different comorbidities in the past. Dravet syndrome, which is primarily caused by heterozygous loss of function mutation in the *SCN1A* gene that encodes voltage-gated sodium channel type-1, termed Nav 1.1. Nav1.1, is a member of a family of voltage-sensitive sodium channels expressed primarily in the brain, including Na_v1.1, Na_v1.2, Na_v1.3, and Na_v1.6. As Na_v1.1 expression is very low in neonates, other alpha subunits such as Na_v1.2 and Na_v1.3 may compensate for reduced Na_v1.1 function during this early stage of development [22]. Therefore, as shown in mouse model, a physiologic decline in Na_v1.3 channel expression in brain development, coupled with the failure of increase in functional Na_v1.1

channels in Dravet syndrome, may lead to wide spread dysfunction of neuronal networks, intractable seizures, and comorbidities, including ataxia, sleep quality and autistic-like behaviors and spatial learning and memory [23].

Electrophysiological studies showed that $\text{Na}_v 1.1$ plays a crucial role in the excitability of cerebellar Purkinje neurons, with major contributions to peak, persistent, and resurgent forms of sodium current and to sustained action potential firing. Loss of these channels in Purkinje neurons of mutant mice may cause loss of excitability of Purkinje neurons leading ataxia, as shown in other study [24].

Patients with DS had reported sleep problems, including disturbance of sleep time, impaired sleep quality and increased incidence of nocturnal seizures [25]. In DS mouse model, the mechanism of sleep disorders is related to mutation of $\text{Na}_v 1.1$ channel in forebrain GABAergic interneurons without involvement of drug treatment and may correlated with cell-specific loss of sodium current and excitability of reticular nucleus of the thalamus GABAergic interneurons. This result confirms that impaired action potential firing of these GABAergic interneurons is responsible for the defect in sleep quality [26]. Regarding other sleep problems, DS children also have a circadian rhythm defect, which influences their sleep-wake cycle [25]. Although our result did not show significant finding in this field, DS mice had an abnormally long circadian cycle length, defects in phase shift after change of their light-dark cycle, and impaired light-induced shifts of their sleep-wake cycle [25]. In heterozygous *Scn1a*^{+/-} mice study, it showed that reduced $\text{Na}_v 1.1$ channel activity impairs suprachiasmatic nucleus of the hypothalamus, the primary site of the circadian clock [27]. This finding supports the relationship between decreased GABAergic transmission and circadian defect [27]. Therefore, some symptoms of DS sleep problems may be treatable by enhancement of GABAergic neurotransmission [27].

Children with DS also exhibit autistic-like behaviors [10]. DS mice also have substantial deficit in social interactions. This deficit may be explained by the specific deletion of $\text{Na}_v 1.1$ channel in forebrain inhibitory neurons, which may reduce action potential firing in inhibitory neurons. Besides, treating with low doses clonazepam may rescue the autistic-like behaviors in DS mice, caused by channel dysfunction rather than the epileptic activity itself as contributor [28]. Furthermore, another study also showed that GABAergic interneurons may include parvalbumin-(PV+) or somatostatin-expressing (SST+) interneurons [29]. Therefore, deletion of $\text{Na}_v 1.1$ in PV + interneurons may cause social interaction deficit rather than hyperactivity; however, deletion of $\text{Na}_v 1.1$ in SST + interneuron may cause hyperactivity behavior. In contrast, synergistic effect of PV + and SST + interneurons were found to impair long-term spatial memory [29]. In these studies, they demonstrated that autistic-related phenotypes and spatial learning deficits resulted from decreasing $\text{Na}_v 1.1$ activity in GABAergic interneurons in hippocampus and cortical interneurons [17, 28, 30].

As we known, sudden unexpected death in epilepsy (SUDEP) is the most common cause of death in intractable epilepsies, but the physiological mechanisms leading to SUDEP are unknown [20]. Although we did not document these events in our study, recent works suggested that SUDEP was caused by parasympathetic hyperactivity following hyperthermia-induced tonic-clonic seizures, which resulted in severe bradycardia and death in the *Scn1a*^{+/-} mouse model of DS [31]. DS mice had been shown to have ventricular myocytes problems via alterations in neuronal excitability and cardiac electrophysiologic abnormalities, which may contribute to the susceptibility for arrhythmogenesis and SUDEP [32]. Furthermore, reductions in $\text{Nav} 1.1$ expression may indirectly affect $\text{Nav} 1.5$ activity and cardiac electrical function [32], leading cardiac problems.

Therefore, regaining the impaired GABAergic neurotransmission may not only lead to improved seizure control but also improved function from prefrontal cortex to cerebellar networks, as has been shown in mice [28, 29, 33] (Fig. 3).

In recent literatures, more and more studies have focused on caregivers of patients with DS owing to different aspects of stress, and, therefore, may need multidisciplinary team to care about the patients. In our study, caregivers viewed additional household tasks, symptoms observation, further medical plan and financial problems as significant factors. A cohort study in Children's Hospital Colorado, they found caregivers suffered from emotional exhaustion and anxiety related to "fear of the next seizure" and "the seizure that kills my child". Besides, caregivers need to quit their jobs or careers to care for their child with DS due to the severity of condition [34]. In another study in Canada, persistent severe seizures, accompanied with developmental, cognitive, behavioral, and sleeping issues increased caregivers' burden [25]. Most caregivers may also concern about sleep deprivation, reduced mental health, deterioration of social relationships, and financial burden problem [35].

Caregivers in this study ranked their top 3 major concerns in the future, including lack of independence/constant care, seizure control, speech and communication problem and sibling impacts (long-term care when parents are gone). In another study, caregivers ranked their top 4 concerns, as speech and communication challenges, the impact of the patient with DS on siblings, cognitive/developmental delay, and behavioral issues including violence and autistic traits [10]. Therefore, recent studies have begun to raise the attention about

caregivers' need and offer further additional support services for the relief the burden of caring for patients with DS in the hope for improving caregivers physical and financial well-being.

There were several limitations in our study. Not all patients with DS from Taiwan were enrolled in the present study. In addition, the most common seizure pattern in adolescents and adults was generalized tonic-clonic, and mostly nocturnal and in cluster [14, 36]. However, in our study, we did not record the serial seizure changes. We could also not prove that broken bones and scoliosis were positively related to DS or other etiologies, such as vitamin D deficiency, due to no related blood tests in patients.

In conclusion, comorbidities are very common in patients with DS. They are related to the involvement of different regions in the brain. Therefore, detailed evaluation of the patients with DS for possible association of different comorbidities may direct the neurologists to correct treatment in addition to seizures.

Methods

Survey design

We recruited the patients and caregivers of patients with diagnosis of DS from most medical centers in Taiwan. All cases had been diagnosed and actively followed up by a pediatric neurologist in different hospitals. An online questionnaire regarding demographic data, gene mutation, clinical features, vaccine use and impact to family was designed and the caregivers and their doctors were requested to fill the form. In this online questionnaire study, all participants in the survey were voluntary, and data were collected anonymously. Permission to use deidentified data was obtained prior to participation, and each survey included a demographic session as well as content-related sections about characteristics, possible comorbidities, medications and efficacy, and caregiver/family dynamics, including Oberst Caregiving Burden Scale and caregiver concerns. Oberst Caregiving Burden Scale is a two-dimensional 15-item scale that evaluate the time and difficulty in performing each of the items measuring tasks to be done. Responses included lists, closed-question multiple choice, and open response. The study had been approved by the Ethical Committee of National Taiwan University Hospital. Informed consent was obtained when the families answered the questionnaire online. All methods were performed in accordance with the relevant guidelines and regulations.

We also assessed the time period between the first seizure activity and the previous vaccination. We defined two groups according to whether seizure activity was within 48 hours (vaccination-proximate group) or not (vaccination-distant group) as previous literatures [7,8].

Statistical analysis

Response frequencies and the mean, standard deviation (SD), and median ranges of interest were summarized using descriptive statistics. Statistical comparisons between groups were performed using Chi-square tests, and a $p < 0.05$ was considered as significant. Statistical analysis was conducted with IBM SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA).

Declarations

Author contributions

W.T.L. conceived the project, devised the experiments. W.T.L and C.H.H were responsible for data analysis and project administration. L.C.W assisted project administration. P.L.H., P.C.F., K.L.L., T.R.S., I.J.C., C.S.H., I.C.C, W.S.L., I.C.L., H.C.F., S.J.C., J.S.L., Y.F.T., T.M.C., and K.L.H. provided patient data. W.T.L. and C.H.H. prepared the manuscript, with support from all co-authors.

Competing interests

The authors declare no competing interests.

References

1. Brunklaus, A.; Ellis, R.; Reavey, E.; Forbes, G.H.; Zuberi, S.M. Prognostic, clinical and demographic features in SCN1A mutation-positive Dravet syndrome. *Brain* **2012**, *135*, 2329-2336, doi:10.1093/brain/aws151.

2. Hurst, D.L. Epidemiology of severe myoclonic epilepsy of infancy. *Epilepsia* **1990**, *31*, 397-400, doi:10.1111/j.1528-1157.1990.tb05494.x.
3. Yakoub, M.; Dulac, O.; Jambaque, I.; Chiron, C.; Plouin, P. Early diagnosis of severe myoclonic epilepsy in infancy. *Brain Dev* **1992**, *14*, 299-303, doi:10.1016/s0387-7604(12)80147-1.
4. Catterall, W.A. Dravet Syndrome: A Sodium Channel Interneuronopathy. *Curr Opin Physiol* **2018**, *2*, 42-50, doi:10.1016/j.cophys.2017.12.007.
5. Dravet, C. The core Dravet syndrome phenotype. *Epilepsia* **2011**, *52 Suppl 2*, 3-9, doi:10.1111/j.1528-1167.2011.02994.x.
6. Zamponi, N.; Passamonti, C.; Petrelli, C.; Veggiotti, P.; Baldassari, C.; Verrotti, A.; Capovilla, G.; Viri, M.; Coppola, G.; Vignoli, A. Vaccination and occurrence of seizures in SCN1A mutation-positive patients: a multicenter Italian study. *Pediatr Neurol* **2014**, *50*, 228-232, doi:10.1016/j.pediatrneurol.2013.09.016.
7. McIntosh, A.M.; McMahon, J.; Dibbens, L.M.; Iona, X.; Mulley, J.C.; Scheffer, I.E.; Berkovic, S.F. Effects of vaccination on onset and outcome of Dravet syndrome: a retrospective study. *The Lancet Neurology* **2010**, *9*, 592-598, doi:10.1016/s1474-4422(10)70107-1.
8. Wong, P.T.; Wong, V.C. Prevalence and Characteristics of Vaccination Triggered Seizures in Dravet Syndrome in Hong Kong: A Retrospective Study. *Pediatr Neurol* **2016**, *58*, 41-47, doi:10.1016/j.pediatrneurol.2016.01.011.
9. Wirrell, E.C.; Nabbout, R. Recent Advances in the Drug Treatment of Dravet Syndrome. *CNS Drugs* **2019**, *33*, 867-881, doi:10.1007/s40263-019-00666-8.
10. Villas, N.; Meskis, M.A.; Goodliffe, S. Dravet syndrome: Characteristics, comorbidities, and caregiver concerns. *Epilepsy Behav* **2017**, *74*, 81-86, doi:10.1016/j.yebeh.2017.06.031.
11. Tro-Baumann, B.; von Spiczak, S.; Lotte, J.; Bast, T.; Haberlandt, E.; Sassen, R.; Freund, A.; Leiz, S.; Stephani, U.; Boor, R., et al. A retrospective study of the relation between vaccination and occurrence of seizures in Dravet syndrome. *Epilepsia* **2011**, *52*, 175-178, doi:10.1111/j.1528-1167.2010.02885.x.
12. Jansen, F.E.; Sadleir, L.G.; Harkin, L.A.; Vadlamudi, L.; McMahon, J.M.; Mulley, J.C.; Scheffer, I.E.; Berkovic, S.F. Severe myoclonic epilepsy of infancy (Dravet syndrome): recognition and diagnosis in adults. *Neurology* **2006**, *67*, 2224-2226, doi:10.1212/01.wnl.0000249312.73155.7d.
13. Rilstone, J.J.; Coelho, F.M.; Minassian, B.A.; Andrade, D.M. Dravet syndrome: seizure control and gait in adults with different SCN1A mutations. *Epilepsia* **2012**, *53*, 1421-1428, doi:10.1111/j.1528-1167.2012.03583.x.
14. Darra, F.; Battaglia, D.; Dravet, C.; Patrini, M.; Offredi, F.; Chieffo, D.; Piazza, E.; Fontana, E.; Olivieri, G.; Turrini, I., et al. Dravet syndrome: Early electroclinical findings and long-term outcome in adolescents and adults. *Epilepsia* **2019**, *60 Suppl 3*, S49-S58, doi:10.1111/epi.16297.
15. Akiyama, M.; Kobayashi, K.; Yoshinaga, H.; Ohtsuka, Y. A long-term follow-up study of Dravet syndrome up to adulthood. *Epilepsia* **2010**, *51*, 1043-1052, doi:10.1111/j.1528-1167.2009.02466.x.
16. Yu, F.H.; Mantegazza, M.; Westenbroek, R.E.; Robbins, C.A.; Kalume, F.; Burton, K.A.; Spain, W.J.; McKnight, G.S.; Scheuer, T.; Catterall, W.A. Reduced sodium current in GABAergic interneurons in a mouse model of severe myoclonic epilepsy in infancy. *Nat Neurosci* **2006**, *9*, 1142-1149, doi:10.1038/nn1754.
17. Ogiwara, I.; Miyamoto, H.; Morita, N.; Atapour, N.; Mazaki, E.; Inoue, I.; Takeuchi, T.; Itohara, S.; Yanagawa, Y.; Obata, K., et al. Nav1.1 localizes to axons of parvalbumin-positive inhibitory interneurons: a circuit basis for epileptic seizures in mice carrying an Scn1a gene mutation. *J Neurosci* **2007**, *27*, 5903-5914, doi:10.1523/JNEUROSCI.5270-06.2007.
18. Wirrell, E.C. Treatment of Dravet Syndrome. *Can J Neurol Sci* **2016**, *43 Suppl 3*, S13-18, doi:10.1017/cjn.2016.249.
19. Gataullina, S.; Dulac, O. From genotype to phenotype in Dravet disease. *Seizure* **2017**, *44*, 58-64, doi:10.1016/j.seizure.2016.10.014.
20. Skluzacek, J.V.; Watts, K.P.; Parsy, O.; Wical, B.; Camfield, P. Dravet syndrome and parent associations: the IDEA League experience with comorbid conditions, mortality, management, adaptation, and grief. *Epilepsia* **2011**, *52 Suppl 2*, 95-101, doi:10.1111/j.1528-1167.2011.03012.x.
21. Delogu, A.B.; Spinelli, A.; Battaglia, D.; Dravet, C.; De Nisco, A.; Saracino, A.; Romagnoli, C.; Lanza, G.A.; Crea, F. Electrical and autonomic cardiac function in patients with Dravet syndrome. *Epilepsia* **2011**, *52 Suppl 2*, 55-58, doi:10.1111/j.1528-1167.2011.03003.x.
22. Brunklaus, A.; Zuberi, S.M. Dravet syndrome—from epileptic encephalopathy to channelopathy. *Epilepsia* **2014**, *55*, 979-984, doi:10.1111/epi.12652.

23. Cheah, C.S.; Westenbroek, R.E.; Roden, W.H.; Kalume, F.; Oakley, J.C.; Jansen, L.A.; Catterall, W.A. Correlations in timing of sodium channel expression, epilepsy, and sudden death in Dravet syndrome. *Channels (Austin)* **2013**, *7*, 468-472, doi:10.4161/chan.26023.
24. Kalume, F.; Yu, F.H.; Westenbroek, R.E.; Scheuer, T.; Catterall, W.A. Reduced sodium current in Purkinje neurons from Nav1.1 mutant mice: implications for ataxia in severe myoclonic epilepsy in infancy. *J Neurosci* **2007**, *27*, 11065-11074, doi:10.1523/JNEUROSCI.2162-07.2007.
25. Nolan, K.J.; Camfield, C.S.; Camfield, P.R. Coping with Dravet syndrome: parental experiences with a catastrophic epilepsy. *Dev Med Child Neurol* **2006**, *48*, 761-765, doi:10.1017/S0012162206001629.
26. Kalume, F.; Oakley, J.C.; Westenbroek, R.E.; Gile, J.; de la Iglesia, H.O.; Scheuer, T.; Catterall, W.A. Sleep impairment and reduced interneuron excitability in a mouse model of Dravet Syndrome. *Neurobiol Dis* **2015**, *77*, 141-154, doi:10.1016/j.nbd.2015.02.016.
27. Han, S.; Yu, F.H.; Schwartz, M.D.; Linton, J.D.; Bosma, M.M.; Hurley, J.B.; Catterall, W.A.; de la Iglesia, H.O. Na(V)1.1 channels are critical for intercellular communication in the suprachiasmatic nucleus and for normal circadian rhythms. *Proc Natl Acad Sci U S A* **2012**, *109*, E368-377, doi:10.1073/pnas.1115729109.
28. Han, S.; Tai, C.; Westenbroek, R.E.; Yu, F.H.; Cheah, C.S.; Potter, G.B.; Rubenstein, J.L.; Scheuer, T.; de la Iglesia, H.O.; Catterall, W.A. Autistic-like behaviour in *Scn1a*^{+/-} mice and rescue by enhanced GABA-mediated neurotransmission. *Nature* **2012**, *489*, 385-390, doi:10.1038/nature11356.
29. Rubinstein, M.; Han, S.; Tai, C.; Westenbroek, R.E.; Hunker, A.; Scheuer, T.; Catterall, W.A. Dissecting the phenotypes of Dravet syndrome by gene deletion. *Brain* **2015**, *138*, 2219-2233, doi:10.1093/brain/awv142.
30. Ito, S.; Ogiwara, I.; Yamada, K.; Miyamoto, H.; Hensch, T.K.; Osawa, M.; Yamakawa, K. Mouse with Nav1.1 haploinsufficiency, a model for Dravet syndrome, exhibits lowered sociability and learning impairment. *Neurobiol Dis* **2013**, *49*, 29-40, doi:10.1016/j.nbd.2012.08.003.
31. Kalume, F.; Westenbroek, R.E.; Cheah, C.S.; Yu, F.H.; Oakley, J.C.; Scheuer, T.; Catterall, W.A. Sudden unexpected death in a mouse model of Dravet syndrome. *J Clin Invest* **2013**, *123*, 1798-1808, doi:10.1172/JCI66220.
32. Auerbach, D.S.; Jones, J.; Clawson, B.C.; Offord, J.; Lenk, G.M.; Ogiwara, I.; Yamakawa, K.; Meisler, M.H.; Parent, J.M.; Isom, L.L. Altered cardiac electrophysiology and SUDEP in a model of Dravet syndrome. *PLoS One* **2013**, *8*, e77843, doi:10.1371/journal.pone.0077843.
33. Tatsukawa, T.; Ogiwara, I.; Mazaki, E.; Shimohata, A.; Yamakawa, K. Impairments in social novelty recognition and spatial memory in mice with conditional deletion of *Scn1a* in parvalbumin-expressing cells. *Neurobiol Dis* **2018**, *112*, 24-34, doi:10.1016/j.nbd.2018.01.009.
34. Campbell, J.D.; Whittington, M.D.; Kim, C.H.; VanderVeen, G.R.; Knupp, K.G.; Gammaitoni, A. Assessing the impact of caring for a child with Dravet syndrome: Results of a caregiver survey. *Epilepsy Behav* **2018**, *80*, 152-156, doi:10.1016/j.yebeh.2018.01.003.
35. Jensen, M.P.; Liljenquist, K.S.; Bocell, F.; Gammaitoni, A.R.; Aron, C.R.; Galer, B.S.; Amtmann, D. Life impact of caregiving for severe childhood epilepsy: Results of expert panels and caregiver focus groups. *Epilepsy Behav* **2017**, *74*, 135-143, doi:10.1016/j.yebeh.2017.06.012.
36. Connolly, M.B. Dravet Syndrome: Diagnosis and Long-Term Course. *Can J Neurol Sci* **2016**, *43 Suppl 3*, S3-8, doi:10.1017/cjn.2016.243.

Figures

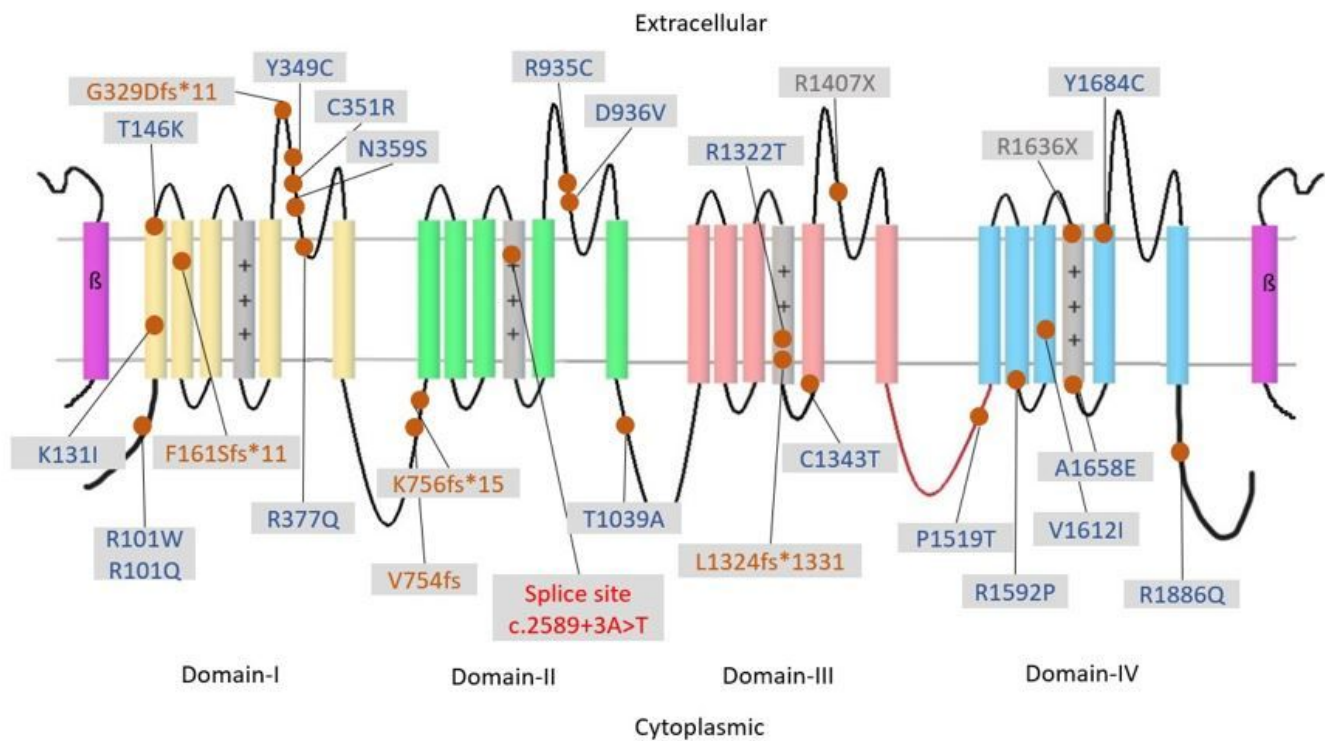


Figure 1

Schematic representation of the sodium channel type 1 mutations in our study. SCN1A alpha unit has four domains (I–IV). Each domain includes 6 transmembrane segments (S1–S6). Inactivation gate (red line); Voltage sensor (gray column). There were another 2 deletion mutations not marked: (1) 2q24.3q31.1 deletion; (2) Microdeletion 2q chromosome. Missense (Blue); Frameshift (Brown); Nonsense (Gray); Splice site (Red)

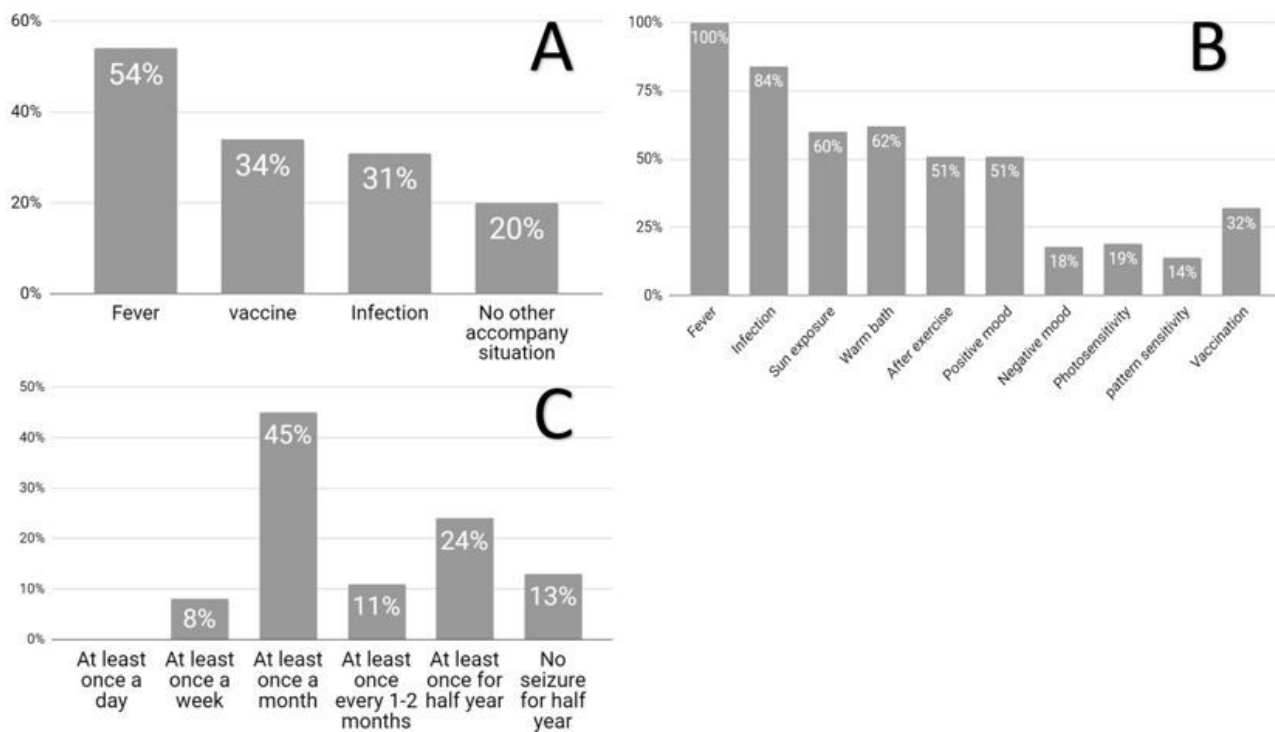


Figure 2

Questionnaire results about seizure evaluation. (A) The situation accompanying with first seizure; (B) Triggering factors for seizure attack; (C) Seizure frequency.

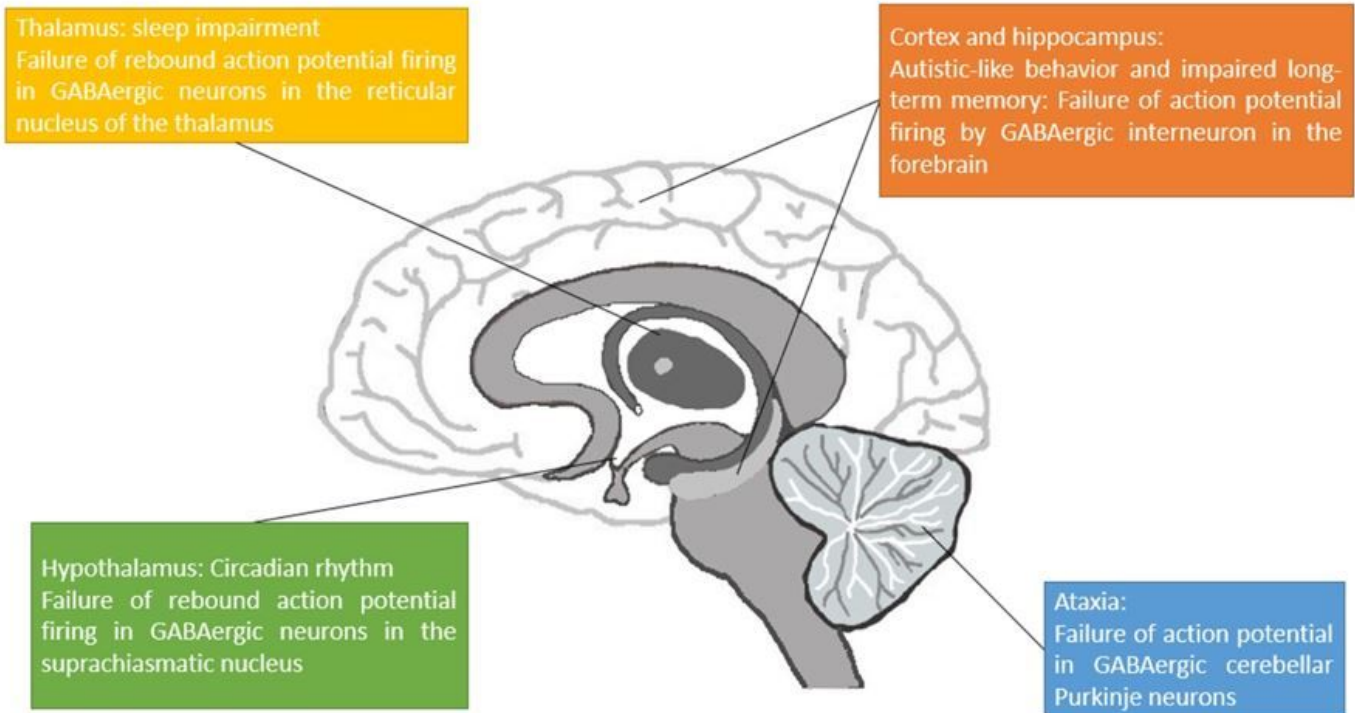


Figure 3

Schematic representation about the possible comorbidity mechanisms in Dravet syndrome.

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