Ascertaining the epidemiology, patient flow and disease management for Dravet syndrome in Spain

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Introduction. Dravet syndrome (DS) is a rare, drug resistant epilepsy that starts very early in life with febrile seizures followed by cognitive impairment and diverse seizure types.

Aim. To generate evidence on the epidemiology of DS, its diagnosis, patient-flow, treatment and unmet needs from the perspective of Spanish experts.

Development. A two-round Delphi study involving 19 physicians was conducted. Questionnaires were based on literature review and validated by clinical experts. Consensus was reached when topics were subject to routine clinical practice and individual experience, or the coefficient of variation among answers was ≤ 0.3. The estimated number of new DS patients is 73 per year. Prevalence is estimated to be between 348-540 patients. DS is mostly diagnosed in children. Survival varies from 5 to 60 years. There is no standardised follow-up of patients beyond the age of 18 and mortality rates are uncertain. No standard guidelines exist for diagnosing or treating DS. It takes 9 to 15 months to confirm the diagnosis and genetic testing is unevenly available. Valproic acid, clobazam, stiripentol and topiramate are commonly used. Poor efficacy and safety are the main reasons for treatment switch.

Conclusions. The epidemiology of DS in Spain is not well known and several areas of unmet needs still exist. Experts' views offer a starting point for further research into the reality of DS in Spain. Epidemiological studies, consensus criteria, easy access to genetic testing, treatment options, training and research into quality of life aspects are highly needed.

Key words. Consensus. Diagnosis. Disease management. Epidemiology. Myoclonic epilepsies. Spain.

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Introduction

Dravet Syndrome (DS) is a severe epileptic encephalopathy characterised by intractable seizures that begins in infancy (onset during the first year of life) and regarded as one of the most serious genetic epilepsies of childhood [1]. DS is associated with mutations in the sodium channel α_1 subunit gene *SCN1A*.

Most frequently, DS children start to develop febrile or afebrile seizures that evolve towards refractory mixed seizure types, psychomotor retardation, ataxia, and hyperkinesia after 1 to 4 years of age. The key feature that characterises DS is fever sensitivity, although photosensitivity and pattern-sensitivity have also been seen. The prognosis is unfavourable in most cases, as seizures become drug-resistant and persist with many patients suffering also from progressive motor and cognitive impairment.

DS is a rare disease that represents about 3% to 6% of epilepsy cases in infancy, and its incidence is less than one per 40,000 infants [2]. Premature mortality is high, and it is mainly related to the severity of the epilepsy. Sudden and unexpected death (SUDEP) appears in nearly half of the cases [3]. It has been suggested that DS is probably underdiagnosed in adults with treatment-resistant epilepsy who present ataxia, a characteristic crouched gait, and Parkinson's symptoms [4]. Clinical diagnosis is confirmed in approximately 80% of cases by a *SCN1A* genetic test [2].

In Spain, most published works focus on describing the clinical features of the disease [5-8]. There is little information available on its epidemiology, management and on disease burden. The aim of this study was to generate evidence on the prevalence and incidence, use of resources, perceived health-related quality of life (HRQoL), patient-flow, disease treatment and unmet needs for DS patients from the perspective of experts. It pretends to be a starting point to foster future research on the disease.

Methodology

The study was based on the Delphi method [9], considered a reliable alternative for determining expert

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group consensus over a defined healthcare problem where there is little or no definitive evidence and where opinion becomes relevant [10-12]. A two-round Delphi consultation was used which took place during November and December 2016.

The questionnaire used in the first round was based on an extensive review of the literature. Its contents were previously validated (via telephone interviews) by a group of three Spanish expert scientific leaders. The questionnaire contained 29 questions addressing the epidemiology (n = 8), use of resources over one year (n = 3), health related quality of life (n = 2), patient flow (n = 11), patient treatment (n = 4) and unmet needs (n = 1) on the management of DS within the Spanish healthcare system. Questions related to both the paediatric (≤ 18 years old) and the adult (> 18 years of age) population with DS.

The questionnaire used in the second round was based on the responses provided during the first round and comprised only those items where consensus was needed. It included six questions that focused on estimates of the prevalence and incidence of DS in Spain; estimated survival of patients by age groups; time needed to reach a definitive diagnosis; current lines of treatment, and most important unmet needs for DS patients in Spain.

Participants were asked to respond to all questions from a clinical practice perspective and personal experience. The results from the two rounds of consultation were consolidated and validated through an Advisory Board face to face meeting with eight clinical experts that took place in June 2nd 2017.

Literature review

An extensive review of the literature was performed to identify epidemiology, patient flow and best practice evidence for managing DS in Spain. PubMed up to July 2016 was searched for English-language publications. Grey literature as well as reference lists from reviewed publications were also screened to identify additional papers given the paucity of publications identified.

Articles were included if they defined or described appropriate epidemiological, clinical or disease management information related to DS. Articles discussing specific molecular or genetic findings were excluded. Information from relevant publications was extracted and used to develop consensus questions used to build the questionnaire for the first Delphi consultation round. A subgroup of three experts from the panel formed an advisory group that assessed and provided feedback on the literature review findings, information extracted and on the final content of the questionnaire.

Delphi panellists

Panel members were identified from the most renowned hospitals and services for DS care operating in Spain [13-15]. Seven out of the seventeen autonomous communities (Andalusia, Aragon, Castile and Leon, Catalonia, Madrid, Navarra and Valencia) and twelve out of the forty biggest public hospitals existing in Spain were represented by the panel members. Two were paediatric hospitals –Hospital Niño Jesús (Madrid) and Hospital Sant Joan de Déu (Barcelona)– and one of them –Clínica Universidad de Navarra (Pamplona)– focused particularly in caring and researching into DS. Given the rarity of the condition, it was paramount to contact highly specialised, knowledgeable professionals as well as guaranteeing the regional representation to obtain a comprehensive, cross-country depiction of the situation.

Panellists were selected based on their clinical and research expertise in the evaluation and treatment of patients with the disease and included 19 physicians: nine neuro-paediatricians/epileptologists, nine neurologists/epileptologists and one primary care physician.

Consensus definition

Consensus was built from the feedback provided by participants from the two Delphi consultation rounds. Consensus was considered to have been reached when topics were subject to routine clinical practice and individual experience, or if the coefficient of variation [16] among answers was ≤ 0.3. The coefficient of variation is the ratio of standard deviation of a competency area to its corresponding mean among the panellists' answers [17]. A small coefficient of variation value was an indication that the data scatter or variation compared to the mean was small.

Advisory board

The study advisory board was composed of seven neuro-paediatricians and three neurologists (all were epileptologists) working in referral DS hospitals in Spain. They met in June 2017 to validate the Delphi initial findings, to discuss and to agree on a common view on issues for which consensus had not been achieved related to the epidemiology, re-

source use, patients' HRQoL, patient flow, disease management and unmet needs.

Results

All 19 panel members participated in the first consultation round while 18 panellists, excluding one neuropaediatrician, took part in the second round. The perspective adopted to answer the questionnaires was always that of usual practice of experts in Spain.

Epidemiology of Dravet syndrome in Spain

In order to establish the prevalence and incidence data of DS in Spain, experts in the advisory board agreed to use a range between the lowest and the highest number of patients reported in the bibliography [16,18-20], and to extrapolate the results to the Spanish population using the National Institute of Statistics [21] data. The estimated total number of new DS patients per year is 73: 50 individuals in the paediatric population and 23 in the adult population. The yearly incidence of DS varies between 1/15,700 and 1/40,000 patients (equivalent to 10-26 DS patients every year) in Spain. The average incidence rate among paediatric and adult patients is 1.1 cases and 0.5 cases per million inhabitants, respectively.

Current annual prevalence is estimated at approximately 348-540 DS patients. A total of 116 patients, 91 paediatric and 25 adult patients with a known diagnosis of DS are cared for by the Delphi participants.

DS is mostly diagnosed in children (77.4% vs 22.6% adults, average). A total of 18 children and 11 adults were diagnosed during 2016 with most physicians diagnosing one or two patients, on average, each year. Most paediatric patients (58.6%) and a slightly smaller proportion of adults (48.5%) were male. An underdiagnosed rate of 60% in adults and of 20% in children is estimated by the experts.

Participants' estimates of survival vary from 5 to 60 years, based on the individual experience. There is no standardised follow-up of paediatric patients beyond the age of 18 and mortality rates are uncertain since follow up of adults is inconsistent amongst specialists.

Health related quality of life in Dravet syndrome patients

Several dimensions of the patients' HRQoL are affected by DS according to the panellists' opinion. Pain and discomfort as well as anxiety and depression are the factors most commonly perceived as contributing to HRQoL deterioration in children and adults. A specific questionnaire with an appropriate mixture of qualitative and quantitative dimensions to capture the problem of DS patients is missing, and no HRQoL questionnaires are administered to DS patients in usual clinical practice.

Disease management and use of medical resources

In general, children with DS tend to make a greater use of medical resources than adults over a year (emergency department: 7 vs 3; neuro-paediatricians: 5 vs 2; primary care: 7 vs 4; neurologists: 4 vs 5; rehabilitation: 5 vs 4; psychologists: 6 vs 4, and speech therapists: 8 vs 5 visits on average.

Some adults are followed up by neuro-paediatricians, according to panellists. Paediatric patients are admitted into hospital more frequently (4 times/patient/year on average) than adult patients (1-2 times/patient/year), especially during the first four years of life.

Patient flow

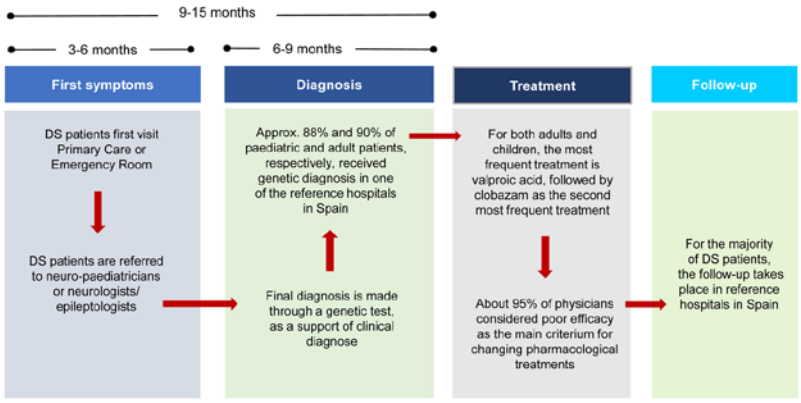
According to the panellists' opinion, more than a third of children (36.0%, SD: 30) and almost half of adults (45.1%, SD: 40) received a wrong diagnosis before confirmation of DS. It might take about 9 to 15 months to confirm the diagnosis of DS (Figure). While the average time between the emergence of the first symptoms of disease and a referral to a neurologist might range between 3 to 6 months (SD: 7; range: 0-24), confirmation of diagnosis might take an extra, 6 to 9 (average) months (SD: 3; range: 1-12).

More than a third of children are referred to the paediatric neurologist for diagnosis by primary care (37.3%) or emergency care (30.0%) paediatricians from the same healthcare area. Diagnosis is achieved through a combination of clinical and genetic testing, with the latter used to confirm the former.

Genetic testing to confirm the diagnosis of DS has been offered in Spain since 2003. Significant inequalities exist in its availability at regional level and amongst public and private centres. While within the private sector, test results are ready within a month, in the public sector it can vary between 3 and 6 months.

Clinical diagnosis criteria are well defined [22], but a variety of opinions existed among experts on their applicability. No standard clinical guidelines exist for DS in Spain, although some protocols are in place in certain hospitals.

Figure. Dravet syndrome patients' flow in Spain.



Patients' follow-up takes place in any hospital with a paediatric neurology unit. However, the majority of patient follow-up takes place in tertiary hospitals. To date, there are no specific reference centres, units or services for DS within the Spanish National Healthcare System (NHS). Clínica Universidad de Navarra (Pamplona), a private hospital, has a specific unit dedicated to Dravet within its Paediatric Neurology department, with experience in treating more than 60 patients including some referrals from the NHS.

Disease treatment

The most common pharmacological therapies used to treat DS in either children or adults include valproic acid, clobazam, stiripentol and topiramate, alone or in combination. Very few patients respond well to monotherapy and a combination is usually prescribed. Treatment with stiripentol requires valproic acid and clobazam combination therapy if tolerated [23]. Combinations vary based on clinical response and on individual patient's needs.

While the most important objective of treatment is lengthening the interval between seizures, current therapies are specifically indicated for seizure frequency reduction only and not the lengthening of this interval. Minimising the chances of convulsive and non-convulsive status with the least possible adverse effects and to improve patients' HRQoL are essential purposes of therapy.

The frequency, severity and persistence of seizures are common criteria for establishing the efficacy of treatments in children and adults. Poor efficacy, defined as the sustained repetition of seizures in a year, is the main reason for switching pharmacological treatments in paediatric patients. Safety issues (42% vs 37%) are also frequent causes of treatment failure and switch in children and adults.

Unmet needs

Experts agreed that more treatment options with a demonstrated efficacy to control the disease are highly needed for both the paediatric and the adult populations with DS in Spain. Easy access to genetic testing, consensus on diagnosis and disease management criteria, epidemiological studies, advanced treatment research and specific training of healthcare professionals are extensively required by study participants. A specific HRQoL questionnaire is also desirable to inform about the true burden of the disease for patients.

Conclusions

This is the first study conducted to unveil the views of experts on the epidemiology, disease burden, management and unmet needs for patients with DS in Spain. Their views, based on their experience from usual clinical practice, provide a great deal of validity to the findings.

Experts' estimates of DS incidence and prevalence are in line with findings reported in other studies with some differences explained by the differing methods applied [18,24]. No previous and reliable data on the incidence and prevalence of the disease in Spain are available to contrast or analyse its trends in the population [25]. The creation of registries within countries and the collaboration of registries at the European level, based on consensus, synergies and shared criteria is an initiative proposed to facilitate accounting for rare diseases, such as DS epidemiology, risk factors, potential underlying pathophysiological mechanisms and treatment opportunities [26].

A confirmatory diagnosis of DS can take between 6-9 months in Spain [22]. Results from other studies on children with rare diseases show that delayed or wrong diagnosis is frequent [27,28]. Anxiety, loss of confidence, frustration, fears of disease progression and wrong treatments are common consequences. In many cases, parents acknowledge that key reasons for diagnostic delays are lack of knowledge about the disease among health professionals, lack of symptom awareness and difficulties accessing tests [29].

Once diagnosed, it is expected that the flow of patients within the healthcare system will vary greatly depending on the characteristics of the system, on its organization and on the resources being available. However, lost to follow up of the adult population is a major problem in Spain. Report from other studies show that although multiple epileptic seizures types tend to become less frequent and less severe after childhood, generalized convulsive seizures tend to persist in almost all of the patients together with developmental delay/learning disability, language impairment, and some personality disorder which make dependency in adulthood nearly constant [30]. Altogether, these data imply that the truly humanistic burden of DS is largely unknown in Spain, as in other countries [31].

Treatment lines described by experts are coincident treatment choices described by experts are in alignment with recent findings from a European survey conducted amongst parents of DS children [32]. The most common drug combination are valproate, clobazam and stiripentol. However, many patients remain uncontrolled despite such multiple therapies. As in many other rare diseases, carrying research into DS treatments is challenging due to the rarity and geographical dispersion of patients, rapidly evolving scientific knowledge, requiring the revision of therapies and the definition of a significant treatment effect, amongst many others [33]. Despite many years of research, DS is still a poorly treated condition.

HRQoL is greatly compromised by DS. Several studies found that the cognitive, physical and psychosocial health of DS children is particularly deteriorated while domains related to daily motor activities, speech and communication, are equally affected [34]. HRQoL deterioration as well as poor social and school function of children has been directly related to parents' low satisfaction with life reflecting the negative repercussion of DS on the family life [35,36].

Seizure freedom significantly improves HRQoL and this is one of the main reasons for seeking the longest possible time free of seizures in DS patients [29,34]. In line with experts' perception, early and long-term seizure freedom improves both social adjustment and occupational integration as well as HRQoL. Individuals with high frequency of seizures suffer from more comorbidities, report more emergency treatments, and have worst HRQoL [22].

Most limitations of this study are inherent to its design based on the opinion of experts which is the weakest level of evidence and that requires the development of further studies with more robust designs. Nevertheless, it provides a view based on the experience coming from usual practice on a rarely studied clinical condition. Complementary and highly valuable information on the profile and overall clinical characteristics of patients, such as median age at seizure onset, median age at diagnosis, prevalence of intellectual disability, other neurological deficits or the efficacy of therapies to reduce seizures in clinical practice was not collected in this study.

Specific training, agreed criteria for diagnosis and treatment, clinical guidelines and care pathways, innovative therapeutic alternatives, epidemiological studies and patient registries for follow up information are highly needed in Spain if DS patients are to benefit from future initiatives.

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Determinación de la epidemiología, el flujo de pacientes y el tratamiento del síndrome de Dravet en España

Introducción. El síndrome de Dravet (SD) es una epilepsia rara y resistente a los fármacos que comienza en etapas muy precoces de la vida con convulsiones febriles, seguidas de deterioro cognitivo y diversos tipos de crisis epilépticas.

Objetivo. Generar datos objetivos sobre la epidemiología del SD, su diagnóstico, el flujo de pacientes, el tratamiento y las necesidades no cubiertas desde el punto de vista de expertos españoles.

Desarrollo. Se efectuó un estudio Delphi de dos rondas en el que participaron 19 médicos. Los cuestionarios se basaron en una revisión de la bibliografía y fueron validados por expertos clínicos. Se alcanzó consenso si los temas se referían a la práctica clínica habitual y la experiencia individual, o si el coeficiente de variación entre las respuestas era ≤ 0,3. El número estimado de pacientes nuevos con SD es de 73 al año. La prevalencia se calcula entre 348 y 540 pacientes. El SD se diagnostica principalmente en niños. La supervivencia varía entre los 5 y los 60 años. No existe ningún seguimiento normalizado para los pacientes de más de 18 años de edad, y las tasas de mortalidad son inciertas. No existen guías normalizadas para diagnosticar o tratar el SD. Se tarda de 9 a 15 meses en confirmar el diagnóstico, y la disponibilidad de los análisis genéticos es irregular. Normalmente se utilizan el ácido valproico, el clobazam, el estiripentol y el topiramato. La escasa eficacia y la seguridad son los motivos principales de los cambios de tratamiento.

Conclusiones. La epidemiología del SD en España es poco conocida, y sigue habiendo necesidades no cubiertas en algunas áreas. Las opiniones de expertos suponen un punto de partida para poder investigar la realidad del SD en España. Los estudios epidemiológicos, los criterios de consenso, el acceso fácil a las pruebas genéticas, las opciones de tratamiento, la formación y la investigación de la calidad de vida relacionada con la salud constituyen todos ellos aspectos muy necesarios.

Palabras clave. Consenso. Diagnóstico. Epidemiología. Epilepsias mioclónicas. España. Tratamiento de la enfermedad.