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

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INTRODUCTION
- Dravet syndrome (DS) is a rare, refractory epilepsy typically involving multiple co-morbidities, including motor, cognitive, and behavioral impairments of variable intensity.
- 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 lives.

OBJECTIVES
- The aim of this study was to develop an understanding of the association between time to diagnosis, seizure frequency, management, and comorbidities in the 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).

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-5L index)
- Recruitment was through email invitations to patient advocacy groups associated with the Dravet Syndrome European Federation (DSEF) and through social media.
- Response frequencies were collected for the full cohort and for 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-5L index score and subgroups with the highest and lowest burden were defined (Table 1).

RESULTS

Demographics
- A total of 284 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 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 - 7%, 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)

Patient QoL
- The mean EQ-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 (Table 2).

TDD
- 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 first visit reported a DS diagnosis over 4 y after their first seizure.

Association 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 ± 0.28).
- More patients age 2 y or older in the highest seizure frequency subgroup reported a motor (83% vs 53%, p<0.001) and speech impairment (89% vs 71.4%, p<0.005) (Table 2).

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

Table 1. Scoring system for patient characteristics and co-morbidities. (1) CSF score=tonic-clonic score + myoclonic score + focal/spinal score + atonic drop attack score; (2) Co-morbidity score = motor 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 therapeutic score + usag nerve stimulus score. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; AED, antiepileptic drug; CSF, composite seizure frequency; mo, months; TTD, time to diagnosis; wks, weeks; yrs, years.

DISCUSSION
- 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 (5% vs 30%, p<0.0001) (Figure 3).

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

Figure 2. Percentage of patient groups in lowest and highest 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 score.

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

TREATMENT PATTERNS

- Patients older than age 5 y using a high number of 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 AED treatments.

CONCLUSIONS
- Families caring for a member with DS must manage multiple impurities in addition to epilepsy symptoms.
- DS patients with a high current seizure frequency suffer more from 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.

REFERENCES

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