Impact of COVID-19 on Spanish patients with Dravet syndrome and their caregivers: consequences of lockdown

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Introduction. The COVID-19 pandemic caused a state of alarm in Spain in March 2020. The necessary approach to the care of patients with Dravet syndrome (DS) makes them and their caregivers a vulnerable group in emergency situations.

Objectives. To explore the impact of the COVID-19 pandemic on the management and condition of Spanish patients with DS and their caregivers and families.

Materials and methods. Analysis of data belonging to Spanish families taken from a European online survey (April 14-May 17, 2020). It included data on DS patients, on the disease and on caregivers before and after lockdown during the state of alarm.

Results. Sixty-nine Spanish families participated; average age of patients: 12.6 years. Except in 19% of the cases that were isolated, protective/isolation measures for patients were followed without increasing. Epilepsy remained stable, with no medication or resource/personnel availability issues. Sleep-wake pattern (61%) and behavior (41%) of patients changed. Behavior change was associated with seizures during lockdown and with caregiver emotional state (changes in 76%). Psychological support was offered to only 9% of caregivers. Thirty-eight per cent of patients did not receive remote care.

Conclusions. The experience gathered during the lockdown has allowed the detection of points of improvement to ensure the proper management of DS and to keep the situation of patients and caregivers stable. All of this with a prominent role of telemedicine.

Key words. COVID-19. Dravet syndrome. Emergency situation. Healthcare assistance. Lockdown. Telemedicine.

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Disclaimers:
The analysis of the anonymized data was carried out with the consent of the working group of the original initiative on the basis of current European data protection regulations. The authors of the study make available, upon reasonable request, the data used in an aggregated form, always with the prior permission of the original study's working group.

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Introduction

Dravet syndrome (DS) is an epileptic encephalopathy that debuts in the first year of life [1-3], often associated with the *SCN1A* gene mutation [4].

It is a rare disease that accounts for 3-7% of cases with infantile epilepsy [1,5]. The annual incidence of DS ranges from 1/16,000-40,000 children worldwide [1,6-9]; in Spain it is estimated at 1/15,700 (50 children and 23 adults per year) [1].

The main DS manifestation is the drug-resistant epilepsy [10], with febrile (first 4-8 months of life) and unfebrile (from the first year) seizures [11] triggered, among other factors, by infections and intermittent light stimuli [12,13]. DS also has a high premature mortality rate (10-15%), with half of the cases associated with sudden unexpected death in epilepsy [14].

In addition to epileptic seizures, patients suffer from comorbidities (cognitive/motor impairment, language disorder, behavioral problems and recurrent respiratory infections) [12,15,16] which impact on the quality of life of patients and caregivers [1,2,17,18].

DS management includes pharmacological and non-pharmacological treatment to reduce the risk of seizures and the impact of associated comorbidities [13]. This requires a multidisciplinary approach and close monitoring of patients to comply with all recommendations and to control seizures and side effects [11].

Exceptional healthcare situations such as the recent SARS-CoV-2 coronavirus disease (COVID-19) pandemic [19], which led to a state of alarm in Spain on 14-March-2020, makes DS patients and their caregivers a vulnerable group due to the risk of infection and possible lack of care.

The aim of this study is to explore the impact of the COVID-19 alarm situation and lockdown on the management, condition and daily life of Spanish patients with DS and their caregivers/families. For this purpose, data from Spanish patients were

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extracted from an international survey [20] that collected the situation of patients and caregivers before and after lockdown (health status, behavior, protection and health resources).

Table I. Characteristics of DS patients and disease before (3 months) the COVID-19 pandemic.

Characteristics of DS patients (*n* = 69)		
Gender, *n* (%)		
Male	41 (59)	
Female	28 (41)	
Age, years		
Mean	12.6	
SD	9.9	
Median	10.1	
Range	0.6-49.3	
Age groups, *n* (%)		
≤ 2 years	3 (4.3)	
3-7 years	18 (26.1)	
8-17 years	37 (50.7)	
≥ 18 years	13 (18.8)	
Normal residence, *n* (%)		
House with garden or open space	28 (41.2)	
House without garden	7 (10.3)	
Apartment with terrace	16 (23.5)	
Apartment without terrace	16 (23.5)	
Residence	1 (1.5)	
Own bedroom, *n* (%)	6 (8.7)	
Education, *n* (%)		
School	50 (72.5)	
Specialized Centers	15 (21.7)	
Home	4 (5.8)	
Type of family[a] (*n* = 67), *n* (%)		
Single-parent family	7 (10.4)	
No single-parent family	58 (86.6)	
Number of brothers		
0	13 (19.4)	
1	36 (53.7)	
2	12 (17.9)	
3	5 (7.5)	
4	1 (1.5)	
Number of other relatives[b]		
0	51 (76.1)	
1	11 (16.42)	
2	4 (6)	
3	1 (1.5)	
Treatment, *n* (%)		
Clinical trial	14 (20.3)	
Disease characteristics (*n* = 69) 3 months prior to lockdown		
Seizures, frequency; *n* (%)	Awake	Sleep
0	27 (39.1)	38 (55.1)
1-5	33 (47.8)	21 (30.43)
6-10	5 (7.2)	7 (10.1)
≥ 11	4 (5.8)	3 (4.3)
Fever, episodes; *n* (%)		
0	0 (0)	
1-5	37 (53.6)	
6-10	30 (43.5)	
≥ 11	1 (1.4)	

[a] 2 answers with 0 parent; non single-parent family includes 3 (*n* = 2) and 4 (*n* = 1) parents; [b] includes uncles, grandparents and others.

Materials and methods

Design

Online survey aimed at caregivers of patients with DS completed by 229 families, 71 of them Spanish (April 14-May 17, 2020) recruited through European patient organization platforms (e-mails, Facebook and Twitter). The international study [20] was approved by the ethics committee of Necker-Enfants Malades University Hospital (France).

The survey, designed and developed in collaboration with disease experts [20], had 111 items divided into three blocks: 1) Demographic and patient health status information; and aspects of the disease and its management 2) before, and 3) during lockdown by COVID-19. The information recorded by caregivers included: seizures (frequency), protective measures, daily activities, medication and emergency protocols (specific plan for each DS patient developed by the neurologist with indications on the management of epileptic status in the emergency department), availability and adaptation of resources, communication modalities and unmet needs. Answers could be multiple choice or single answer (drop-down list or free text).

Statistical analysis

Variables were described using summary statistics: frequencies and percentages for categorical variables, and frequencies, mean, standard deviation, minimum and maximum values, median and range for continuous variables, as well as bar and pie charts. Comparisons between categorical variables were made using the chi-square test or Fisher's exact test. STATA 16 software (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC) was used for analysis.

Results

Data from 69 Spanish families with DS patients recruited through the Dravet Syndrome Foundation in Spain were analyzed. Data from two of the participants in the survey (*n* = 71) were excluded because they were duplicated.

The patients belonged to 14 Autonomous Communities, with greater representation in Andalusia (26%), Madrid (19%), Extremadura (9%) and Catalonia (6%). The respondents were mothers (64%), fathers (35%) or others (1%). Patients and DS characteristics are shown in table I.

Isolation/protection measures

Prior to lockdown, no isolation measures had been taken for patients in 73.9% of cases. During lockdown, 13 patients were isolated (18.8%), 11 of them (15.9%) with a person exclusively dedicated to their care.

Measures to isolate/protect patients were maintained in 37.7% of cases, varying in 23.2% of cases (mostly for relaxation, 14%).

Eighty-seven percent of the caregivers changed their habits to protect the DS patient. Protective measures during lockdown are shown in table II.

COVID-19

Three cases (4.4%) were in contact with patients with COVID-19; 85.5% declared they had not been in contact and 10.1% did not know it. Apart from fever (Table II), COVID-19 related symptoms reported in 6 patients (8.7%) included: dry cough, dyspnea, sore throat, chills, diarrhea and other respiratory symptoms. No patient was tested for COVID-19 by nasopharyngeal mucus PCR test.

The information on the COVID-19 was mainly provided by the news and/or the Internet (64.7%), patient organizations (18.0%) and the neurologist/pediatrician (12.9%).

Impact on the disease and its management

Table II shows the situation of the patient and the disease since the beginning of the lockdown.

Fever

During lockdown, fever episodes were significantly reduced ($p = 0.0015$) (Tables I and II). The link between the fever and the type of lockdown (residence where it was kept) could not be established because of the small number of cases.

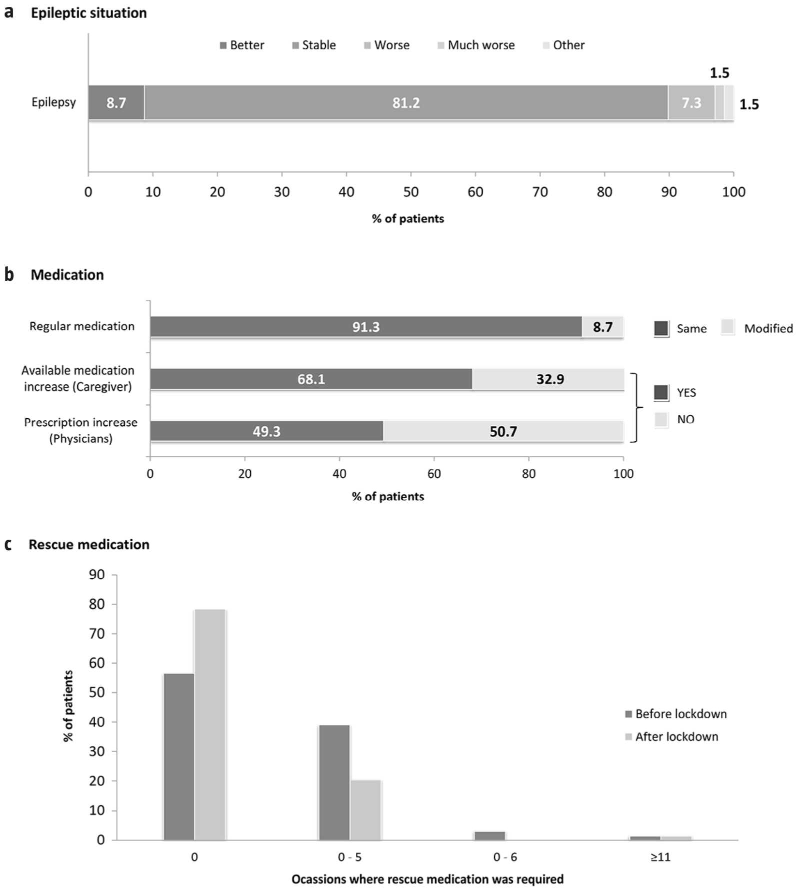
Seizures

Epileptic seizures remained stable in 81.2% of patients (Fig. 1a). During lockdown, 40 patients suffered seizures (64.6%) (Table II). During this period the type of seizure was not related to age, type of isolation, or sleep/wake time. A second and third

Table II. Protective measures and status of the Dravet syndrome's patient from the start of the lockdown ($n = 69$).

Mask, *n* (%)	46 (66.7)	
The entire family	25 (54.3)	
Caregiver	14 (30.4)	
Patient and caregiver	7 (15.2)	
Patient	0 (0)	
Behavior of patients who wore masks, *n* (%) (*n* = 8)		
Rejection	2 (25)	
Problem-free acceptance	3 (37.5)	
Short-term periods of acceptance	3 (37.5)	
Gloves, *n* (%)	42 (60.9)	
The entire family	19 (45.2)	
Caregiver	22 (52.4)	
Patient and caregiver	1 (2.4)	
Patient	0 (0)	
Decontamination after leaving the residence, *n* (%)		
Personal	65 (94.2)	
Soap and water	33 (50.8)	
Shower	24 (36.9)	
Alcohol	8 (12.3)	
Objects	54 (78.3)	
Fever (episodes in the last month), *n* (%)		
0	62 (89.9)	
1-5	6 (8.7)	
6-10	0 (0)	
≥ 11	1(1.45)	
Temperature		
≤ 37.5 °C	0 (0)	
37.6-38.5 °C	3 (4.3)	
38.6-39.5 °C	3(4.3)	
≥ 39.5 °C	0 (0)	
Seizures (*n* = 40), frequency (%)		
Type 1:		
Generalized tonic-clonic	22 (26.8)	
Unilateral clonic	1 (1.2)	
Generalized clonic	5 (6.1)	
Type 2:		
Atypical absence	11 (13.4)	
Myoclonic	8 (9.8)	
Focal	6 (7.3)	
Hospitalizations, *n* (%)	4 (5.8)	
Sleep/Wake time, *n* (%)	Morning	Afternoon
Not applicable (no sleep)	0 (0)	28 (40.6)
No change	34 (49.3)	23 (33.3)
+ 0.5 hours	2 (2.9)	8 (11.6)
+ 1 hour	20 (29)	6 (8.7)
+ 1.5 hours	5 (7.2)	0 (0)
+ 2 hours	7 (10.4)	4 (5.8)
> 2 hours	1 (1.45)	0 (0)

Figure 1. Changes in epileptic situation (a) and DS medication during lockdown (b, c).



episode was experienced in 10 and 3 patients, respectively. The seizures were related to fever in three cases (4.3%).

The seizures varied in 9 patients (14.1%): higher frequency (7.0%), different type (4.2%) and longer duration (2.8%).

It was necessary to call the emergency department in 4 cases (5.8%), with the same availability (doctors/ambulance) as before lockdown in 2 cases, higher in one and lower in the other. Only 1 patient remained in the emergency department (1.4%), finding no difference in availability.

Medication

Most of the patients (91.3%) did not have to modify their usual treatment (Fig. 1b). The emergency protocol was already updated in more than half of the patients (62.3%). No problems with the availability of medicines were reported in 97.1% of cases.

Fourteen (20.3%) patients participated in clinical trials (none related to COVID-19): 12 fenfluramine (1 compassionate use), 1 cannabidiol+fenfluramine, 1 soticlestate. Visits continued according to protocol in 28.6% of cases. When the visits were postponed, the study medication was sent to the home (50.0%) or collected by the caregiver (21.4%). The use of rescue drugs was reduced (Fig. 1c), although not significantly.

Sleep-wake disturbance, patient-behavior and caregiver's emotional state

The sleep/wake pattern varied in 60.9% of patients (Table II). The change affected the schedule of care therapy in a third of these patients (21.1% of the total), significantly only in the afternoon ($p = 0.023$).

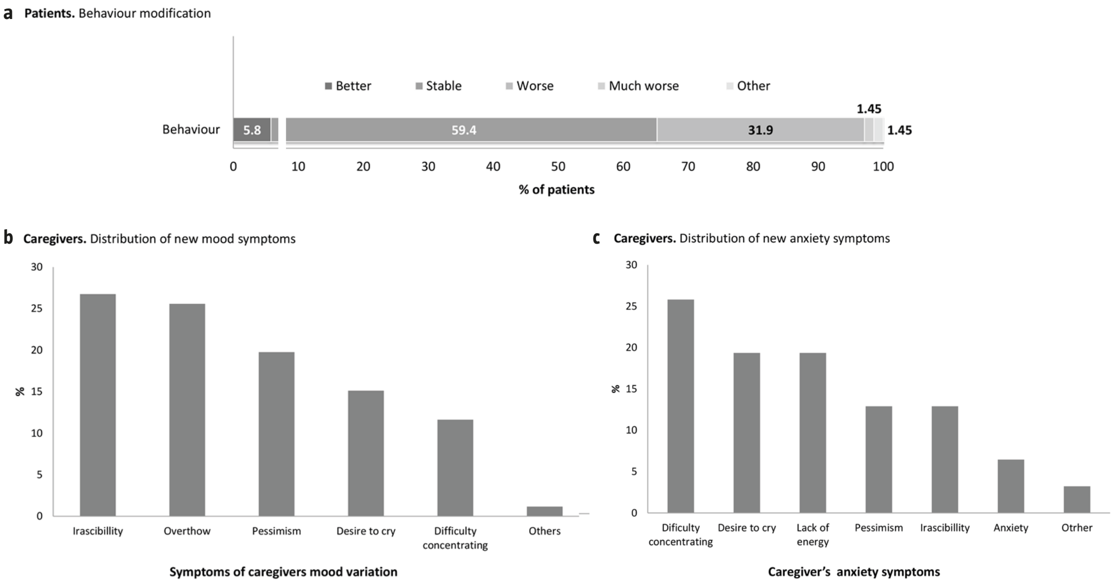
Behavior changed in 40.6% of patients (Figure 2a). Reasons in case of improvement included: peace of mind at home (no hurry), staying in the family circle (more connection and interaction), less exposure to infections, etc. In case of worsening -including apathy, nervousness, irritability-, sleep disturbance, lack of activity (boredom), anxiety generated by lack of contact with acquaintances and change of routines, leaving the center where patient lived, etc.

The type of isolation did not show any relation with the change of the patients' behavior, except in those who were previously in residences or schools. In this situation, the patients´ behaviour was worse ($p = 0.03$). Variation in sleep/wake time and whether or not this variation affected therapy hours also showed no relationship with behavioral changes. No relationship was found between the patient's behavior and seizures (night/day) in the 3 months prior to lockdown, but there was a relationship with those of lockdown ($p = 0.014$).

Seventy six percent (76.1%) of the caregivers reported changes in their mood (Fig. 2b), and 80% reported some new symptoms of anxiety (Fig. 2c), both unrelated to the type of lockdown or the seizures experienced during lockdown. A relationship was found between the caregiver's mood (but not anxiety) and the patient's behavior ($p = 0.012$). Relationship between caregiver's mood with nocturnal seizures prior to lockdown (3 months) was also observed ($p = 0.037$).

Psychological support was offered to six (8.7%) patients/caregivers, half by telephone (considered insufficient), two by videoconference (VC, one person considered it useful and the other insufficient)

Figure 2. Variations in the behavior of DS patients (2a) and mood (2b) and caregiver anxiety (2c).



and one by message (e-mail or WhatsApp, considered insufficient). More than half of those who did not have this support would have been interested in receiving it.

Remote consultations/care

Table III shows the changes in consultations during lockdown.

Almost 38% (37.7%) of the patients did not receive telematic medical care/assistance (Fig. 3a). Less than half of the caregivers contacted the neurologist by phone (Fig. 3b).

The degree of satisfaction with telematic care was mostly moderate-mild (Fig. 3c), with no relationship observed with age or type of seizure. Some of the advantages reported were: maintaining routine (necessary) and contact, increasing motivation as patients paid less attention to parents (sometimes the emotion/stimulation was excessive), and usefulness as a guide for schoolwork, which was highlighted as excessive. Some stated that they did not consider it necessary or only the telephone contacts because the attention of the patients to the VC was poor because they were more used to the face to face.

Of the respondents who had not received contact with the specialist (by telephone or VC), 52.2% stated that they did not wish to do so because: they had had the visit just before the state of alarm, controlled disease or preferred the face-to-face visit. The reasons among those who did wish to have the remote contact were mainly: to review medication (safety), to obtain information and resolve doubts, not to stay so long without contact/follow up and to establish the emergency protocol.

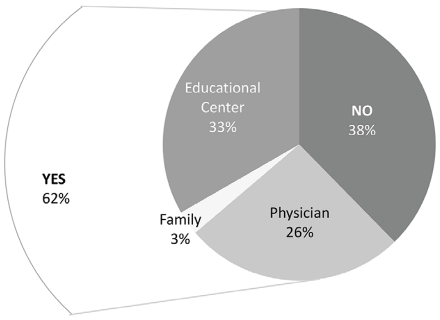
Table III. Changes in health care as a result of the lockdown.

Consultations (physician/therapist) (*n* = 69), *n* (%)	
Postponed	36 (52.2)
Telematic (phone calls + video conference)	28 (40.6)
Both options	2 (2.9)
Other	3 (4.35)
Scheduled consultations (*n* = 43), *n* (%)	
Postponed with defined date	19 (44.2)
Postponed without defined date	12 (27.9)
Performed by phone + VC	12 (27.9)
Scheduled electroencephalogram (*n* = 7), *n* (%)	
Postponed without defined date	6 (85.7)
Performed	1 (1.45)

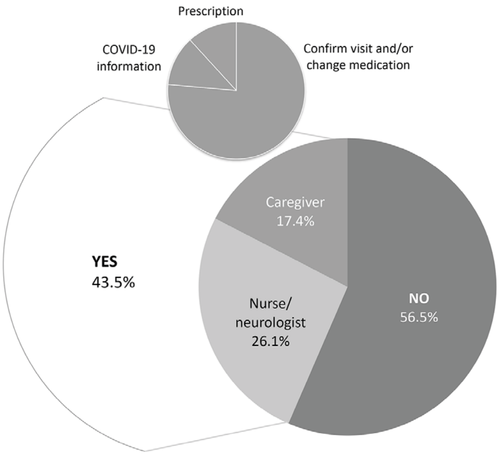
In Spain, 57.9% said that remote medical evaluations would be useful after the situation had normalized and 55.1% said that they could be advantageous in terms of waiting time, travel costs, etc. A preference for VC with parents and patients, followed by calls/VC with the physician to solve

Figure 3. Telematic assistance (telephone/videoconference) during lockdown.

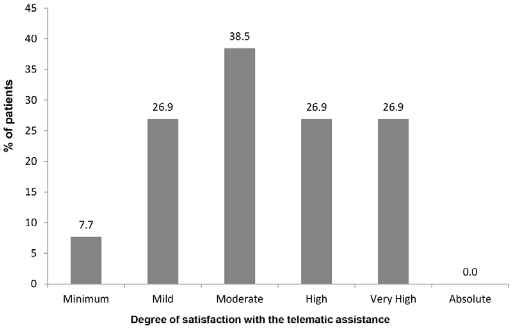
a Patients (%) who received telematic care and collective that proposed/started it (*n* = 69)



b Patients (%) who contacted the neurologist by phone (*n* = 30)



c Satisfaction with telematic assistance (*n* = 26)



doubts (26.1%) and telephone surveys or questionnaires (18.8%) was reported.

Discussion

DS patients and their caregivers represent a population that is vulnerable to the emergency situation promoted by the COVID-19 pandemic, because of the implications for them of infections and the change in care/assistance due to the lockdown [21,22].

It is essential that caregivers are well informed to improve, among other things, the protection and management of patients, reducing anxiety and stress of the situation [23]. In this study we observe the involvement of the organizations disseminating information (18%), agreeing to increase it for greater benefit.

Protection against infection/contagiousness is essential for DS patients in any situation. This, together with the fact that DS has not been described as increasing the risk of COVID-19 [23], justifies that patient isolation measures were not increased, and that the recommendations of the health authorities were followed.

As described in DS Spanish patients [21], the epilepsy situation remained stable during lockdown. In the majority of cases seizures did not vary. When variations occurred, there was hardly any change in the type and duration of seizures with respect to the previous situation. No significant relationship between seizures and age was observed, confirming the presence of seizures at all ages [11].

Fever episodes decreased significantly - discarding the possibility of less temperature monitoring due to continuous supervision of the patient by his or her caregiver during lockdown - which would explain the reduced number of fever-associated seizures observed (3 cases). Despite the possible positive effect of lockdown on fever, it should not be forgotten that there are other related negative aspects, such as increased stress [24] and decreased quality of life due to social distancing [25].

The stability of epilepsy is also reflected in the maintenance of routine medication, the reduced number of emergency calls and hospitalizations, and the decreased use of rescue medication (not significant) observed.

Unlike that described in other rare diseases [26], there were hardly any problems with drug supply, confirming what was described in Spanish patients with genetic epileptic syndromes [21]. Caregivers showed to be prepared by stocking up on medication in response to the health alarm. Physicians also reacted, although to a lesser extent, and prescribed medications for longer periods to avoid interruptions. This difference could be justified by the complexity of this new situation, especially for neurologists/neuropediatricians who must assist all their chronic patients and especially those recruited to attend COVID-19 patients in the Emergency department and ICU.

The emergency protocol was outdated in approximately 40% of cases. Although the results did not reflect problems in the availability of resources when emergency services were needed, we emphasized the importance of regular updates of this protocol for proper action in prolonged seizures. And this is even more so in the case of a global health emergency, due to the risk of not finding staff in these services who know well the disease.

In those patients participating in a clinical trial, there were also no problems with access to medication; it was dispensed at scheduled visits that were not postponed, sent to the patient's residence or collected by the caregiver. This system should be implemented in the future and trials should be design to reduce unnecessary visits and tests. In this way, the impact on the daily life of patients and caregivers would be reduced (maintaining routines and avoiding loss of work days, for example) especially for those families who reside far from the trial site.

Sleep habits are often altered in children with epilepsy [27]. In the survey, lockdown altered the sleep/wake pattern in more than half of the patients, in the morning (+1-2h) and in the afternoon (+0.5-1h). This variation was not significantly related to the patients' behavior, although it was one of the reasons reported for its worsening, along with the alteration of routines. Both of these reasons could justify that, even varying only by one hour the duration of the siesta, it significantly affects the normal hours of therapy. Changing sleep and activity schedules could benefit patients by reducing stress levels.

A specific comorbidity of DS is severe behavioral problems, beginning at the age of 4-7 [2]. During the lockdown, the behavior worsened in 32% of the cases. It is important to note that the change in behavior was related to the seizures experienced during the lockdown, contrary to what was previously described [25], and also to the type of life prior to the lockdown. The great impact on patients' quality of life associated with behavioral problems [25] suggests the need for greater remote support and assistance to achieve a reduction in these changes.

During the lockdown, the state of mind was altered in 76.1% of the caregivers. As described before [28], a relationship between the caregiver's state of mind and the patient's behavior, and also with nighttime seizures was observed. Anxiety worsened in a similar way (new symptoms in 80% of the caregivers), with no relationship detected with the patient's behavior or type of isolation.

Psychological support is very important for caregivers of DS patients [28], especially in situations of lockdown where they must deal with the patient all day long. However, it was only offered remotely to 8.7% of caregivers, without reaching a sufficient degree of satisfaction. Approximately half of those who did not have it were interested in receiving it.

The need to maintain social distance and avoid infection caused more than half of the (physician/therapist) appointments and scheduled consultations to be postponed, 28% of them and all the EEGs without a date. This uncertainty could be considered as another stress factor for caregivers in this situation.

Telemedicine (VC and calls) was used to continue patient care and education, but it was found to be insufficient and not entirely satisfactory. Many of the participants did not consider it necessary and it may reflect some comfort with the control of the disease during the lockdown. However, the positive aspects observed with telemedicine, including in the field of clinical trials, open the door to change in the approach to patient care that can bring many benefits in normal circumstances, as stated by more than half of the respondents. Taking into account the opinion and preference of the caregivers (VC with patients and caregivers and resolution of doubts of the caregivers [VC and phone calls]) and with the collaboration and experience of the professionals of the multidisciplinary team, a telemedicine could be designed that benefits all involved.

The data shown belong to 69 families, which is a considerable representation of the DS Spanish population (13-20% considering the prevalence of 348-540 patients [1]). There are possible limitations of the study. One of them is the heterogeneous distribution among the communities with the highest incidence of COVID-19 (Madrid and Barcelona), with the situations experienced in each case varying. Other limitation is the potential impact on the reliability of the retrospective nature of some data communicated by caregivers (e. g. seizure frequency). However, the voluntary participation in the survey reflects the involvement and goodwill of the caregivers.

In conclusion, the experience gathered during the lockdown of families of DS patients shows us applicable changes to improve the condition of DS patients and their caregivers in Spain, which may also apply for other countries.

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Impacto de la COVID-19 en pacientes españoles con síndrome de Dravet y sus cuidadores: consecuencias del confinamiento

Introducción. La pandemia por COVID-19 implicó el estado de alarma en España en marzo de 2020. El abordaje necesario para el cuidado de los pacientes con síndrome de Dravet (SD) los convierte, junto con sus cuidadores, en un grupo vulnerable en situaciones de emergencia.

Objetivos. Explorar el impacto de la pandemia por COVID-19 en el manejo y la condición de los pacientes españoles con SD, y de sus cuidadores y familias.

Materiales y métodos. Análisis de los datos pertenecientes a familias españolas extraídos de una encuesta en línea europea (14 de abril-17 de mayo de 2020). Incluía datos de los pacientes con SD, de la enfermedad y de los cuidadores antes y después del confinamiento, durante el estado de alarma.

Resultados. Participaron 69 familias españolas; edad media de los pacientes: 12,6 años. Excepto en el 19% de los casos que fueron aislados, las medidas de protección/aislamiento del paciente continuaron sin incrementar. La epilepsia se mantuvo estable, sin problemas de medicación ni disponibilidad de recursos/personal. Cambió el patrón de sueño/vigilia (61%) y la conducta (41%) de los pacientes. El cambio de conducta se asoció con las crisis durante el confinamiento y el estado anímico del cuidador (cambios en el 76%). Sólo se ofreció apoyo psicológico al 9% de los cuidadores. El 38% de los pacientes no recibió atención telemática.

Conclusiones. La experiencia recogida durante el confinamiento ha permitido detectar puntos de mejora para asegurar el apropiado manejo del SD y mantener estable la situación de los pacientes y cuidadores, todo ello con un papel destacado de la telemedicina.

Palabras clave. Asistencia sanitaria. Confinamiento. COVID-19. Síndrome de Dravet. Situación de emergencia. Telemedicina.