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A European pilot study in Dravet Syndrome to delineate what really matters for the patients and families

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Abstract (199/200 words)

We aimed to identify caregivers' opinions on the outcome measures that matter in clinical trials in individuals with Dravet syndrome (DS). We conducted a prospective European multicentre study based on a 11-closed questions' survey developed by the French reference centre for rare epilepsies and DS patients' advocacy groups. Items included questions on seizures and daily life outcomes that a clinical trial on a therapy for individuals with DS should target. Statistical analyses were performed to evaluate the impact of the country of residence and of the patients' age.

The survey was answered by 153 caregivers (68%: France, 28%: Germany and 24%: Italy) for individuals with DS. Individuals with DS included 86 males (mean age of 11.4 [interquartile:7-20.4] years). Families ranked as important almost all the items proposed. However, items related to daily life had the highest rank in all 3 countries compared to items about seizures (p=0.02). Increase of individuals' age was associated with a higher age at diagnosis (ρ =0.26, p=0.02) and a less important impact of seizure duration (ρ =-0.25, p=0.005) and of the need of hospital referral (ρ =-0.26, p=0.005). These data can help tailor patient-centered outcome measures in future clinical and real-life trials for DS.

Keywords: Meaningful outcomes, PCOMs, families' expectations, meaningful change, burden of the disease

Abbreviations

AE: Adverse Event, ASM: AntiSeizure Medication, DEE: Developmental and Epileptic Encephalopathy, DS: Dravet Syndrome, ER: Emergency Room, ICU: Intensive Care Unit, PCOM: Patients-Centered Outcome Measure, PRO: Patients Reported Outcome, POM: Primary Outcome Measure, PR: PharmacoResistant, RCTs: Randomized Controlled Trials.

1. Introduction

Determining what really matters, i.e., the meaningful outcomes for the health of individuals, is a key point in clinical trials, especially for rare diseases. Indeed, rare diseases generally involve several organs with high inter-individual variability leading to great disparity in terms of clinical presentations and consequences in the daily life. The use of primary outcome measures (POMs) elaborated by practitioners might be simplistic and misrepresents the multiple facets of the impact of a disease[1]. In epilepsy, evaluation of clinical trials is mainly based on POMs targeting efficacy, like responder rate (defined as the number of affected individuals with at least 50% reduction in total seizure frequency) or the proportion of subjects who achieved seizure-free status[2–5], and safety, using incidence of adverse events (AEs) and withdrawals rate due to AEs[6,7]. However, it is important to question the meaning of these endpoints, particularly in the context of developmental and epileptic encephalopathy (DEE) characterized by major drug resistance and associated comorbidities beyond seizures. Dravet Syndrome (DS), one of the archetype of DEEs, is commonly related to pathogenic variant of *SCN1A* leading to a loss-of-function of voltage dependent sodium channel[8–12]. This DEE is associated with various degrees of intellectual disabilities, autism spectrum disorder in almost one third and behavioral disorders which incidence increases with age[8,9,13]. Several additional features are frequently reported: eating and sleep disorders, gait deterioration, dysautonomia, and a higher predisposition to infections[14–16]. Research into the impact of DS beyond seizures increased in the last years and allowed to describe DS whole phenotype based on families and practitioners reports[14,15,17–20]. In addition, the burden-of-illness of individuals with Dravet syndrome also have a high impact on the caregivers. Compared to caregivers of individuals with difficult-to-treat epilepsy, caregivers of DS had higher depression scores and were more likely to change their employment status, including leaving their job[21].

The aim of this study is to explore the domains that really matters for individuals with DS and their families emphasizing that a therapy targeting these domains would have a positive meaningful impact on their outcome.

2. Methods

2.1. Survey development

We developed, with three national patients' advocacy groups of DS in Europe ("Alliance Syndrome Dravet" in France, "Dravet-Syndrom e.V." in Germany and "Dravet Italia Onlus"), a 11-closed questions survey based on our preliminary surveys[17,22] and other literature reports[14,15,18]. This survey explored different items related to current seizures (frequency, duration, seizures requiring rescue therapy, seizures needing of referral to emergency room (ER) or intensive care unit (ICU)) and to daily life aspects (sleep, eating disorders, language, motor skills, daily activity, behavior, communication, and interaction) using a Likert's scale from 1 to 5 (not important at all = 1, not important = 2, neutral = 3, important = 4 and highly important = 5).

2.2. Participants

This study was a prospective cohort study with convenience sampling. The survey was filled during annual associations meeting (France and Germany) or shared online with families for a period of 6 weeks (may to June 2019, Italy). For every individual with DS, a unique caregiver completed the survey. Written informed consent to participate in this study was provided by the participants. This study was approved by the ethics committee of our institution (Necker Hospital, APHP).

2.3. Statistics

Results are expressed as the average ± standard deviation in case of Likert's scale data and as median [25^{th}-75^{th} percentile] otherwise. To study the impact of countries on the responses, we used one-way ANOVA in case of homogeneity of variance (Levene test) . Otherwise, we used a more robust test called Brown Forsythe test with the same factors[23]. Bonferroni post-hoc tests after ANOVAs or Tamhane post-hoc tests after Brown Forsythe tests were then applied in case of significance. For qualitative data, khi^2 tests were used to study the presence or the absence of significant difference between the different countries. We correlated different quantitative answers to affected individuals' age using Spearman's rank correlation coefficient (Rho) coefficients. To illustrate the possible correlation with age, we presented the data in relation to three age groups: <6 years, 6-12 years and >12 years.

3. Results

A total of 153 surveys were filled by parents with 96.5% of response rate (missing data: 81/2295). Table 1 summarized the characteristic of the population. There was no significant difference between the three countries regarding demographic characteristics. Concerning the age at diagnosis, a significant correlation with patients' age was identified (Table 2, ρ =0.26, p=0.002). A lower age of diagnosis was associated with the younger age group.

Families ranked as important almost all the items proposed (Table 2). They rated similarly communication, sleep, behavior, daily activity, and motor skills (4.05+/-1.34) compared to lower scores for items related to seizures (3.96+/-1.22, p=0.02) (Figure 1A). For items regarding seizures, the highest score was achieved for seizure frequency (4.25+/-0.78) followed by seizure duration (4.15+/-1.11).

Caregivers in the three countries agreed on the importance with a descending order for sleep, communication, behavior, daily activities, motor skills, language, seizure duration, seizures requiring rescue therapy, and seizures necessitating referral to ER or ICU. In relation to age, only seizure duration and the need of referral to ER or ICU were negatively correlated with individuals' age, i.e., the highest scores were reported in the youngest individuals (ρ =-0.25, p=0.005 for seizure duration and ρ =-0.26, p=0.005 for seizure with referral to ER or ICU) (Figure 1C). There were few significant differences in the evaluation of the different items according to countries (Figure 1B). These differences were mainly about seizure frequency, which had higher score in Italy compared to France (4.57+/-0.55 in Italy and 4.03+/-0.77 in France, p= 0.0005, Germany: 4.36+/-0.72, p=ns) and those of eating disorders, which was higher in France compared to Germany (3.89+/-0.8 in France and 2.88+/-1.45 in Germany, p=0.004, Italy: 3.68+/-0.95, p=ns).

4. Discussion

Caregivers of individuals with DS across 3 EU countries expressed their needs for therapies that improve behavior, communication, sleep, daily activities, motor skills and language beyond their efficacy on seizures. These are the first direct results from families across 3 countries in Europe supporting smaller studies hypothesis[17,22].

In order to improve the evidence of efficacy in clinical trials, Food and Drug Agency in 2009 and the European Medicines Agency in 2010[6,24], have encouraged the Patient Reported Outcomes (PROs) as self-assessment of affected individuals' health status, and validated it as a possible secondary endpoint to complement the evaluation of clinical

trials. The use of PROs in clinical trials, defined as "any report coming directly from patients, without interpretation by physicians or others, about how they function or feel in relation to a health condition and its therapy"[25], has increased significantly since 2005[26–28]. The development of specific PROs for DS may seem anecdotic because there are generic PROs, such as the health-related quality of life. However, generic PROs are not accurate enough to assess the quality of life of individuals with rare diseases and intellectual disability[29]. This is why, given the lack of standardized PROs dedicated to individuals with rare diseases, the International Rare Diseases Consortium has decided to set up the Patient-centered outcome measures (PCOMs) initiatives[30]. Determining the domains that are important to individuals with DS and their families is the first step of PRO development[31,32].

Our study showed that different needs can emerge in individuals with DS. In addition, the major needs can vary with age[12]. These results are correlated to the 3-phases of natural history of individuals with DS[9]. In the first two phases, seizures are at the forefront. During the first 15 to 18 months, affected individuals present seizures triggered by fever often prolonged evolving to status epilepticus. Till around 5-6 years, individuals show different types of seizures as atypical absences, focal and tonic seizures with frequency drug resistant epilepsy in addition to the emergence of developmental slowing and behavioral disorders. Finally, in the third phase, seizures often decrease in term of frequency[9,18] and might become nocturnal and brief[33]. Intellectual disability and behavior problems move to the front scene with the families struggling for the education and rehabilitation special needs[19]. In this survey, families rated a decreasing need with age for a therapy targeting seizures' reduction and referral to ER or ICU. This data can be interesting in designing age related outcomes as ER and ICU needs are significantly more frequent in infants and pre-school children with DS compared to adolescents and adults[18]. However, the need of treatment to reduce seizure frequency and of the need to rescue treatment remains stable with age highlighting the persistence of high drug resistance throughout life[34]. Refining the age-related outcomes in DEEs might be the first step toward a precision design of CTs in such rare diseases.

Another key finding of this study is the age at diagnosis of affected individuals (18 [12-33.6] months), showing a significant decrease in the age of diagnosis in the youngest individuals. These data confirm the improvement in the early diagnosis of DS over the

last years[18,35,36]. Importantly, this earlier diagnosis age might question a younger age of inclusion in RCTs where the median age of inclusion in recent trials was between 7.6 and 9.3 years[2,4,5,37,38]. An earlier therapy can be a clue for a better neurodevelopmental outcome[39].

Some limitations must be highlighted. This is a cross-sectional study to assess the impact of age on caregivers' expectations regarding what should treatment target. A longitudinal study will be probably more efficient to identify the evolution of caregivers' perspectives. However, to date, there is no study with this design probably due to its complexity and the rarity of this pathology. The convenient sample of this study might have led to a selection bias. Indeed, the identification of affected individuals through national families' associations might encourage the recruitment of families with specific profile and individuals with possibly more severe phenotypes. This survey is not accompanied by a qualitative study of the patients' opinions using for example Delphi methodology[40], as we previously reported in DS[17,22]. However, the design of this study is complex, time consuming, requires the definition of experts and does not allow us to have as large a population as in this study[41].

In conclusion, this study highlights the domains that a therapy in development for DS should target in addition to seizures. target non-epileptic features. The next step would be to develop measurable and reproducible scales adding these items to seizures frequency as outcome measures for coming trials. For more accuracy and precision, an age related approach might refine these measures. This shift in our thinking in developing outcomes measures with more participatory approaches is urgent to establish in the era of gene therapy. Indeed, these therapies based on correction of the underlying genetic defect aim to rescue the genetic defect and to change the present path of affected individuals achieving disease modifying therapies beyond seizures decrease[39].

Declarations

1 Competing interests

The authors declare that they have no competing interests.

2 Funding

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4 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.

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	Total	France	Italy	Germany	*p*
N (%)	153	73 (47.7%)	37 (24.2%)	43 (28.1%)	
Sex (m/f)	86/67	41/32	19/18	26/17	*ns*
Current age (y)	11.4 [7 - 20.4]	11 [5-20.5]	10.8 [6.6-17.7]	12.8 [9-23.8]	*ns*
Age at seizure onset (m)	5 [3.5 - 6.5]	5 [3.5-7]	5 [3.5-6]	5 [3-6]	*ns*
Age at diagnosis (y)	18 [12 - 33.6]	13.2 [9.6-27.6]	18 [12-72]	21.6 [13.2-33.6]	*ns*

Table 1: Demographic characteristics

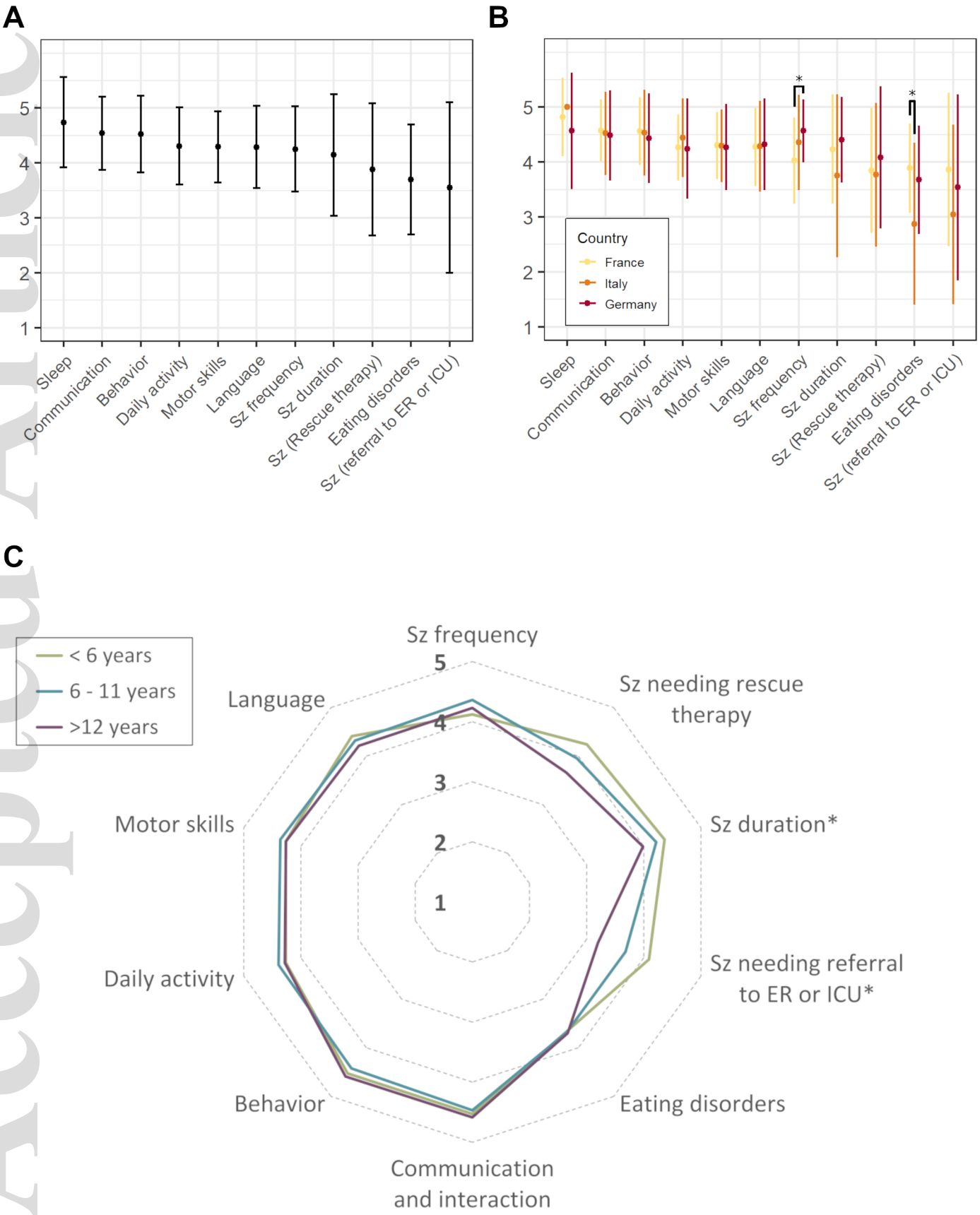
	Tot	<6 years	From 6 to 12 years	>12 years	Spearman's ρ	*p*
Countries (France/Italy/Germany)	73 / 37 / 43	22 / 3 / 9	19 / 14 / 14	32 / 20 / 20	-	-
Current age (year)	11.4 [7 - 20.4]	4 [3.3 - 4.5]	8.8 [8 - 10.7]	21 [16.3 - 26.5]	-	-
Age at seizure onset (month)	5 [3.5 - 6]	5.5 [4 - 6.8]	5 [3 - 6.7]	4 [3.5 - 6]	ns	ns
Age at diagnosis (month)	18 [12 - 33.6]	13.2 [9.6 - 21.6]	18 [12 - 27.6]	20.4 [12 – 60.5]	0.26	0.002
Behavior	4.52 +/- 0.7	4.55 +/- 0.64	4.43 +/- 0.85	4.58 +/- 0.56	ns	ns
Communication and interaction	4.54 +/- 0.67	4.55 +/- 0.71	4.47 +/- 0.72	4.59 +/- 0.51	ns	ns
Daily activity	4.31 +/- 0.7	4.24 +/- 0.75	4.39 +/- 0.61	4.28 +/- 0.71	ns	ns
Motor skills	4.29 +/- 0.65	4.24 +/- 0.7	4.36 +/- 0.64	4.26 +/- 0.57	ns	ns
Language	4.29 +/- 0.75	4.39 +/- 0.81	4.32 +/- 0.75	4.21 +/- 0.61	ns	ns
Sleep	4.27+/-0.83	4.52+/-0.85	4.2+/-0.96	4.21+/-0.51	ns	ns
Sz frequency	4.25 +/- 0.78	4.12 +/- 0.87	4.36 +/- 0.74	4.24 +/- 0.6	ns	ns
Sz duration	4.15 +/- 1.11	4.38 +/- 1.16	4.22 +/- 1.09	4 +/- 0.99	-0.25	0.005
Sz (Rescue therapy)	3.88 +/- 1.21	4.25 +/- 1.31	3.96 +/- 1.23	3.67 +/- 0.79	ns	ns
Eating disorders	3.7 +/- 1	3.65 +/- 1.17	3.68 +/- 0.88	3.72 +/- 0.73	ns	ns
Sz (referral to ER or ICU)	3.55 +/- 1.55	4.09 +/- 1.65	3.68 +/- 1.49	3.22 +/- 1.26	-0.26	0.005

Table 2: Impact of age on the different domains.

The statistical impact of age was identified using Spearman's rank test and illustrated using three groups of affected individuals, namely <6 years, between 6 and 12 years and > 12 years.

Figure 1: Caregivers' opinions (Likert's scales from 1: not at all to 5: very important) about the domains that a therapy should improve for their children with Dravet syndrome (A), same results according to the 3 countries (B) and to the different age groups (C).

Sz: seizure



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