

Association of Seizure Frequency, Co-Morbidities and Quality of Life in Dravet Syndrome in a Large Multinational Survey Cohort^T

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INTRODUCTION

- Dravet syndrome (DS) is a rare, refractory epilepsy typically involving multiple comorbidities, including motor, cognitive, and behavioral impairments of variable intensity¹
- The refractory seizures and wide scope of co-morbidities associated with this condition can be expected to result in a high impact on caregivers, affecting all aspects of their lives²

OBJECTIVES

- The aim of this study was to develop an understanding of the association between time to diagnosis, seizure frequency, management, and co-morbidities in a large survey cohort of DS patients and their caregivers in Europe and test the hypothesis that higher seizure burden in DS is associated with increased co-morbidities and lower quality of life (QoL)³

METHODS

- DISCUSS was an anonymous online survey conducted in 2016 measuring:
 - Disease severity (current seizure frequency, co-morbidities, emergencies)
 - Disease management (current and past antiepileptic drugs [AEDs], non-AED treatments, and therapy for co-morbidities)
 - Time to diagnosis
 - Quality of life (including EQ-5D-5L⁴; family, career, leisure, childcare)
- Only fully completed surveys^(a) were accepted for submission. Gate questions ensured negative responses were not probed further
- Recruitment was through email invitations to patient advocacy groups associated with the Dravet Syndrome European Federation (DSEF) and through social media
- Response frequencies were analyzed for the full cohort and by age group (infant [<2 years (y)], pre-school [2-5 y], middle childhood [6-11 y], adolescent [12-17 y], and adult [18 y and older])
- Patient characteristics were ranked by current seizure frequency, time to diagnosis (TTD), co-morbidities, and EQ-5D-5L index score and subgroups with the highest and lowest burden were defined (**Table 1**)

(a)with the exception of one question about the cost of non-pharmacological treatments.

Patient Characteristic	Maximum Score [Survey Response]	Minimum Score [Survey Response]
Tonic-clonic seizure frequency	10 [>150 in past 4 wks]	0 [none in past 3 mo]
Myoclonic seizure frequency	10 [>150 in past 4 wks]	0 [none in past 3 mo]
Partial/focal seizure frequency	10 [>150 in past 4 wks]	0 [none in past 3 mo]
Atonic seizure/drop attack frequency	10 [>150 in past 4 wks]	0 [none in past 3 mo]
Motor impairment	3 [Yes]	0 [No]
Speech impairment	3 [Yes/does not talk at all]	0 [No]
Learning impairment	3 [Yes]	0 [No]
Autism	3 [Yes]	0 [No]
ADHD	3 [Yes]	0 [No]
Motor impairment	3 [Yes]	0 [No]
Herbal medicine	2 [Yes]	0 [No]
Vitamins	2 [Yes]	0 [No]
Amino acids	2 [Yes]	0 [No]
Ketogenic diet	2 [Yes]	0 [No]
Other nutritional therapy	2 [Yes]	0 [No]
Vagus nerve stimulation	2 [Yes]	0 [No]
TTD (after the first seizure)	10 [>4 y]	0 [immediate diagnosis]
Composite Score	Maximum Score Observed	Minimum Score Observed
CSF ⁽¹⁾	39	0
Co-morbidity ⁽²⁾	18	0
Non-AED treatment ⁽³⁾	12	0

Table 1. Scoring system for patient characteristics and composite scores. (1) CSF score=tonic-clonic score + myoclonic score + partial/focal score + atonic/drop attack score; (2) Co-morbidity score = motor impairment score + speech impairment score + learning impairment score + autism score + ADHD score + other behavioral impairment score; (3) Composite non-AED treatment score = herbal medicine score + vitamins score + amino acids score + ketogenic diet score + other nutritional therapy score + vagus nerve stimulation score. Abbreviations: ADHD, attention-deficit-hyperactivity disorder; AED, antiepileptic drug; CSF, composite seizure frequency; mo, months; TTD, time to diagnosis; wks, weeks; y, years.

- For each characteristic, patient scores (TTD score, composite seizure frequency [CSF] score, composite co-morbidity score, composite non-AED score, and EQ-5D-5L index score) were ranked and patients in the highest and lowest strata were compared
- Differences between subgroups were assessed in a z test for proportions

RESULTS

Demographics

- A total of 584 fully completed surveys were submitted by caregivers (mothers 86%, fathers 12%, and other caregivers 2%) of pediatric (83%) and adult (17%) patients with DS (<1 y–48 y old, mean 10 y, median 9 y)
- Only 31% of patients aged 6–17 y attended mainstream school. The rest attended special school (57%), had home schooling (2%), or did not attend school (4%)
- The majority (92%) lived in Europe: Italy - 14%, the UK - 12%, Germany - 12%, France - 11%, the Netherlands - 10%, Spain - 10%, and Poland - 7% of the total responses

Disease Severity

- Despite broadly following clinical guidance, less than 10% of all patients were seizure-free in the previous 3 mo (**Figure 1**)

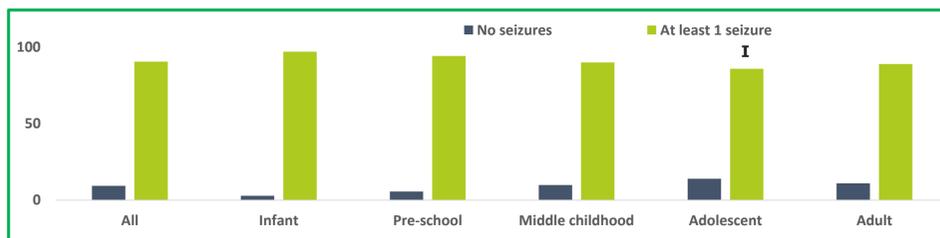


Figure 1. Seizure frequency in previous 3 mo. Statistically significant differences ($p<0.05$) in proportions are indicated (I=difference to infant group).

- Half of patients required at least one emergency admission and 46% at least one ambulance call in the past 12 mo
- Nearly all (99.6%) patients 5 y or older experienced at least one or more motor, speech, learning, or behavioral impairment. More males than females older than 2 y had a speech impairment (84% vs 76.5%, $p=0.035$), autism (40% vs 31%, $p=0.028$), and ADHD (28% vs 14%, $p<0.0001$)

Patient QoL

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

TTD

- Doctors immediately recognized DS in 45% of pre-school vs only 12% of adult patients
- In contrast, 83% of adults but only 20% of middle childhood patients not diagnosed at their first visit reported receiving a DS diagnosis over 4 y after their first seizure

Associations Between Disease Characteristics, Co-morbidities, and QoL

High and low seizure frequency burden

- Patients in the highest seizure frequency subgroup reported more co-morbidities (4.08 ± 0.97) than in the lowest (3.41 ± 1.28)
- More patients age 2 y or older in the highest seizure frequency subgroup reported a motor (83% vs 53.8%, $p<0.0001$) and speech impairment (89.4% vs 71.4%, $p<0.005$) (**Figure 2**)

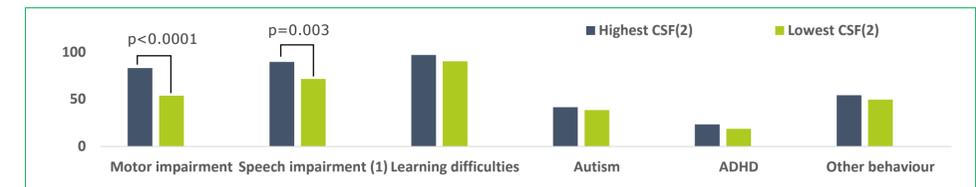


Figure 2. Percentage of patients in highest and lowest strata for the CSF score for whom the indicated co-morbidity was reported. All p-values suggesting statistically significant differences between groups are indicated. (1) Includes patients who do not talk at all; (2) Excluding infant age group. Abbreviations: ADHD, attention-deficit-hyperactivity disorder; CSF, composite seizure frequency.

- Those in the highest compared to the lowest seizure frequency subgroup more frequently reported one or more emergency admissions (56% vs 36%, $p<0.006$) or ambulance calls (55% vs 30%, $p<0.0001$) (**Figure 3**)

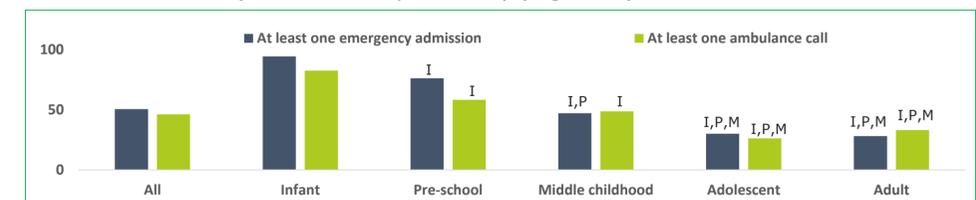


Figure 3. Percentage of age group experiencing at least one emergency admission or ambulance call in the previous 12 months. All statistically significant ($p<0.05$) differences in proportions are indicated (I, P, and M=difference to infant, pre-school, and middle childhood, respectively).

High and low QoL

- In the group with poorest QoL (lowest EQ-5D-5L index), less than 3% of patients were seizure-free vs 15% in the highest QoL group ($p<0.002$)

Long and short TTD

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

Treatment patterns

- Patients older than age 5 y using a high number of non-AED treatments tended to have a higher disease burden: patients with the highest use reported more motor (87% vs 64%, $p<0.0001$) and speech impairments (85% vs 69%, $p<0.01$) than those not using any non-AED treatments

CONCLUSIONS

- Families caring for a member with DS must manage multiple impairments in addition to epilepsy symptoms
- DS patients with a high current seizure frequency suffer from more co-morbidities, reported more emergency treatments, and have a lower QoL compared to patients with a low current seizure frequency
- Therefore, more effective antiepileptic treatment options are still needed for DS patients

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