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The European patient with Dravet syndrome: Results from a parent-reported survey on antiepileptic drug use in the European population with Dravet syndrome

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ABSTRACT

Dravet syndrome is a rare form of epilepsy largely refractory to current antiepileptic medications. The only precedents of randomized placebo-controlled trials in Dravet syndrome are the two small trials that led to the approval of stiripentol. With the arrival of new clinical trials for Dravet syndrome, we sought to determine the characteristics of the patient population with Dravet syndrome in Europe today, which has possibly evolved subsequent to the approval of stiripentol and the ability to diagnose milder clinical cases via genetic testing. From May to June 2014, we conducted an online parent-reported survey to collect information about the demographics, disease-specific clinical characteristics, as well as current and past use of antiepileptic medications by European patients with Dravet syndrome. We present data from 274 patients with Dravet syndrome from 15 European countries. Most patients were between 4 and 8 years of age, and 90% had known mutations in *SCN1A*. Their epilepsy was characterized by multiple seizure types, although only 45% had more than 4 tonic–clonic seizures per month on average. The most common drug combination was valproate, clobazam, and stiripentol, with 42% of the total population currently taking stiripentol. Over a third of patients with Dravet syndrome had taken sodium channel blockers in the past, and most had motor and behavioral comorbidities. Our study helps define the current typical European patient with Dravet syndrome. The results from this survey may have important implications for the design of future clinical trials that investigate new treatments for Dravet syndrome.

1. Introduction

Severe myoclonic epilepsy of infancy, also known as Dravet syndrome, is an epileptic encephalopathy that presents during the first year of life and affects 1 in 20,000 to 40,000 people [1–3]. Patients who have Dravet syndrome display multiple seizure types including tonic–clonic, myoclonic, absence, and focal seizures. A characteristic of this syndrome is that seizures can be provoked by fever and visual stimuli and can also lead to status epilepticus [1–3]. In addition to epilepsy, Dravet syndrome is associated with cognitive delays, behavioral disorders, and an elevated risk of sudden death [1–3].

Although traditionally diagnosed according to clinical criteria, genetic mutations are known to be a major cause of Dravet syndrome [4,5]. Mutations in the sodium channel-encoding gene *SCN1A* account for the majority of Dravet syndrome cases [6,7] and have also been found to cause milder forms of epilepsy, migraine, and autism without epilepsy [8–10]. Mutations in *SCN1B* [11], *SCN2A* [12], and *GABRG2* [13] are also known causes of Dravet syndrome, with additional genes such as *PCDH19* and *CHD2* found to cause Dravet-like phenotypes when mutated [14,15]. The discovery of these genes represents a major scientific advance, making it possible to perform genetic testing of patients with suspected Dravet syndrome that leads to the identification and diagnosis of milder or clinically "atypical" Dravet syndrome cases [5,16].

Despite these major advances with regard to the genetic causes of this rare disease, Dravet syndrome remains largely pharmacoresistant to antiepileptic drugs [17]. After more than 30 years since its initial description, only one drug has been approved for the treatment of Dravet syndrome (stiripentol, marketed by Biocodex as Diacomit® [18,19]). There remains, therefore, a high need for new therapeutics able to better control seizures as well as to preserve or improve cognition and behavior in Dravet syndrome.

Unprecedentedly, two new experimental drugs are expected to start clinical trials for Dravet syndrome in Europe between 2014 and 2015: cannabidiol, developed by GW Pharmaceuticals and INSYS Therapeutics, and fenfluramine, developed by Brabant Pharma. To date, all three have obtained orphan drug designation for Dravet

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syndrome by the US Food and Drug Administration while fenfluramine and cannabidiol developed by GW Pharmaceuticals have also obtained the designation as an orphan drug by the European Medicines Agency.

The only precedents of randomized placebo-controlled trials in Dravet syndrome are the two trials in France and Italy that led to the approval of stiripentol as an adjunctive treatment in Europe (2007), Canada (2012), and Japan (2012). The two studies combined involved 65 children between 3 and 18 years of age with Dravet syndrome and compared the efficacy of stiripentol with placebo when added to the children's existing treatment with valproate and clobazam. The use of a very homogeneous patient population made it possible for both trials to be strongly positive despite the small number of patients.

With the arrival of new clinical trials for Dravet syndrome, we sought to determine the characteristics of the patient population with Dravet syndrome in Europe today, which has possibly evolved subsequent to the approval of stiripentol and the ability to diagnose milder clinical cases through genetic testing. This parent-reported survey was set up to assess the most relevant demographic and disease-specific clinical characteristics, to collect information on the current and past use of antiepileptic medications by this population, and to try to define the current "typical European patient with Dravet syndrome".

2. Methods

2.1. Study design, assessment, and patient selection

The study was an international, voluntary, anonymous, single-assessment, web-based survey administered by the Dravet Syndrome Foundation Spain (http://www.dravetfoundation.eu/drugs-survey/, see Supplemental materials). It was distributed by European organizations for patients with Dravet syndrome through the Dravet Syndrome European Federation. The study took place from May to June 2014.

The study population consisted of patients with Dravet syndrome identified by patient organizations through their affiliated distribution lists. The questionnaire was developed in Spanish and English. Because of the cognitive state and generally low age of the identified patients with Dravet syndrome, the survey was completed by parents or caregivers. No ethics approval was required because of the anonymous nature of the study.

2.2. Data analysis

The data entered by responders though the webform were automatically collected in an Excel sheet. Both the Spanish and English versions of the survey were collected in a single file. A total of 278 entries from 15 countries were registered during the study period. After eliminating 4 duplicates, a total of 274 entries were used for the study. Data were numerical (e.g., age and number of seizures) or binary (e.g., having taken or not a specific drug) with the exception of two textboxes habilitated for responders to input additional medications not prespecified in the survey. The content of these boxes often corresponded to actual antiepileptic drugs that the responders failed to recognize in the prespecified list because of brand name variations between countries. These were manually curated to populate the appropriate cells in the file. Data are reported as total count or percentage for the different categories without performing any statistical analysis. Because clinical trials often have an inclusion criterion of minimum 4 tonic–clonic seizures per month on average, we analyzed antiepileptic drug use both for the total population and for this trial subpopulation.

3. Results

3.1. Demographics and clinical characteristics

Two hundred seventy-four patients from 15 European countries were included in our study (Table 1). One hundred fifty-seven patients were male and 117 female. The highest numbers of responses were from Spain, Netherlands, Italy, Germany, and France (Table 1). These countries have strong patient groups and/or physicians and a relatively high number of identified patients. The low number of UK patients in this cohort is due to the UK patient organizations not being yet affiliated with the Dravet Syndrome European Federation, which was used as the distribution channel for the survey, and has been described by Brunklaus et al. [20]. Genetic analysis was reported for 262/274 patients (Table 1). Of these, the large majority (246/262) had a confirmed mutation in *SCN1A*, accounting for 90% of the total population. Although the survey did not ask for mutations in other genes (see survey questions in Supplemental materials), data from the Spanish registry of patients with Dravet syndrome indicate that the 10% *SCN1A* negative population includes patients with mutations in *PCDH19*, *SCN1B*, and *SCN1B*, as well as patients with unknown genetic causes (unpublished data), with many of the patients carrying mutations in *PCDH19* choosing to become affiliated with specific patient organizations. Patients were aged between 1 and 47 years, with the largest group aged 4 to 8 years (Table 2). The adult subpopulation accounted for 15% of the responders (42/274).

Dravet syndrome is characterized by multiple seizure types, and a minimum of convulsive seizures per month is usually an eligibility criterion for participation in clinical trials. We, therefore, asked responders to list the average number of seizures per month that patients had, taking as a reference the last 6 months (Table 3). The most frequent seizure type was tonic–clonic, with 45% of the population reporting more than 4 seizures per month, followed by myoclonic, absence, partial, and atonic seizures (Table 3). By countries, the percentage of patients with Dravet syndrome with more than 4 tonic–clonic seizures per month was 26% for France, 67% for Germany, 56% for Italy, 54% for Netherlands, and 36% for Spain. A particularly dangerous type of seizures in patients with Dravet syndrome is status epilepticus, which can lead to mortality. We, therefore, asked responders about the number of times that the patients had been admitted to the emergency room as a result of status epilepticus during the previous 12 months (Table 4). In both the total population and the subpopulation with more than 4 tonic–clonic seizures per month, one-third of the patients had one or more status

Table 1
Country and genetic type of the survey population.

Country	Patients	*SCN1A* mutation		
		Yes	No	Not determined
Austria	3	2	1	0
Azerbaijan	1	1	0	0
Belgium	7	7	0	0
Czech Republic	1	1	0	0
France	22	15	3	4
Germany	30	27	0	3
Italy	50	44	5	1
Moldova	1	1	0	0
Netherlands	54	49	4	1
Poland	13	13	0	0
Portugal	10	10	0	0
Romania	10	9	0	1
Spain	59	54	3	2
Switzerland	11	11	0	0
United Kingdom	2	2	0	0
Total	274	246	16	12

Table 2
Age distribution of the survey population.

Age bands	Patients	%
>4	39	14
4–8	104	38
9–13	52	19
14–17	37	14
≤18	42	15
Total	274	100