

Quality of life and comorbidities associated with Dravet syndrome severity: a multinational cohort survey

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This article is commented on by Gataullina and Dulac on page 8 of this issue.

PUBLICATION DATA

Accepted for publication 6th September 2017.

Published online 6th October 2017.

ABBREVIATIONS

AED	Antiepileptic drug
CSF	Composite seizure frequency
QoL	Quality of life
TTD	Time to diagnosis

AIM To test the hypothesis that higher seizure burden in Dravet syndrome is associated with increased comorbidities and lower quality of life (QoL) in a large cohort of patients with Dravet syndrome and their caregivers in Europe.

METHOD An extensive survey of caregivers of patients with Dravet syndrome on experiences of diagnosis, seizure burden, management, social and financial impact, and health services use was administered online in 10 languages.

RESULTS The survey received 584 unique responses from caregivers of paediatric (83%) and adult (17%) patients with Dravet syndrome (aged <1–48y). Despite broadly following current treatment guidance, less than 10% of patients were seizure free in the previous 3 months. Nearly all (99.6%) patients aged 5 years or older experienced at least one or more motor, speech, learning, or behavioural impairment. High seizure frequency was related to more reports of emergency treatment, comorbidities, and a lower QoL (as measured by the standardized instrument EQ-5D-5L). If not diagnosed at the first instance, the majority (83%) of adults, but less than 20% of 6- to 11-year-olds were diagnosed after 4 or more years.

INTERPRETATION Patients with Dravet syndrome with the highest current seizure frequency suffer from more comorbidities and have a lower QoL. Therefore, more effective antiepileptic treatments are needed.

Dravet syndrome is a rare, refractory epilepsy typically involving multiple comorbidities, including motor, cognitive, and behavioural impairments.¹ The wide scope of comorbidities associated with this condition, combined with it being a rare disease, can be expected to result in a high impact on caregivers, affecting all aspects of their lives.²

Dravet syndrome typically presents with febrile and afebrile, generalized tonic-clonic or hemiclonic epileptic seizures in the first year of life in an otherwise healthy child. At around 1 to 2 years of age the patient begins to experience additional seizure types. Cognitive slowing or stagnation, behavioural disorders, motor problems, and other comorbidities appear during childhood. In late childhood or early adolescence there is usually a decrease in seizure frequency.¹ Dravet syndrome is primarily a clinical diagnosis, frequently supported by the identification of a mutation in *SCN1A*, as the majority of children (70–80%) carry such a mutation.³ At all stages seizures are usually refractory to standard antiepileptic medication.⁴ While some studies have linked a greater degree of cognitive and behavioural impairment to a higher convulsive and non-convulsive seizure frequency, the extent to which comorbidities and their severity arise and develop independently from seizures is still unknown.^{5–7} Also, it is unclear

whether a delay in correct diagnosis is correlated with later and more severe comorbidities.

In collaboration with the extensive pan-European network of the Dravet Syndrome European Federation, the study described here sought to acquire, in a large sample size, an overall picture of factors that may have an impact on patients with Dravet syndrome and their caregivers, such as quality of life (QoL), disease severity, socioeconomic and financial impact, and health care resource utilization. This report describes the overall clinical and demographic data collected in the survey and explores associations between disease characteristics (e.g. current seizure frequency and time to diagnosis [TTD]), comorbidities, and QoL. Our hypothesis was that there is an association between 'severity' of the disease (as expressed by the current seizure frequency) and the known comorbidities in Dravet syndrome, such as motor and cognitive problems and overall QoL. We also specifically examined whether a delay to the correct diagnosis was associated with a worse outcome.

METHOD

Research design and survey procedure

The Dravet syndrome caregiver survey was an anonymous cross-sectional study of caregivers of patients with Dravet

syndrome open to participants from 23 June to 15 September 2016 (Appendix S1, online supporting information for survey questions) and available in 10 languages (English, Spanish, Portuguese, French, Dutch, German, Italian, Polish, Croatian, and Romanian) and two dialects (Latin American Spanish and Brazilian Portuguese). Participants were recruited through e-mail invitations to approximately 1000 members of different countries' patient advocacy groups associated with the Dravet Syndrome European Federation, as well as through Internet-based sources (Facebook and Twitter).

Each language version of the Dravet syndrome caregiver survey was hosted online by the survey platform Formstack. The survey was developed in English and translated by specialist translators into all languages except Croatian, Dutch, and Romanian, which were translated by native-speaking patient advocacy group members. All surveys were tested by local-language speakers before survey launch.

The Dravet syndrome caregiver survey consisted of 150 questions about the caregiver household (demographic information), health status of the patient (including current seizure frequency), current and past treatments, experiences of diagnosis, QoL, social and financial caregiver impact, and health services use. A pilot study of the English version was conducted with 13 families to establish questionnaire validity.

Answers to survey questions were given in checkboxes (multiple choices possible), radio buttons (a single choice only), dropdown lists (single choice only), or free text. Questions were gated and only fully completed surveys (with the exception of question number 109 regarding the cost of non-pharmacological treatments) were accepted for submission by Formstack.

Seizure frequency

Parents were asked how often (0, 1–12, 13–30, 31–60, 61–150, or >150 times) their child had experienced a seizure type (tonic-clonic, myoclonic, partial/focal, absence, atonic/drop attack, and unidentified seizure) in the past 3 months.

Patient health-related QoL

As a measure of the health-related QoL of patients with Dravet syndrome, caregivers completed in proxy for their son or daughter the standardized instrument EQ-5D-5L.⁸ Index values were based on the UK value set. We elected to use the EQ-5D-5L without the visual analogue scale.

Data processing

Responses were retrieved from Formstack in Excel format. Non-English-language data were translated back into English and collated into a single data file. Nine duplicates, identified by matching Internet protocol addresses and identical answers, were removed from the data set.

Descriptive analysis

Data are reported as total counts, frequency of responses, and summary statistics (mean and standard deviation [SD])

What this paper adds

- The survey captured about 15% of all patients with Dravet syndrome in Europe.
- Less than 10% of patients had current seizure freedom.
- Patients with a high current seizure burden have more comorbidities and lower quality of life.

of the pooled sample and differing age ranges: infant (<2y) pre-school (2–5y, inclusive), middle childhood (6–11y, inclusive), adolescent (12–17y, inclusive), and adult (≥18y).

Statistical analysis

Statistical significance of differences between frequencies was determined using a two-tailed *z*-test for two proportions with a 95% confidence interval using the statistical software XLSTAT (Addinsoft SARL, Paris, France) in Excel. All *p*-values less than 0.05 were regarded as statistically significant.

Stratification by patient characteristics

Scores

Patient characteristics were assigned numerical values. Based on survey answers, each patient received a score for the frequency of each seizure type (maximum 10 [>150 in past 4wks], minimum 0 [none in past 3mo]) and for their TTD (maximum 10 [>4y], minimum 0 [immediate diagnosis]), and a composite score for total seizure frequency (composite seizure frequency [CSF] score) (maximum 39, minimum 0; only countable seizures and seizures with a motor component were used for this score), comorbidities (maximum 18, minimum 0), and non-antiepileptic drug (AED) treatments (maximum 12, minimum 0) (Table I).

Scores in the lowest and highest strata

For each characteristic, patient scores (TTD score, CSF score, composite comorbidity score, composite non-AED score and EQ-5D-5L index score) were ranked and patients in the highest and lowest strata were compared. Since multiple patients could have identical scores for a characteristic, the cut-off point for the highest and lowest strata was defined by the score closest to the twentieth or eightieth centile. Thus, the highest and lowest strata for ranked CSF scores contained patients above the eighty-third centile (101 patients; scores 14–39) and below the sixteenth centile (94 patients; scores 0–2) respectively; for EQ-5D-5L index scores, above the eightieth centile (118 patients; scores 0.706–1) and below the twenty-first centile (123 patients; scores 0.157 to –0.594) respectively; for TTD, above the seventy-sixth centile (138 patients; TTD score 10) and below the twenty-eighth centile (164 patients; TTD score 0) respectively; for composite comorbidity scores, above the eighty-first centile (110 patients; scores 7–10) and below the twenty-second centile (126 patients; scores 0–2) respectively; for composite non-AED treatment scores, above the seventieth centile (178 patients; scores 4–10) and below the twenty-seventh centile (155 patients; score 0) respectively (Appendix S2, online supporting information).

Table 1: Scoring system for patient characteristics

Scores assigned to survey answers		Q 4:	Q 5:	Q 7:	Q 8:	Q 12:	Q 111:	Q 119:	Q 125:	Q 131:	Q 137:	Q 143:	Q 103:	Q 104:	Q 105:	Q 106:	Q 107:	Q 108:
Score		Tonic-clonic	Myoclonic	Partial focal	Atonic/drop attack	Time to diagnosis	Motor impairment	Speech impairment	Learning difficulties	Autism	ADHD	Other behaviour	Herbal medicines	Vitamins	Amino acids	Ketogenic diet	Other nutrition	VNS
0		None	None	None	None	0	No	No	No	No	No	No	No	No	No	No	No	No
1			1–12		1–12	<6mo ^a							In the past ^b		In the past ^b	In the past ^b	In the past ^b	In the past ^b
2						6–12mo ^a	Yes	Yes/does not talk at all	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3		1–12																
4		13–30																
5		13–30	13–30	13–30	13–30	1–2y ^a												
6			31–60															
7		31–60		31–60	31–60													
8			61–150			3–4y ^a												
9		61–150	>150	61–150	61–150													
10		>150		>150	>150	>4y ^a												

See Appendix S1 (online supporting information) for full questions. Composite seizure frequency score=tonic-clonic score+myoclonic score+partial/focal score+atonic/drop attack score. Composite comorbidity score=motor impairment score+speech impairment score+learning difficulties score+autism score+attention-deficit-hyperactivity disorder (ADHD) score+other behaviour impairment score. Composite non-antiepileptic drug treatment score=herbal medicine score+amino acids score+ketogenic diet score+other nutritional therapy score+vagus nerve stimulation (VNS) score. ^aAfter the first seizure. ^bFull answer: 'In the past – but not anymore'. Q, question.

RESULTS

Demographics

A total of 584 fully completed surveys were submitted by caregivers (mothers 86%, fathers 12% and other caregivers 2%) of patients. The majority (92%) lived in Europe, with Italy, the UK, Germany, France, the Netherlands, Spain, and Poland representing 14%, 12%, 12%, 11%, 10%, 10%, and 7% of the total responses respectively. Twenty per cent of caregivers identified themselves as living in a single-adult household and 78% in a household with more than one adult. The mean age of the patients was 10.6 years (median 9y). The middle-childhood age group was most represented with over a third of survey submissions (35%). Most other age groups were represented between 25% and 15% (pre-school, adolescent, and adult groups). The infant group was the smallest with 6% submissions (34 children) (Fig. 1a). Slightly more than half (52%) of patients were male. In the middle-childhood and adolescent groups (spanning ages 6–17y), only 31% attended mainstream school. The rest attended special school, had home schooling, or did not attend school (Appendix S3, online supporting information).

Clinical characteristics

Epilepsy type and frequency

Overall, only 9% of patients, and fewer young than old patients, were reported to be seizure free in the previous 3 months. Only 3% of infants but 14% of adolescents ($p=0.039$ compared with infants) and 11% of adults (the difference compared with infants was not statistically significant) were seizure free (Table II).

The most frequent seizure types reported in the past 3 months were tonic-clonic (78% of patients), followed by myoclonic and absence seizures (each in about 50% of patients); focal and atonic attacks were less frequent (Table II, Fig. 1b). While the proportion of patients experiencing at least one tonic-clonic seizure decreased significantly from 85% in the pre-school to 74% in the middle-childhood group ($p=0.017$); thereafter, the proportion remained very drug resistant into adulthood. In older patients, the frequency of reported myoclonic, absence, and partial/focal seizures declined, whereas that of atonic/drop attack seizures did not change significantly across age groups (Fig. 1b).

Emergencies

Half of patients required at least one emergency admission and 46% at least one ambulance call in the past 12 months (Table II and Appendix S3). More young than old patients reported at least one emergency admission (94% and 76% vs 30% and 28% in infant and pre-school vs adolescents and adults respectively [both $p<0.001$]). Similar proportions were observed for ambulance calls (Fig. 1c).

Pharmacological treatment

Patients were reported to be taking an average (SD) of three AEDs (3.14 [1.3]) ranging from 0 to 12 per patient and had previously taken an average of three drugs (3.35 [3.5]) ranging from 0 to 28 per patient. Valproic acid,

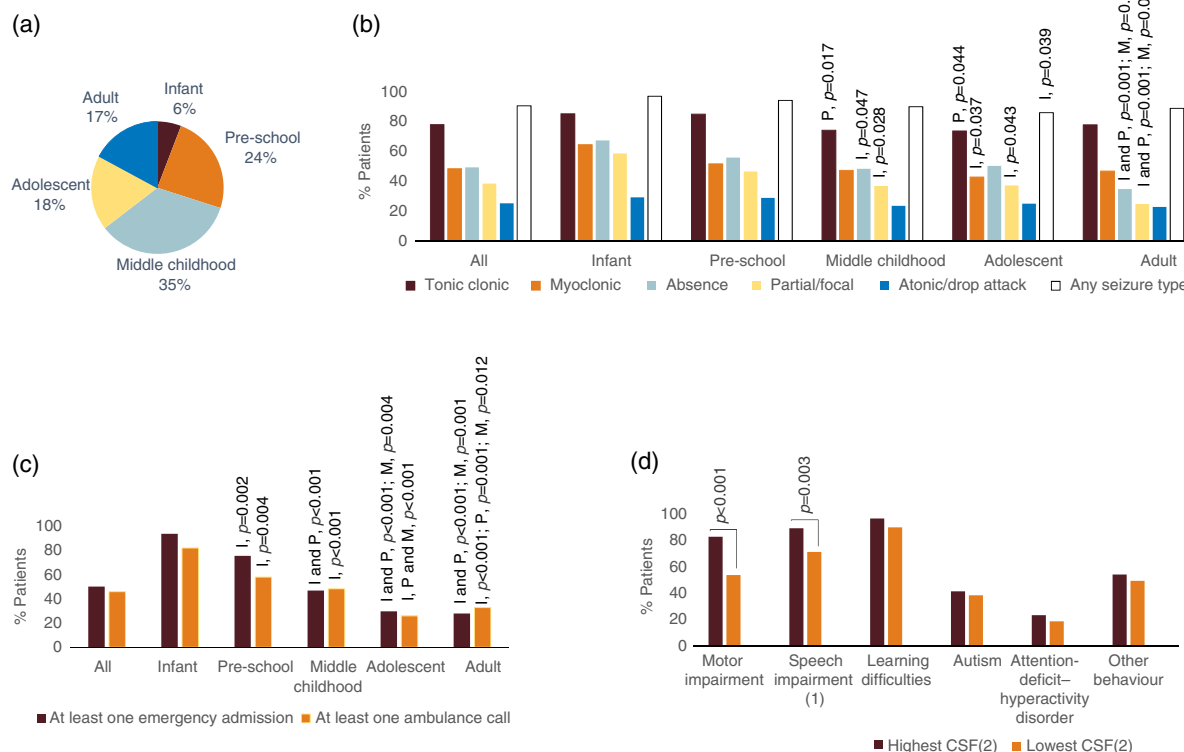


Figure 1: (a) Age distribution of patients. (b) Percentage of age group experiencing at least one seizure in the previous 3 months. For each seizure type, a z-test for difference in proportions was performed for all age groups against each other. All *p*-values suggesting statistically significant differences in proportions are indicated in the graph (I, P, M, and A=difference to infant, pre-school, middle-childhood and adolescent group respectively). (c) Percentage of age group experiencing at least one emergency admission or ambulance call in the previous 12 months. A z-test was performed for all age groups against each other. All *p*-values suggesting statistically significant differences in proportions are indicated in the graph (I, P, M, and A=difference to infant, pre-school, middle-childhood, and adolescent group respectively). (d) Percentage of patients in highest and lowest strata for the composite seizure frequency (CSF) score for whom the indicated comorbidity was reported. All *p*-values suggesting statistically significant differences between groups are indicated. (1) Includes patients who do not talk at all; (2) excluding infant age group. [Colour figure can be viewed at wileyonlinelibrary.com; correction added on 13 October 2017, after first online publication: the *p*-values for the “tonic clonic” and “atonic/drop attack” data of adolescent patients in (b) have been updated].

typically used as first-line treatment,^{4,9,10} is currently taken by 76%. Other first- or second-line treatments such as stiripentol, topiramate, clobazam, or the ketogenic diet, are currently taken by 47%, 34%, 53%, and 7% respectively (Table III and Appendix S4, online supporting information). Across age groups, use of valproate, clobazam, and topiramate (except in infants with 11.8%) were constant, whereas that of stiripentol decreased with age: 31% in the adult versus 51.8% in the pre-school group ($p=0.001$). Also, ketogenic diet use decreased with age (11.8% in infants vs 2% in adults). However, more than 20% of adolescents and adults had tried a ketogenic diet in the past. Vagus nerve stimulation was not used in the younger age groups but considered as a possible treatment option more often in older patients (17% in adults vs 5.9% in middle childhood; $p=0.012$).

Very few (0–2%) patients reported currently taking antiepileptic agents known to exacerbate seizures in Dravet syndrome;⁹ however, many adults had taken these previously, including carbamazepine (54%), lamotrigine (56%), phenobarbital (42%), and vigabatrin (35%) (Table III and Appendix S4). Also of note is that 21% of infants had been exposed to carbamazepine or oxcarbazepine, typical first-line drugs for focal seizures.

The use of pharmacological treatments for the associated comorbidities appeared limited. Only 6% of patients reported currently taking antipsychotics and 6% attention-deficit-hyperactivity disorder (ADHD) medication. Of the various non-AED treatments explored in the survey, only complementary medicine (16%) and vitamin supplements (>50%) were currently taken by more than 10% of patients (Table III).

Table II: Disease severity

	% Total responses	% Responses within age group					
		I	PS	MC	A	Adult	
Epilepsy type and severity							
Seizure free ^a	9.4	3	5.7	10	14	11	
Frequency of at least one seizure in the past 3mo							
Tonic-clonic	78.1	85.3	85.1	74.3	73.8	78.0	
Myoclonic	48.6	64.7	51.8	47.5	43.0	47.0	
Absence	49.5	67.6	56.0	48.5	50.5	35.0	
Partial/focal	38.7	58.8	46.8	37.1	37.4	25.0	
Atonic/drop attack	25.5	29.4	29.1	23.8	25.2	23.0	
Unidentified	24.5	29.4	24.8	24.3	26.2	21.0	
Time to diagnosis							
Immediate diagnosis ^b	28.1	29.4	44.7	27.7	21.5	12.0	
Self-diagnosis ^{c,e}	12.0	17.6	15.6	10.9	14.0	5.0	
Time to diagnosis ^{d,e}							
<6mo	9.3	33.3	20.5	8.9	1.2	1.1	
6–12mo	23.1	54.2	37.2	29.5	10.7	3.4	
1–2y	19.3	8.3	30.8	23.3	19.0	5.7	
3–4y	15.5	0.0	10.3	18.5	28.6	6.8	
>4y	32.9	4.2	1.3	19.9	40.5	83.0	
Emergency events in the past 12mo							
No emergency admissions	49.7	5.9	24.1	53.0	70.1	72.0	
No ambulance calls	53.9	17.6	41.8	51.5	73.8	67.0	
Comorbidities and impairments							
	% Total responses		% Responses within age group				
	All age groups	Excluding (a) I or (b) I and PS age group	I	PS	MC	A	Adult
Motor impairment ^f	71.7	(a)72.7 (b)74.3	55.9	68.1	77.2	68.2	75.0
Speech impairment ^{g,h}	64.0	(a)66.0 (b)67.0	32.4	63.1	71.8	67.3	57.0
Does not talk ^h	14.9	(a)14.4 (b)13.4	23.5	17.0	11.9	11.2	19.0
Learning difficulties ⁱ	87.8	(a)91.1 (b)97.8	35.3	71.6	97.0	99.1	98.0
Autism ^j	33.6	(a)35.6 (b)42.1	0.0	17.0	39.1	51.4	38.0
ADHD ^k	20.2	(a)21.3 (b)23.5	2.9	14.9	26.7	21.5	19.0
Behaviour ^l	45.5	(a)47.1 (b)51.1	20.6	35.5	49.0	55.1	51.0
No other comorbidities or impairments ^m	7.5	(a)7.8 (b)9.3	2.9	3.5	8.9	9.3	10
EQ-5D-5L (mobility dimension)							
1. I have no problems in walking about	21.4	(a)21.1 (b)20.5	26.5	22.7	21.8	24.3	14.0
2. I have slight problems in walking about	30.7	(a)31.1 (b)30.6	23.5	32.6	35.1	27.1	25.0
3. I have moderate problems in walking about	28.3	(a)29.5 (b)29.3	8.8	29.8	27.7	28.0	34.0
4. I have severe problems in walking about	12.3	(a)12.9 (b)14.2	2.9	9.2	10.9	17.8	17.0
5. I am unable to walk about	7.4	(a)5.5 (b)5.4	38.2	5.7	4.5	2.8	10.0

Because of rounding, percentages might not add up to exactly 100. For all answers to disease-severity questions see Appendix S3 (online supporting information). ^aSeizure free' is defined as a participant who selected the option 'none' for all questions (4–9) asking about seizures in the past 3mo. ^bParticipants answered 'yes' or 'no' to the question 'Did the doctor you first saw recognize Dravet syndrome?'. ^cParticipants answered 'yes' or 'no' to the question 'Did you (parents or other family members) at some point suggest the diagnosis of Dravet syndrome to your doctor?'. ^dTime to diagnosis after the first seizure. ^ePercentage of patients that were not immediately diagnosed, i.e. whose caregivers answered 'no' to the question 'Did the doctor you first saw recognise Dravet syndrome?'. ^fCaregivers selected either 'yes' or 'no' to the question 'Does your son/daughter have a motor impairment (such as problems walking about)?'. ^gDoes not include patients who do not talk at all. ^hCaregivers selected either 'Yes, my son/daughter's speech is impaired', 'No', or 'My son/daughter does not talk at all' to the question 'Does your son/daughter have a speech or language impairment? (e.g. impaired articulation or a voice impairment)'. ⁱCaregivers selected either 'yes' or 'no' to the question 'Does your son/daughter have learning difficulties?'. ^jCaregivers selected either 'yes' or 'no' to the question 'Has your son/daughter been diagnosed with autism/autistic like symptoms?'. ^kCaregivers selected either 'yes' or 'no' to the question 'Has your son/daughter been diagnosed with attention-deficit-hyperactivity disorder (ADHD)?'. ^lCaregivers selected either 'yes' or 'no' to the question 'Does your son/daughter experience behavioural problems that have NOT been diagnosed as autism or ADHD?'. ^mNo other diagnoses' is defined as a participant who selected the option 'no' for all for all questions (111, 119, 125, 131, 137, 143) asking about diagnoses. I, infant (<2y); PS, pre-school (2–5y); MC, middle childhood (6–11y); A, adolescent (12–17y); Adult, adult (≥18y). [Correction added on 13 October 2017, after first online publication: Footnote ^e has been added to "self-diagnosis"].

Comorbidities or impairments

Caregivers were asked whether their son or daughter had a motor impairment, speech impairment, a diagnosis of autism or autistic-like behaviour, a diagnosis of ADHD, or behavioural problems not diagnosed as autism or ADHD. Nearly all (91%) patients older than 5 years of age

reported at least one other comorbidity or impairment in addition to seizures as follows: motor impairment (74%), speech impairment (80%), learning difficulties (98%), autism (42%), ADHD (24%), and behavioural difficulties not related to autism or ADHD (51%) (Table II). Patients older than 5 years of age had, on average, four (3.7 [1.2])

Table III: Current and previously taken antiepileptic drugs (AEDs) and non-pharmacological treatments

	% Total responses	% Responses within age group				
		I	PS	MC	A	Adult
Pharmacological treatment						
Patients taking AEDs	98.1	97.1	98.6	98.0	99.1	97.0
Current and previous AEDs						
Valproic acid						
Current	75.5	82.4	82.3	75.2	68.2	72.0
TP	13.7	2.9	9.2	12.4	22.4	17.0
Clobazam						
Current	52.7	61.8	55.3	54.5	44.9	51.0
TP	19.0	5.9	14.2	21.3	23.4	21.0
Stiripentol						
Current	47.1	41.2	51.8	55.4	42.1	31.0
TP	11.1	8.8	5.7	12.4	13.1	15.0
Topiramate						
Current	34.2	11.8	28.4	38.6	42.1	33.0
TP	25.7	8.8	14.2	26.7	34.6	36.0
Bromide						
Current	9.6	8.8	11.3	10.9	9.3	5.0
TP	4.6	0.0	0.7	5.0	9.3	6.0
Cannabinoid ^a						
Current	2.7	0.0	2.1	4.5	2.8	1.0
TP	2.2	0.0	0.7	3.5	2.8	2.0
Other cannabis derivatives ^b						
Current	7.0	2.9	7.1	10.4	3.7	5.0
TP	4.1	2.9	2.8	6.9	0.9	4.0
Carbamazepine						
Current	1.7	2.9	2.1	1.5	0.9	2.0
TP	26.4	8.8	9.2	19.3	42.1	54.0
Oxcarbazepine						
Current	1.2	0.0	0.7	1.0	0.9	3.0
TP	10.1	11.8	6.4	9.9	8.4	17.0
Phenytoin						
Current	0.5	0.0	0.7	1.0	0.0	0.0
TP	8.0	11.8	5.7	3.5	8.4	19.0
Lamotrigine						
Current	1.7	0.0	0.0	1.0	2.8	5.0
TP	27.9	5.9	8.5	20.8	47.7	56.0
Vigabatrin						
Current	0.3	0.0	0.7	0.5	0.0	0.0
TP	11.3	0.0	2.1	8.4	10.3	35.0
Phenobarbital						
Current	1.7	5.9	0.7	2.0	1.9	1.0
TP	23.5	5.9	17.7	18.8	28.0	42.0
Rufinamide						
Current	0.2	0.0	0.7	0.0	0.0	0.0
TP	1.5	0.0	0.7	1.0	1.9	4.0
Other antiepileptic treatment						
Ketogenic diet						
Current	6.5	11.8	6.4	9.4	3.7	2.0
Not anymore ^c	17.5	2.9	9.2	18.8	27.1	21.0
VNS						
Current	7.4	0.0	0.7	5.9	12.1	17.0
Not anymore ^c	1.9	0.0	0.0	0.5	5.6	4.0
Other drugs and treatments						
Antipsychotics						
Current	6.3	2.9	1.4	6.9	10.3	9.0
Not anymore ^c	2.4	0.0	0.0	2.0	1.9	8.0
Stimulants or antistimulants ^d						
Current	5.5	2.9	0.7	8.9	8.4	3.0
Not anymore ^c	3.6	0.0	0.7	4.5	5.6	5.0
Complementary medicine ^e						
Current	16.6	14.7	14.2	18.3	16.8	17.0
Not anymore ^c	7.0	5.9	2.8	7.4	9.3	10.0
Vitamin supplements						
Current	51.7	44.1	47.5	53.5	52.3	56.0
Not anymore ^c	9.2	11.8	5.0	9.4	15.0	8.0
Amino acids ^f						
Current	8.4	14.7	9.9	10.4	5.6	3.0
Not anymore ^c	8.4	5.9	5.0	6.4	13.1	13.0

Table III: Continued

	% Total responses	% Responses within age group				
		I	PS	MC	A	Adult
Nutritional therapy ^g						
Current	7.0	5.9	7.1	5.4	7.5	10.0
Not anymore ^c	4.5	0.0	4.3	4.0	7.5	4.0

Because of rounding, percentages might not add up to exactly 100. A full list of treatments is given in Appendix S4 (online supporting information). ^aPurified compound. ^bIncluding cannabidiol oil. ^cTaken in the past but not anymore. ^dStimulants or anti stimulants for attention-deficit-hyperactivity disorder other than or in addition to a ketogenic diet. ^eComplementary medicine such as herbal medicine. ^fAmino-acid supplements. ^gNutritional therapy. I, infant (<2y); PS, pre-school (2–5y); MC, middle childhood (6–11y); A, adolescent (12–17y); Adult, adult (≥18y); TP, taken previously; VNS, vagus nerve stimulation.

of the six surveyed impairments or comorbidities. Of interest, 13% of all patients older than 5 years of age were reported as not speaking at all.

Mobility impairments with respect to walking were further explored in the EQ-5D-5L section of the survey. Very few (5%) patients older than 5 years were unable to walk, most indicating slight (31%), moderate (29%), or severe problems (14%). Twenty-one per cent indicated no problems in walking (Table II).

More males than females 2 years of age or older had a speech impairment, including not talking at all (84% vs 76%; $p=0.035$), autism (40% vs 31%; $p=0.028$), and ADHD (28% vs 14%; $p<0.001$). Motor impairments, learning difficulties, and behavioural difficulties were reported in similar proportions by both sexes (Appendix S5, online supporting information).

Patient QoL

The mean EQ-5D-5L index value for all patients 2 years of age or older was 0.42 (0.29) and ranged from less than 0 to 1 (Appendix S3). No large difference in index values across age groups was observed.

TTD and comorbidities

This survey data suggest that physician awareness of Dravet syndrome has markedly improved over time. Doctors immediately recognized Dravet syndrome in 45% of pre-school versus only 12% of adult patients. Furthermore, in contrast to 83% of adults, only 20% of middle-childhood patients not diagnosed at their first visit reported receiving a Dravet syndrome diagnosis over 4 years after their first seizure (Table II). In infants, the diagnosis of Dravet syndrome was made in 88% within the first year after presentation.

Associations between disease characteristics, comorbidities, and QoL

Associations between disease characteristics, comorbidities, and QoL were explored by comparing patients with the highest and lowest disease burden, as expressed by seizure frequency, comorbidities, TTD, treatment pattern (number of current, failed, seizure-exacerbating or non-AED medications), and QoL.

High and low seizure frequency burden

A wide range of seizure frequency in the previous 3 months was reported, from no seizures to multiple occurrences of each seizure type, and patients with high and low seizure frequencies (high and low seizure frequency are represented in this study by the highest and lowest strata of CSF scores respectively) reported emergency events, comorbidities, and QoL to different extents.

Patients in the highest versus the lowest CSF stratum more frequently reported at least one emergency admission (56% vs 36%; $p<0.006$) or ambulance call (55% vs 30%; $p<0.001$) in the previous 3 months. Patients older than 5 years of age in the highest CSF stratum reported more comorbidities (4.08 [0.97]) than in the lowest (3.41 [1.28]). More patients older than 2 years of age in the highest than lowest CSF stratum reported a motor (83% vs 53.8%; $p<0.001$) and speech impairment (including not talking at all; 89.4% vs 71.4% [$p<0.005$]) (Fig. 1d and Appendix S5).

High and low comorbidity burden

Having more comorbidities was associated with higher seizure frequencies. More patients older than 5 years of age in the lowest than the highest stratum for composite comorbidity scores reported no seizures in the past 3 months (20% vs 7%; $p=0.044$) (Appendix S5). The severity of patients' motor impairment (as indicated in the walking mobility section of the EQ-5D-5L questionnaire) was also associated with seizure frequency. No patients older than 5 years and unable to walk reported no seizures in the previous 3 months versus 10%, 5%, 14%, and 20% in patients with severe, moderate, slight, or no problems walking respectively.

High and low QoL

Less than 3% of patients in the lowest versus 15% in the highest EQ-5D-5L stratum were seizure free in the previous 3 months ($p=0.002$). Patients in the lowest stratum also reported more seizures of each type (Appendix S5). More patients older than 2 years of age in the lowest than the highest stratum reported at least one or more seizure type (tonic-clonic [71% vs 86%; $p=0.008$], myoclonic [34% vs 67%; $p<0.001$], absence [38% vs 62%; $p<0.001$], partial focal [31% vs 49%; $p=0.005$], and atonic seizure [18% vs 32%; $p=0.022$]).

Long and short TTD

Overall, there were no clear differences in disease characteristics for patients in the highest versus the lowest TTD stratum.

Treatment patterns

Patients older than 5 years using a high number of non-AED treatments tended to have a higher disease burden: patients with the highest use (expressed as a high non-AED treatment composite score) reported more motor (87% vs 64%; $p < 0.001$) and speech impairments (85% vs 69%; $p = 0.009$) than those not using any non-AED treatments (Appendix S5). Patients grouped by treatment patterns (high or low number of current, failed, or seizure-exacerbating medications) did not display statistically significant differences in disease characteristics (data not shown).

DISCUSSION

This survey is the first large pan-European study of families caring for an individual with Dravet syndrome and provides representative data on clinical, social, QoL, and economic impact. Italy, the UK, Germany, France, the Netherlands, and Spain were each represented by 10% or more of the sample, indicating a broad coverage of families in Europe.

The survey confirms Dravet syndrome to be a very severe and difficult-to-treat epilepsy syndrome throughout childhood and into adulthood, with seizures remaining frequent despite appropriate treatment.⁵ Even in adults, only 11% of patients were reported to be seizure free. Seizure types also remain very similar across age groups, with generalized tonic-clonic seizures being most frequently reported.

The survey revealed that patients' overall seizure frequency decreases with age, as previously described,¹¹ as do ambulance calls and emergency admissions. However, emergency admissions remain notably high in adults, of whom 28% reported at least one emergency admission in the previous 12 months. While this figure is much less than the 94% reported for infants, it is nevertheless very high compared with the 7% of epilepsy-related emergency admissions previously reported for all patients with epilepsy.¹² Although the exact reason for the emergency admission was not asked, we found that ambulance calls and emergency admissions were higher in the stratum with the highest current seizure frequency.

Almost all patients suffer from several comorbidities and the QoL in all age categories is low. Only 31% of school-age patients attended mainstream school. The proportion of patients reporting a diagnosis of autism, ADHD, other behavioural problems or learning disabilities aligns with those reported by Brunklaus et al. for a cohort of 241 patients with *SCN1A* mutation-positive Dravet syndrome.^{13,14} However, the proportion with motor impairments (including ataxia) was higher than described by others,¹⁴ and may be owing to the difference between parents' perceptions and clinical criteria applied by the

authors. Similar to the study findings of Brunklaus et al.,^{13,14} the proportion of patients reporting each comorbidity increased with age, although these plateaued or even decreased in adults for diagnoses of autism (51% in adolescents, 38% in adults), ADHD (22% in adolescents and 19% in adults), or other behavioural problems (55% in adolescents and 51% in adults) (Table II), possibly reflecting a difference in the cohort makeup (age distribution was not reported in Brunklaus et al.¹³).

Dravet syndrome exhibits a range of severities in terms of seizure frequency and comorbidities,¹⁵ and there is evidence that in addition to the *SCN1A* phenotype,⁵ the magnitude of cognitive and behavioural impairment in Dravet syndrome is related to seizure frequency.¹⁶ We therefore hypothesized that the patients with the highest current seizure frequency in our population reflect a sub-population of patients with more severe Dravet syndrome and are thus expected to show a higher number of concurrent comorbidities. To some extent, our study confirms this hypothesis. Indeed, patients in the highest seizure stratum displayed a more severe motor and speech profile than those in the lowest. The causality of this relationship cannot be explored using the questions asked in the survey, and other studies would be required to distinguish between epileptic versus non-epileptic manifestations of the disease. For example, ataxia and crouching gait seen in Dravet syndrome may be related to *SCN1A* mutations,¹⁷ whereas spastic paralysis, seen in a small number of patients with Dravet syndrome, may be the sequelae of acute encephalopathy caused by status epilepticus.^{18–20} Our analysis of patients in the lowest and highest seizure strata also did not reveal a significant difference between the two groups for autism, ADHD, and other behavioural problems. These discrepancies indicate that seizure frequency is not the only factor to explain comorbidities, as already shown in other smaller studies.

One other important factor to be considered in this respect is the TTD. Early diagnosis of Dravet syndrome is associated with earlier access to appropriate drug therapy (e.g. avoiding sodium channel blockers) and earlier access to, for instance, specialized rehabilitation programmes. Patients in the Dravet syndrome caregiver survey cohort experience a diagnostic journey typical of rare diseases,^{21,22} involving late or initially incorrect diagnoses. Encouragingly, and possibly a reflection of increased awareness and genetic testing availability, the TTD in younger patients is far less than in older patients, indicating improvements in diagnosis.

As expected, most of the adult population received a diagnosis 4 years or more after the first seizure. However, surprisingly, there was no clear correlation for the overall group between delay in diagnosis and occurrence of comorbidities.

Antiepileptic medication use among respondents was consistent across age groups and in accordance with

existing clinical guidance. Currently, only a minority of patients are taking drugs known to possibly exacerbate seizures. As expected, many patients in older age groups were reported to be taking contraindicated medicines at some point in their medical history. Whether previous treatment with contraindicated medicines affected disease progression or comorbidity development was not explored in this study. While AED efficacy and side effects were also not explored in the survey, some of the reported treatment patterns raise interesting questions, for example, whether the decreasing use of stiripentol with age reflects a lower retention rate because of efficacy or side effects.

Over 50% of patients also take vitamin supplements. More recent but unlicensed therapies, such as cannabidiol,^{23,24} are not (yet) frequently used in European patients.

Previous studies have shown that children with Dravet syndrome have a worse health-related QoL than healthy children.¹³ Similarly in this survey, QoL for patients is much lower than in the general population. The average EQ-5D-5L index score of patients older than 2 years was 0.46 points lower than an average population,²⁵ and 0.38 points lower than patients with epilepsy.^{26,27} The wide range of EQ-5D-5L values may reflect the broad range of severity found in Dravet syndrome, as patients with the lowest EQ-5D-5L values reported the occurrence of more seizures than patients with the highest EQ-5D-5L values. This observation also supports evidence that seizure burden is a large determinant of QoL for people with epilepsy.^{28,29}

This study has some methodological limitations. Most participants (84%) reported belonging to a patient advocacy group, whose members possibly represent more engaged caregivers, more informed and with access to expert care. One can also speculate that families experiencing particular challenges with the condition may be more likely to join advocacy groups. These factors may have introduced a bias, with more affected patients included in our survey. That said, we do see that families with seizure-free children also participated in our survey. The infant group was small (6% of submissions, 34 children) compared with the other age groups, which were more evenly represented by between 15% and 35% of the cohort. The smaller number possibly reflects the survey's recruited population of primarily patient advocacy group members, to which parents of infants might not yet belong.

A further limitation is that diagnostic information about the patients was reported by parents and not expert physicians. Thus, details about ADHD and autism diagnoses were not requested, and the survey relied on parents' ability to identify their child's seizure type and recall its frequency. Indeed, tonic-clonic seizures were the most frequently reported type, possibly reflecting the difficulty of parents in differentiating between tonic, tonic-clonic, myoclonic, and focal seizures, which generalize to bilateral tonic-clonic seizures. Absences may also be very difficult to measure. We attempted to mitigate this

limitation by only asking about seizure frequency in the last 3 months and in our composite score for seizure frequency we only included seizure types which can be counted reliably. Furthermore, when examining possible associations between seizures and other outcomes, we only considered the two extremes in the population (the highest or lowest strata of patient characteristic scores, each constituting about 20% of the total population).

We estimate that this survey captured about 15% of the population of patients with Dravet syndrome under the age of 18 years in the 'European Union Five' (France, Germany, Italy, Spain, UK) assuming a prevalence of 1 in 45 700 in a population of 340 million, of which about 20% are under the age of 18.³⁰⁻³² This makes it the largest survey ever conducted with families impacted by Dravet syndrome. Further analysis suggests we have not under-sampled because at 250 responses, the median for all variables assessed, such as participating countries and age groups, were the same as at 500 responses (data not shown).

This survey, the largest and most comprehensive of its kind carried out to date, provides a representative depiction of the clinical profile and QoL of families with children with Dravet syndrome in Europe. We found evidence that a high current seizure burden is associated with more comorbidities (especially motor and speech) and lower QoL. The study therefore clearly identifies the need for effective treatment options to reduce the seizure burden in Dravet syndrome.

ACKNOWLEDGEMENTS

The authors would like to thank everyone who took the time to respond to the survey. We would also like to thank Dravet Syndrome European Federation-affiliated patient-advocacy group members for piloting the English survey, and translating and proofreading the survey and campaign materials. The authors would also like to thank Dingeman Wolfert and Najida Begum for their help with data analysis. This study was sponsored by Zogenix International Ltd. LL received consultancy fees and is on advisory boards of Zogenix, UCB, Novartis, Shire, LivaNova, GW Pharma, and Takeda. EG and AB are employed by Wickensstones Ltd and received support from Zogenix International Ltd to complete this study. IB and AM have no conflicts of interest.

SUPPORTING INFORMATION

The following additional material may be found online:

Appendix S1: Dravet Syndrome caregiver survey questionnaire items.

Appendix S2: Patient numbers in the highest and lowest strata of ranked characteristics.

Appendix S3: Seizure frequencies, frequency of emergencies, patient education, and EQ-5D-5L index scores.

Appendix S4: Current and previously taken antiepileptic drugs (full list).

Appendix S5: Patient proportions in highest and lowest strata of ranked characteristics.

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