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Outcomes and comorbidities of *SCN1A*-related seizure disorders

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ABSTRACT

Purpose: Differentiating between Dravet syndrome and non-Dravet *SCN1A*-related phenotypes is important for prognosis regarding epilepsy severity, cognitive development, and comorbidities. When a child is diagnosed with genetic epilepsy with febrile seizures plus (GEFS+) or febrile seizures (FS), accurate prognostic information is essential as well, but detailed information on seizure course, seizure freedom, medication use, and comorbidities is lacking for this milder patient group. In this cross-sectional study, we explore disease characteristics in milder *SCN1A*-related phenotypes and the nature, occurrence, and relationships of *SCN1A*-related comorbidities in both patients with Dravet and non-Dravet syndromes.

Methods: A cohort of 164 Dutch participants with *SCN1A*-related seizures was evaluated, consisting of 116 patients with Dravet syndrome and 48 patients with either GEFS+, febrile seizures plus (FS+), or FS. Clinical data were collected from medical records, semi-structured telephone interviews, and three questionnaires: the Functional Mobility Scale (FMS), the Pediatric Quality of Life Inventory (PedsQL) Measurement Model, and the Child or Adult Behavior Checklists (CBCL/ABCL).

Results: Walking disabilities and severe behavioral problems affect 71% and 43% of patients with Dravet syndrome respectively and are almost never present in patients with non-Dravet syndromes. These comorbidities are strongly correlated to lower quality-of-life (QoL) scores. Less severe comorbidities occur in patients with non-Dravet syndromes: learning problems and psychological/behavioral problems are reported for 27% and 38% respectively. The average QoL score of the non-Dravet group was comparable with that of the general population. The majority of patients with non-Dravet syndromes becomes seizure-free after 10 years of age (85%).

Conclusions: Severe behavioral problems and walking disabilities are common in patients with Dravet syndrome and should receive specific attention during clinical management. Although the epilepsy course of patients with non-Dravet syndromes is much more favorable, milder comorbidities frequently occur in this group as well. Our results may be of great value for clinical care and informing newly diagnosed patients and their parents about prognosis.

1. Introduction

Pathogenic variants in *SCN1A* can cause several different epilepsy syndromes, with varying disease severities [1–5]. The most common and severe associated condition is Dravet syndrome, which is characterized by intractable epileptic seizures and a slowing of the psychomotor development in the second year of life, which results in mild to severe intellectual disability (ID). Walking difficulties and behavioral problems are common comorbidities [6–9]. Milder phenotypes include genetic epilepsy with febrile seizures plus (GEFS+) syndrome and febrile seizures (FS and febrile seizures plus (FS+)), in which usually no ID is present, and the epilepsy has a milder course [4,10]. Although the majority of school-aged, adolescent, and adult patients with *SCN1A*-related disease can easily be classified as having Dravet syndrome or not, these different phenotypes may have a similar presentation at onset [11,12].

SCN1A encodes for the α-subunit of a neuronal sodium channel, Nav1.1. Pathogenic variants cause a reduction in sodium currents in gamma-aminobutyric acid (GABA)-ergic inhibitory interneurons, which leads to hyperexcitability of neuronal networks and the occurrence of seizures [13,14]. These reduced sodium currents, furthermore, impair Purkinje cells, causing motor disorders [15,10] and contribute to the development of behavioral problems and cognitive disabilities

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[16]. The association of *SCN1A* pathogenic variants with multiple syndromes can be partly explained by the consequences of different mutation types: pathogenic variants that lead to a complete loss of function of the channel are virtually always associated with severe phenotypes whereas milder disturbances in channel function usually cause milder phenotypes [17]. However, in clinical practice, it remains difficult to fully predict the effects of all variants on channel function.

Differentiating between Dravet syndrome and non-Dravet *SCN1A*-related phenotypes is understandably of extreme importance for families and physicians. The presence or absence of ID and the frequency and severity of seizures both significantly alter the level of care an affected child requires. Furthermore, severe comorbidities, such as walking disabilities or behavioral problems, are frequently reported in Dravet syndrome [7–9,18–23] and may pose a heavy burden on affected families. Behavioral problems have been identified as the strongest independent predictor for lower quality-of-life (QoL) scores [24] and are reported to often be a cause of stress and concern for parents [23,25]. Motor disorders have been shown to contribute significantly to lower health-related QoL (HRQoL) scores as well [24].

However, also, when a child is diagnosed with a milder *SCN1A*-related disorder, such as GEFS+ or FS, accurate information about the disease course and prognosis is essential. Many studies have reported on the clinical spectrum of different *SCN1A*-related syndromes [12,17,26], but detailed information on seizure course, seizure freedom, medication use, and comorbidities is lacking for the milder patient group. Although ID is thought to be exclusive to patients with Dravet syndromes, there are reports of patients with non-Dravet syndromes that show a mild cognitive impairment or neuropsychiatric symptoms [27–29]. However, the incidence of these problems in patients with non-Dravet *SCN1A*-related epilepsy is unknown, as they are mostly described in case reports.

We describe here the detailed clinical data of a large cohort of Dutch patients affected by *SCN1A* pathogenic variants (n = 164), consisting of patients with Dravet syndrome as well as GEFS+, FS+, or FS. We explore the nature, occurrence, and relationships of *SCN1A*-related comorbidities in both the Dravet and non-Dravet groups, to improve the counseling of patients and their parents. We furthermore give a detailed overview of the disease course of patients with non-Dravet syndromes to provide more insight in the clinical spectrum of the less severe *SCN1A*-related disorders.

2. Methods

2.1. Participants

A previously described cohort [11,30] of 164 patients affected by *SCN1A*-related seizures was included in this study. Only symptomatic participants with heterozygous pathogenic or likely pathogenic variants (classes IV and V, according to the American College of Medical Genetics and Genomics criteria [31]) in *SCN1A* were included. All eligible individuals of at least 4 years of age known to the University Medical Center Utrecht were approached. Patients below the age of 4 years were excluded since syndrome classification and estimation of disease severity are less reliable for younger children. Informed consent was obtained from participants or their legal caretakers, according to the Declaration of Helsinki. The study was approved by the Ethical Committee of the University Medical Center Utrecht.

2.2. Clinical data

Detailed clinical data were retrospectively collected from medical records of all participants, and a semi-structured telephone interview was conducted when possible at the time of inclusion (n = 155). Interviews were conducted with participants themselves if they were adults and mentally competent; in all other cases, interviews were conducted with parents of patients. Participants, or parents of participants, were asked the kind of education the participants were following or had followed and whether they had any learning problems or psychological problems. If parents of patients were interviewed and not the patients themselves, they were also asked whether their children showed any behavioral problems (for other patients reported as missing data). The same information was extracted from medical files. Furthermore, three questionnaires were completed by participants in specific age groups, or their parents, at the time of inclusion:

- The Dutch version of the Functional Mobility Scale (FMS), to classify the general functional mobility in six categories for children aged 4–18 years [32] (Hugh Williamson Gait Laboratory, The Royal Children's Hospital Melbourne, Australia, Part of the Gait CCRE, www.rch.org.au/gait, Graham 2004);
- The Dutch version of the PedsQL Measurement Model, to measure HRQoL on a 0–100 scale for participants aged 0–25 years [33];
- The Dutch parent report version of the Child Behavior Checklist 1.5–5 years (CBCL 1.5–5) or 6–18 years (CBCL), or the Dutch version of the Adult Behavior Checklist 18–59 years (ABCL) to evaluate behavioral and emotional problems [34,35]. Behavioral problems in the clinical range on the "total problems" scale are reported (p-scores >90, according to the CBCL manual).

Cognitive functioning at the time of inclusion was classified in a consensus meeting by a child neurologist, neuropsychologist, and clinical geneticist and rated on a five-point scale based on available data on intelligence quotient (IQ) and developmental level, (1 = no ID (IQ or developmental quotient (DQ) >85), 2 = borderline ID (IQ or DQ 70–85), 3 = mild ID (IQ or DQ 50–70), 4 = moderate ID (IQ or DQ 30–50), 5 = severe or profound ID (IQ or DQ <30)). When no (recent) IQ or DQ was available, the assessment was made based on school functioning, communication, and/or adaptive behavior. All participants were categorized into two clinical subgroups: Dravet syndrome or non-Dravet syndrome. Dravet syndrome was diagnosed based on previously published criteria [36]. The diagnoses were in line with recently published recommendations [37]. The non-Dravet group consisted of patients with either GEFS+ or FS. Seizure severity was classified based on seizure frequency for both minor seizures (defined as short absences, short focal seizures, or myoclonias) and major seizures (defined as all other seizure types with loss of consciousness or prolonged seizures) at the time of inclusion (score 4 = daily seizures, score 3 = weekly seizures, score 2 = monthly seizures, score 1 = yearly seizures, score 0 = seizure-free (>1 year)).

2.3. Descriptive analyses

Data on major disease outcomes (cognitive functioning, seizure severity, walking difficulties, behavioral problems, and HRQoL) are reported as total counts, percentages, or mean/median scores for all patients, and additional detailed clinical information (on seizure frequency, antiepileptic drug (AED) use, learning problems, and psychological/behavioral problems) is reported per age group for patients with non-Dravet syndromes.

2.4. Statistical analyses

No statistical testing was performed to formally assess differences in outcomes between patients with Dravet and non-Dravet syndromes, since these outcomes were used to classify each patient and therefore, differ per definition between the groups. Correlations between different outcomes were calculated with Spearman's rank-order correlation. Differences between groups were calculated with either Pearson's chi-square test or Fisher's exact test for binary and categorical variables or a Mann–Whitney U test for continuous and ordinal variables. Statistical analyses were performed using SPSS statistics software (IBM SPSS Statistics for Windows V21, Armonk, NY: IBM Corp.).

All reported tests were performed 2-tailed with an alpha-level for significance of $p < 0.05$. Correlations for the non-Dravet group only were only investigated for the group of patients below 20 years old, because childhood learning and behavioral problems may not have been reported reliably for older patients because of recall biases.

3. Results

The characteristics of the study population are depicted in Table 1. The Dravet syndrome subgroup consisted of 116 patients belonging to 112 different families, and the non-Dravet group consisted of 48 patients belonging to 28 different families. Six families had members in both the Dravet and non-Dravet categories. The median age of patients with Dravet syndrome and patients with non-Dravet syndromes was 14 years and 22 years respectively. Important differences between both groups were seen for all five major outcomes.

3.1. Cognitive outcome

All patients could be assessed for cognitive outcome. Almost half of all patients with Dravet syndrome had a severe cognitive disability (score 5, 45%) whereas almost all patients with non-Dravet syndromes had normal cognitive capacities (score 1, 90%) except for five, who had a slight delay (score 2, 10%) (Table 1). Since cognitive functioning is a defining characteristic used to classify Dravet syndrome, this is an expected outcome. Cognitive disabilities worsened with age in patients with Dravet syndrome; over 60% of patients of 20 years and older had a score of 5, in contrast to only 25% of patients aged 7–8 years (Fig. S1).

Table 1
Characteristics of the study population.

	Complete cohort	Dravet	Non-Dravet
n	164	116	48
Age median (years, range)	15 (4–67)	14 (4–48)	22 (4–67)
Age grouped (years, n)			
– 4–7	29	20	9
– 8–11	28	22	6
– 12–15	31	25	6
– 16–19	11	8	3
– 20+	65	41	24
Sex: male (n)	83 (51%)	65 (56%)	18 (38%)
Mutation type (n)			
– Missense	87 (53%)	44 (38%)	43 (90%)
– Pore region/loop	58	29	29
– Elsewhere	29	15	14
– Splicing	16 (10%)	13 (11%)	3 (6%)
– Nonsense/frameshift/rearrangement	61 (37%)	59 (51%)	2 (4%)
Cognition score[a] (n)			
– 1: no ID (IQ or DQ >85)	46	3 (3%)	43 (90%)
– 2: borderline ID (IQ or DQ 70–85)	15	10 (9%)	5 (10%)
– 3: mild ID (IQ or DQ 50–69)	20	20 (17%)	0 (0%)
– 4: moderate ID (IQ or DQ 30–49)	31	31 (27%)	0 (0%)
– 5: severe or profound ID (IQ or DQ <30)	52	52 (45%)	0 (0%)
Slowing of development after first year of life (yes, n)	106 (65%)	97 (87%) (4 missing)	9 (19%)
Development of epilepsy with multiple seizure types (yes, n)	133 (83%)	113 (97%)	20 (44%)
Major seizure frequency[b] (n)			
– Seizure-free	43 (26%)	8 (7%)	35 (73%)
– Yearly seizures	27 (17%)	16 (14%)	11 (23%)
– Monthly seizures	27 (17%)	25 (22%)	2 (4%)
– Weekly seizures	51 (31%)	51 (44%)	0
– Daily seizures	16 (10%)	16 (14%)	0
Minor seizure frequency[b] (n)			
– Seizure-free	76 (46%)	31 (27%)	45 (94%)
– Yearly seizures	9 (6%)	7 (6%)	2 (4%)
– Monthly seizures	8 (5%)	8 (7%)	0
– Weekly seizures	23 (14%)	23 (20%)	0
– Daily seizures	48 (29%)	47 (41%)	1 (2%)
Quality of life[c]			
– Completed questionnaires (n)	93	71	22
– Average total score (range)	61.1 (13–99)	52.6 (13–86)	88.5 (63–99)
Behavioral problems[d]			
– Completed ABCL/CBCL questionnaires (n)	122	80	42
– Clinical range (n)	37 (30%)	34 (43%)	3 (7%)
– Behavioral problems reported by parents during telephone interview	72 (54%) (31 missing)	70 (66%) (10 missing)	2 (7%) (21 missing)
FMS score[e] (n)			
– Uses a wheelchair (1)	26 (31%)	26 (41%)	0
– Independent walking on flat surfaces (5)	19 (23%)	19 (30%)	0
– Independent walking on all surfaces (6)	38 (46%)	18 (29%)	20 (100%)
– Missing	81	53	28

[a] Based on available data on IQ and developmental level, adjusted for age at assessment. When no (recent) IQ or DQ was available, the assessment was made based on school functioning, communication, and adaptive behavior.
[b] Currently. 4 = daily seizures, 3 = weekly seizures, 2 = monthly seizures, 1 = yearly seizures, and 0 = seizure-free. Minor seizures: short absences, short focal seizures, or myoclonias. Major seizures: all other seizure types with loss of consciousness or prolonged seizures. Numbers of participants are given for dichotomized scores (score 0–1 = rarely, score 2–4 = often).
[c] Quality-of-life total score, based on results of PedsQL Measurement Model questionnaire. Scaled 0–100; a higher score indicates a higher health-related quality of life.
[d] Clinical range: patients that score >90% on the "total problems" scale on the Child Behavior Checklist 1.5–5, 6–18 years, or the Adult Behavior Checklist 18–59 years.
[e] Scores measured by the Functional Mobility Scale (FMS) to classify functional mobility for children aged 4–18 years. Scores for the 500-meter range are used. No participants scored 2, 3, or 4 (uses a walker or frame, uses crutches, or uses sticks, respectively).

Interestingly, nine patients with non-Dravet syndromes experienced a slowing of development after the first year of life as well; however, in two cases, the delay was only temporary, and none of these patients developed ID.

3.2. Seizure severity

All patients could be assessed for seizure frequency. Many patients with Dravet syndrome experienced major seizures weekly (44%) and minor seizures daily (41%). In the non-Dravet group, both major and minor seizures occurred much less frequently, with most patients being seizure-free at the time of inclusion (73%) (Table 2). If seizures did still occur in the non-Dravet group, these were mostly yearly events (23%). The youngest patients with non-Dravet syndromes had most seizures: only 38% of 4- to 9-year olds were seizure-free whereas 82% of 10- to 19-year olds and 100% of patients older than 40 years were seizure-free. Although 71% of patients with non-Dravet syndromes had used maintenance treatment, 60% was medication-free at the time of inclusion. Larger percentages of older patients were medication-free than younger patients were medication-free than younger patients (87% of 40+-year olds versus 38% of 4- to 9-year olds). Interestingly, one patient with non-Dravet syndrome experienced minor seizures (myoclonias) daily. This 16-year old girl used to have generalized tonic–clonic seizures but had been seizure- and medication-free between ages 4 and 10 years old, after which seizures reappeared. At the time of study, she had monthly focal seizures with impaired awareness and a few myoclonias per day while being treated with topiramate and levetiracetam. She was not diagnosed with Dravet syndrome because she had a normal intellect (IQ 91), and her seizure course is unusual for Dravet syndrome.

3.3. Functional mobility

Sixty-three patients with Dravet syndrome and 20 patients with non-Dravet syndromes could be assessed for functional mobility. Patients with Dravet syndrome showed either no walking disabilities (independent walking on all surfaces, score 6), minor walking disabilities (independent walking on level surfaces, score 5), or used a wheelchair (score 1) on a 500-meter range. Over 40% of patients with Dravet syndrome already used a wheelchair at age 4–8 years; this was 50% at 14–18 years (Fig. 1). Patients with non-Dravet syndromes did not show any walking disabilities on the FMS.

3.4. Behavioral problems

Eighty patients with Dravet syndrome and 42 patients with non-Dravet syndromes could be assessed for behavioral problems by CBCL/ABCL questionnaires. Thirty-seven patients (30%) showed behavioral problems in the clinical range (Table 1); all but three were patients with Dravet syndrome (43% versus 7%). One of the patients with non-Dravet syndromes with behavioral problems in the clinical range is a 32-year-old father of a son with Dravet-syndrome, who was found to be mosaic for their pathogenic *SCN1A* variant in previous research [30,38]. Since his epilepsy was well controlled and no ID was present, he was not diagnosed with Dravet syndrome; he, however, does have psychosocial problems, among which an autism spectrum disorder, an active substance addiction, and aggressivity. The second patient (14 years old) has an autism spectrum disorder and an IQ of 90; she has been seizure-free since 2.5 years but has previously experienced different seizure types, including multiple absences per day. The third patient is 28 years old and has a normal intellect but was schooled at a low level and now works in a sheltered environment because of his epilepsy and memory problems. He has around 10 generalised tonic-clonic seizures (GTCS) per year. Most behavioral problems in the clinical range were reported in younger patients with Dravet syndrome: 60% of 4- to 11-year olds score within the clinical range whereas less than 30% of 20+-year-old patients do (Fig. 2A). One hundred six patients with Dravet syndrome and 27 patients with non-Dravet syndromes could be assessed for behavioral problems during the telephone interview. Parents of patients responded "yes" to the question "are there any behavioral problems?" during the telephone interview in 66% of the patients with Dravet syndrome while only 7% did in patients with non-Dravet syndromes (Table 1). The CBCL/ABCL data were missing for 36 patients; similar percentages of parents reported behavioral problems during the telephone interview for patients with and without CBCL/ABCL results. Most behavioral problems were reported during the telephone interview for patients with Dravet syndrome between 8 and 11 years old (>80%, Fig. 2B).

Table 2
Characteristics of patients with non-Dravet syndromes.

	All patients with non-Dravet syndromes	Patients with non-Dravet syndromes (4–9 years old)	Patients with non-Dravet syndromes (10–19 years old)	Patients with non-Dravet syndromes (20–39 years old)	Patients with non-Dravet syndromes (≥40 years old)
n	48	13 (27%)	11 (23%)	9 (19%)	15 (31%)
Major seizure frequency[a] (n)					
– Seizure-free	35 (73%)	5 (38%)	9 (82%)	6 (67%)	15 (100%)
– Yearly seizures	11 (23%)	8 (62%)	1 (9%)	2 (22%)	0
– Monthly seizures	2 (4%)	0	1 (9%)	1 (1%)	0
– Weekly seizures	0	0	0	0	0
– Daily seizures	0	0	0	0	0
Minor seizure frequency[a] (n)					
– Seizure-free	45 (94%)	12 (92%)	10 (91%)	8 (89%)	15 (100%)
– Yearly seizures	2 (4%)	1 (8%)	0	1 (11%)	0
– Monthly seizures	0	0	0	0	0
– Weekly seizures	0	0	0	0	0
– Daily seizures	1 (2%)	0	1 (9%)	0	0
AED[b] use (n)					
– Has at some point used maintenance treatment	34 (71%)	11 (85%)	9 (82%)	6 (67%)	8 (53%)
– Currently no maintenance treatment	29 (60%)	5 (38%)	7 (64%)	4 (44%)	13 (87%)
Learning problems[c] (n)	13 (27%)	4 (31%)	6 (55%)	3 (33%)	0
Psychological/behavioral problems[d] (n)	18 (38%)	5 (38%)	5 (45%)	5 (56%)	3 (20%)

[a] Currently. Minor seizures: short absences, short focal seizures, or myoclonias. Major seizures: all other seizure types with loss of consciousness or prolonged seizures.
[b] Antiepileptic drugs.
[c] Any problem for which extra educational assistance is necessary: e.g., special education, repeating a class, extra support needed.
[d] Answered "yes" to the question "are there any behavioral issues?" or behavioral issues, psychological symptoms or (signs of) psychiatric disease mentioned in interview or medical files.

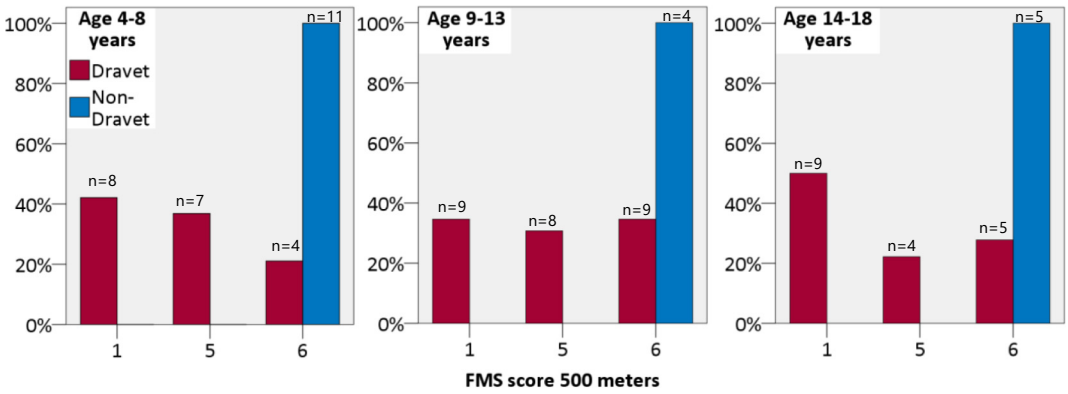

Fig. 1. Functional Mobility Scale (FMS) scores on a 500 m range per age group. Scores range from 1 to 6, although patients only scored 1 ("uses wheelchair"), 5 ("independent on level surfaces"), or 6 ("independent on all surfaces").

3.5. QoL

Seventy-one patients with Dravet syndrome and 22 patients with non-Dravet syndromes could be assessed for HRQoL. Patients with Dravet syndrome showed lower HRQoL scores than patients with non-Dravet syndromes (average 52.6 versus 88.5, Table 1, Fig. 3). Scores tended to worsen with age (Fig. S2).

3.6. Learning and behavioral problems among patients with non-Dravet syndrome

Although patients with non-Dravet syndromes were significantly less affected on all five major outcome scales than patients with Dravet syndrome, we did observe subtle problems in this group (Table 2). Twenty-seven percent had encountered some kind of learning problem for which extra educational assistance was necessary (see Supplementary data 1 for specific problems). None of the patients over 40 years old reported to have experienced problems while following primary or secondary education.

Behavioral problems, like attention-deficit, autistic features, or anxiety, were reported for 38% of patients with non-Dravet syndromes among all age groups, although their CBCL score was not in the clinical range except for three. Two of these 18 patients had not completed the CBCL questionnaires (see Supplementary data 1 for specific problems).

3.7. Correlations between outcomes

In the complete cohort, FMS scores were strongly related to cognitive outcomes, seizure severity, and QoL scores: patients with more severe walking disabilities had a more severe cognitive disability ($r_s = -0.682$, $p < 0.0005$, Fig. S3A), a higher seizure frequency ($r_s = -0.537$ for major seizures and $r_s = -0.492$ for minor seizures, both $p < 0.0005$, Fig. S3B), and a lower QoL score ($r_s = 0.668$, $p < 0.0005$, Fig. S3C). Most behavioral problems were observed in patients with a mild cognitive disability (Fig. 4A, B); less behavioral problems were seen in patients with cognitive outcome scores on both ends of the spectrum. Behavioral problems in the clinical range of the ABCL/CBCL questionnaires were positively related to major seizure frequency ($r_s = 0.260$, $p = 0.004$, Fig. S4A) in the complete cohort; however, in patients with Dravet syndrome, most behavioral problems were reported in patients that are seizure-free or experience daily seizures (Fig. S4B). Furthermore, patients with behavioral problems in the clinical range scored significantly lower on the QoL questionnaire ($r_s = -0.523$, $p < 0.0005$, Fig. S4C). In the complete cohort, cognitive outcome scores were significantly related to major seizures

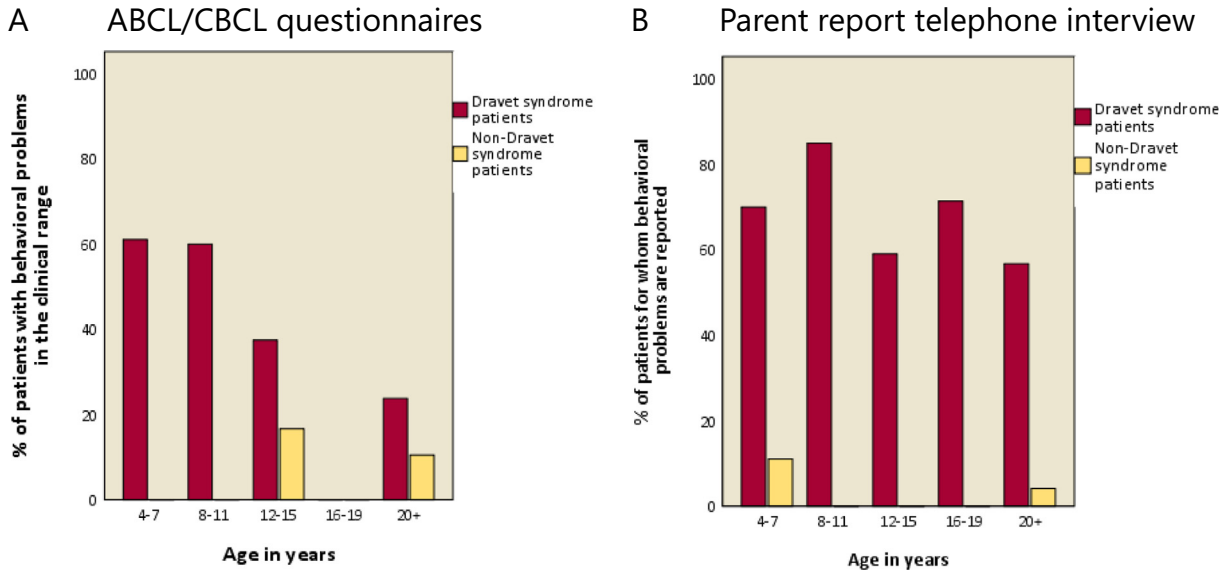

Fig. 2. A: Percentage of patients with behavioral problems in the clinical range according to CBCL/ABCL questionnaires, per age group. B: Percentage of patients for which parents responded "yes" to the question "are there any behavioral problems?" during the telephone interview, per age group.

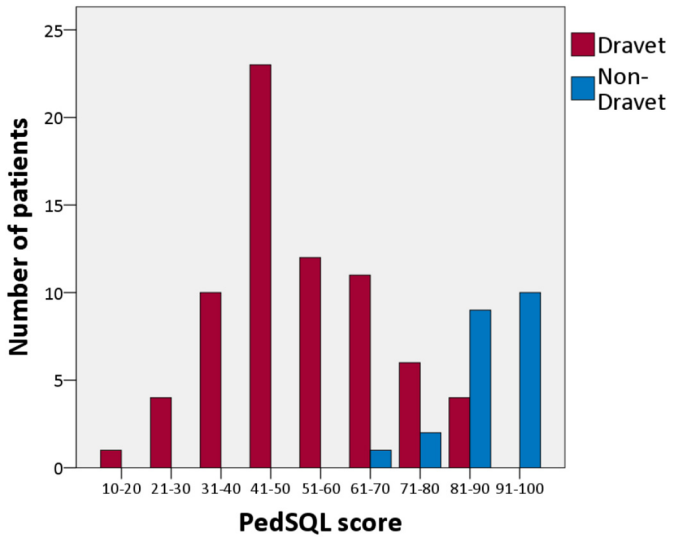

Fig. 3. Distribution of PedsQL scores to indicate health-related quality of life (HRQoL) for patients with Dravet syndrome and non-Dravet syndromes.

($r_s = 0.693$, $p < 0.0005$) and minor seizure frequencies ($r_s = 0.511$, $p < 0.0005$) (Fig. S5A, B).

In the non-Dravet group only, the presence of any learning problems was significantly associated with a lower QoL score (median score of 86.45 versus 92.95, $p = 0.006$ (Mann–Whitney U, $U = 19$, $z = -2.708$), Fig. S6A). No statistically significant differences in QoL scores were found between patients with and without psychological/behavioral problems ($p = 0.188$, Fig. S6B). Patients with psychological or behavioral problems more often used AEDs than patients without these problems ($p = 0.013$, χ^2-test). No differences in percentages of medication-free patients were observed between patients with and without learning problems ($p = 0.408$, χ^2-test). Furthermore, no differences in percentages of seizure-free patients were observed between patients with and without learning problems ($p = 0.421$, χ^2-test) or psychological or behavioral problems (0.421, Fisher's exact test).

4. Discussion

No universally used consensus guidelines for the diagnosis of Dravet syndrome exist, and many studies use different criteria [37,39–41]. The main diagnostic criteria in most studies relate to the epilepsy phenotype and cognitive development. Walking disabilities and behavioral problems are usually not included, even though many studies have already acknowledged that they are common and important features of Dravet syndrome [6–9,18,19,37,42] while they are virtually never present in patients with non-Dravet syndromes with pathogenic *SCN1A* variants. Both walking disabilities and behavioral problems can emerge early in the disease course of Dravet syndrome, affecting a large percentage of patients before the age of 8 years; 79% of children with Dravet syndrome between 4 and 8 years in our cohort had a walking disability, which is in line with recent research [19]. Gait disturbances have already been described in patients as young as 2 years of age [9,19]. Our overall percentage of patients with Dravet syndrome with a walking disability (score 5 or lower, 54%) is between percentages previously reported: Brunklaus et al. [7] found a motor disorder in 36% of patients with Dravet syndrome whereas Lagae et al. [19] found walking disabilities in 79%. These differences are likely due to used definitions; factors such as skeletal malalignment, behavioral issues, epilepsy severity, and pain can affect functional mobility as well. Furthermore, the FMS assesses functional mobility on a distance of maximal 500 m while other studies incorporated no distances [19]. Behavioral problems in the clinical range were most frequently seen between 4 and 11 years of age, when assessed by CBCL/ABCL questionnaires. This is in contrast to previous studies that have found an increase of behavioral problems with age (although these problems had been observed in children <2 years of age already) [7,19]. Our different results might be due to differences in measurement tools and data collection. Interestingly, parents of patients with Dravet syndrome reported behavioral problems more frequently in the interview (66%) than patients scored in the clinical range of the CBCL/ABCL questionnaires (43%); this might indicate that scores in the subclinical range are perceived to be very burdensome as well. This high percentage underlines the impact of these issues on families and the importance of accurate management. Behavioral problems were much more common among patients with Dravet syndrome than in patients with non-Dravet syndromes (43 versus 7%), and the three patients with non-Dravet syndromes that scored in the clinical range of the ABCL/CBCL questionnaires had a relatively severe non-Dravet *SCN1A* phenotype. Our data suggest that walking difficulties and behavioral problems, based on official assessments, could be useful when counseling patients with *SCN1A* pathogenic variants; they are strong indicators for a more severe disorder when observed at a young age.

Both walking disabilities and behavioral problems showed a strong correlation with cognitive outcomes, seizure frequencies, and QoL scores. Similar findings have been reported previously, and behavioral problems have been identified as the most important predictors of a worse HRQoL score [7,19]. Interestingly, the relationship between cognitive disability and frequency of behavioral problems was not linear

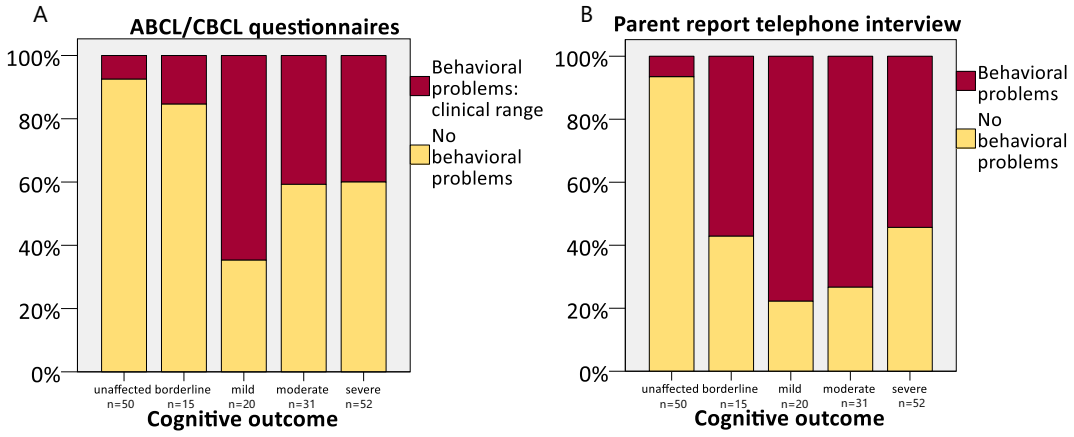

Fig. 4. A: Percentage of patients with behavioral problems in the clinical range according to ABCL/CBCL questionnaires, per cognitive outcome score. B: Percentage of patients for which parents responded "yes" to the question "are there any behavioral problems?" during the telephone interview, per cognitive outcome score.

but hyperbolic: most problems were seen in patients with a mild ID. A reason for this could be that more severely disabled patients are less capable of aberrant behavior; however, it might also be due to the fact that CBCL questionnaires have been proven to be less reliable in the assessment of children with moderate, severe, or profound ID [43]. Total scores cannot be calculated when many questions are not applicable because of cognitive impairment, which occurs more frequently in patients with a worse cognitive outcome. Nevertheless, when parents were asked if they thought their child showed any behavioral problems, a similar pattern was observed. A hyperbolic relationship was also found between seizure frequency and behavioral problems in Dravet syndrome, although inversed: most behavioral problems were seen in patients that were seizure-free or experienced daily seizures. This nonlinear relationship indicates that behavioral problems are not completely subject to an epileptic encephalopathy disease model, as previously suggested [19,44]. Recent research has shown that *SCN1A* variants could lead to changes in the dopamine system that may contribute to behavioral problems, irrespective of seizure activity [45]. This, together with the large impact of behavioral problems on HRQoL scores and the high number of families affected by it, calls for more attention regarding recognition of behavioral problems. Handling these issues and developing coping strategies for parents require more emphasis during treatment, which should not only focus on suppressing seizures.

Patients with non-Dravet syndromes seem to have a good prognosis: the majority of our patients was reported to be seizure-free after 10 years of age, and seizure freedom was reported for all patients over 40 years of age, in most cases, without maintenance treatment. However, some of the older participants represented parents of children with *SCN1A*-related seizures that were tested subsequently after a diagnosis was made in their children. They may have gone undiagnosed if their children had not been assessed for mutations, and our results may therefore not be fully applicable to young probands with *SCN1A*-related epilepsy. Seven of the 15 patients in the 40+ age group were parents of affected children and had never used antiepileptic medication themselves, so it is unlikely that they would have been diagnosed individually. It is, furthermore, worth noting that pathogenic *SCN1A* variants do not have a 100% penetrance: although our study only describes symptomatic patients, we are aware of four mutation-carrying GEFS+ family members that never experienced any seizures (not included in this study). However, although patients with non-Dravet syndromes showed better outcomes on the used questionnaires, subtle comorbidities were still observed in this group. It is known that neuropsychological and cognitive problems are common in epilepsy in general [46–50], and it is, therefore, not surprising that similar problems are observed in the non-Dravet group. Although the use of different methods makes comparing the exact results difficult, and we investigated a small cohort (only 24 patients with non-Dravet syndromes <20 years of age), we, nonetheless, observe relatively similar percentages of problems in our patient group and cohorts consisting of patients only diagnosed with epilepsy: 26% of patients between 7 and 16 years old in our cohort had repeated a grade, and 60% required special educational assistance compared with 26% and 51% respectively in an epilepsy cohort [48]. Psychological/behavioral problems were observed in 40% of patients between 5 and 17 years old and in 37% of patients over 16 years old in our cohort, compared with 31.4% in children with childhood seizures [49] and versus 30.6% in patients with epilepsy [47] in the same age groups. Furthermore, similar percentages of patients with symptoms of attention deficit hyperactivity disorder (ADHD) (10% vs 14.3%), depression (5% vs 4%), and anxiety (15% vs 12.3%) were seen in patients between 5 and 17 years old in our cohort and in patients with idiopathic epilepsy respectively [46]. Although according to the International League Against Epilepsy (ILAE), criteria [51], usually, no developmental impairments are expected in non-Dravet *SCN1A* phenotypes, we report five patients with non-Dravet syndromes (10%) with a cognitive outcome score of 2 (borderline ID). Their disorder could not be classified as Dravet syndrome, since they were seizure-free with minimal or no medication at the time of inclusion, and three had never developed any secondary seizure types. Furthermore, a borderline ID (IQ 70–85) represents the IQ score range between −1 and −2 standard deviation (SD) from the mean (100) and is thus observed in 13.6% of the general population. It can consequently be expected to also occur in a small part of the non-Dravet group, as described by several authors [27–29]. In addition, borderline ID might be a family characteristic in these patients. We therefore argue that a slight cognitive impairment does not necessarily indicate a diagnosis of Dravet syndrome.

Our study has several limitations. In the non-Dravet group, all of the more subtle problems (not captured by the standardized questionnaires) were reported by patients or their parents during telephone interviews or mentioned by clinicians in medical files, and no official assessments were used to evaluate the problems. Our results therefore reflect issues that they regarded most important, rather than structured measurements and may be subject to recall and response biases. To minimize this effect, we limited our analyses in this group to patients younger than 20 years. In these patients, the occurrence of problems at school was independent of seizure and/or medication freedom at the moment of inclusion. These problems may however, already have occurred while medication was still being used or when seizures were still active, so we cannot exclude a causal relationship. Interestingly, although psychological/behavioral problems occurred independently of seizure freedom, they occurred more often in patients that still used medication. This implies that psychological/behavioral problems might at least be partly due to medication side effects. In other studies however, no such relation was found [46,48]. It is worth noting that although significantly lower QoL scores were found in patients with problems at school, the average QoL scores of the non-Dravet group is comparable with that of the general population [33].

By analyzing multiple outcomes in patients with Dravet syndrome together with patients showing milder *SCN1A*-related phenotypes, we are able to assess different disease burdens over a large part of the *SCN1A*-spectrum. Both groups show distributions at different ends of the spectrum, and in general, a clear distinction between these syndromes can therefore be made, not only based on regularly used clinical criteria such as cognitive impairment and seizure severity but also on other comorbidities: severe behavioral problems and walking disabilities, which can already occur at a young age in patients with Dravet syndrome and are almost never seen in patients with non-Dravet syndromes. These issues should receive specific attention during clinical management of the disease. However, as in patients with other epilepsies, comorbidities occur in a substantial part of patients with non-Dravet syndromes as well. Although these problems are less severe than in patients with Dravet syndrome, they can still have a large impact on patients and their families. Our study provides valuable information on the disease course and comorbidities in these patients, which can be of great value when counseling newly diagnosed patients and their parents.

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Competing interests

None of the authors has any competing interests to disclose.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2018.09.041.

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