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# Impact of the COVID-19 lockdown on patients and families with Dravet syndrome

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## Abstract

We explored the impact of coronavirus virus 2019 (COVID-19) pandemic on patients with Dravet syndrome (DS) and their family. With European patient advocacy groups (PAGs), we developed an online survey in 10 languages to question health status, behavior, personal protection, and health services before and after lockdown. Approximately 538 European PAG members received electronic invitations. Survey ran from April 14, to May 17, 2020, with 219 answers; median age 9 year 10 months. Protection against infection was highly used prior to COVID-19, but 88% added facemask-use according to pandemic recommendations. Only one patient was tested positive for COVID-19. Most had stable epilepsy during lockdown, and few families (4%) needed emergency care during lockdown. However, behavior disorder worsened in over one-third of patients, regardless of epilepsy changes. Half of appointments scheduled prior to lockdown were postponed; 12 patients (11%) had appointments fulfilled; and 39 (36%) had remote consultations. Responders welcomed remote consultations. Half of responders were unsatisfied with psychological remote support as only few (21 families) received this support. None of the five of patient in clinical trials stopped investigational treatment. Prior adoption of protective measures against general infection might have contributed to avoiding COVID-19 infections. Protocols for the favored remote contact ought to now be prepared.

## KEYWORDS

behavior disorders, COVID-19, Dravet syndrome, pandemics, social isolation, telemedicine

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## 1 | INTRODUCTION

Dravet syndrome (DS) is characterized by febrile or afebrile seizures starting in the first year of life and often evolves to status epilepticus.<sup>1,2</sup> Over 80% of patients carry a loss-of-function mutation in the *SCN1A* gene. 1. With incidence between 1/16 000 and 1/40 000 infants,<sup>3–6</sup> DS is rare and only represents about 3 to 7% of cases with infantile epilepsy. During the second year of life, patients might experience various seizure types, cognitive plateauing, motor dysfunction, and behavioral problems.<sup>1,2</sup> Premature death occurs in 10%–15% of patients, with half being sudden unexplained death in epilepsy (SUDEP).<sup>7</sup>

Seizure recurrence makes patients with DS and their families a vulnerable population when healthcare systems are compromised, such as has arisen during the coronavirus disease 2019 (COVID-19) pandemic. Infections and fever often trigger seizures and status epilepticus in patients with DS, and recurrent respiratory infections are common<sup>8</sup>; hence, prophylaxis against infections and fever is needed in addition to antiseizure medications (ASMs).<sup>9</sup> Patients need regular and frequent epilepsy specialist assessment and use of emergency facilities is high.<sup>1,2,10</sup>

COVID-19 is an infectious respiratory disease caused by the most recently discovered SARS-CoV-2 coronavirus. Since the first recognized case in December 2019 in the city of Wuhan, China,<sup>9</sup> COVID-19 transmitted rapidly and pandemic was declared by the World Health Organization (WHO) on March 11, 2020. Various degrees of social isolation and physical distancing (“lockdown”) became mandatory from the first two weeks of March until around mid-May 2020 mainly in the EU countries where we performed this study.

We aimed to explore the consequences of the COVID-19 pandemic (including lockdown) on patients with DS and their families with respect to health and everyday life.

## 2 | METHODS

We developed an online survey for caregivers of patients with DS divided into 6 sections exploring the following:

Section I on demographic information of the responder, section II on demographic information of the individual with Dravet syndrome, section III on the use of protective measures and contact before and during the containment/quarantine, section IV on individual with DS and contagion with COVID-19, section V on the symptoms related to DS before and during COVID-19 and organization of care, and section VI on the evaluation of future televisits and contacts. We summarized the survey in Table 1. Questions used checkboxes (multiple selections possible), dropdown lists (single selection only), or free text and were piloted by

### Key Points

- We developed with European patient advocacy groups a survey to explore COVID-19 pandemics impact on individuals with Dravet syndrome
- Protection against infections in this population was highly used prior to COVID-19 and might have contributed in avoiding COVID19 infections
- Most individuals had stable epilepsy during lockdown, however behavior disorders worsened in over one-third of patients
- Psychological remote support was available for few families although families expressed a clear need for such support
- Families are favourable for remote contact in pandemics and beyond for families travelling long distances to reach expert centres

patient advocacy groups (PAGs) from Italy, Spain, France, and Croatia. Developed in English, survey versions were translated by local language-speaking PAG members into Spanish, French, German, Italian, Polish, Croatian, Dutch, and Serbian.

Invitations to participate were emailed to approximately 538 members of PAGs, mainly Dravet Syndrome Foundation Spain, Dravet Italia Onlus, Alliance Syndrome de Dravet (France), and Dravet Sindrom Hrvatska (Croatia), as well as through Internet-based social media (Facebook and Twitter). Survey was available from April 14, to May 17, 2020 (1 month after onset of lockdown in EU and spanning the quarantine period). Answers were anonymous and did not include any data enabling the patient identification.

The ethics committee of Necker Enfants Malades university hospital approved the study.

### 2.1 | Statistical analysis

For descriptive statistics, patients were stratified to four groups according to age at survey: preschool (<6 years), middle childhood (6–12 years, inclusive), adolescent (13–20 years, inclusive), and adults ( $\geq 21$  years).

Both univariate and bivariate statistical analyses were performed. Frequency tables and crosstabs were examined for potential associations between variables. Significance of associations was assessed by Pearson chi-square test ( $P < 0.05$  was regarded as significant).

### 3 | RESULTS

Two hundred and twenty-nine caregivers completed the survey. The patient cohort had 118 (52%) males.

Survey responses from 10 caregivers were excluded from the analysis since they lived in an area without mandatory lockdown. Mothers answered the survey in 75% of cases, fathers in 24%, and another family member in 1%. Median age at study entry of the 219 patients analyzed was 9 years 10 months (range: 4 months to 49 years 4 months). Table 2 shows additional patients data including age at DS diagnosis.

Seizures were reported based on seizures' diaries. Forty-five responders (21%) declared the absence of seizures during the 3 months prior to lockdown. The remaining 174 responders (79%) declared seizures with 132 patients having >2 seizures/month.

Prior to lockdown, patients with DS attended daily activities in either schools or special institutes (60.3% and 15.1%, respectively) or protected work and day centers activities (12.3% and 19.6%, respectively). During lockdown, 116 (53%) families participated in didactic video conferences. These conferences were organized by either the team of the school/institute of their child (90% of cases) or by the families support groups (10% of cases).

Regarding protection measures, 106 families (48%) declared that prior to COVID-19, and they were used to wear similar or higher protections for their children. One hundred ninety-two (88%) responders declared that they modified the protection measures adapting them to the official recommendation as for the face masks. The majority (81%) of the responders implemented decontamination when returning indoors (57% of them washing the exposed parts with soap and water; 26% having a shower and 17% by washing the exposed parts with hydro alcoholic solutions).

In comparison with the situation prior to COVID-19, 106 responders (48%) declared that they used similar or higher-level protective measures against infections to those recommended against COVID-19 regarding individual isolation of individuals with DS and environment hygiene. Restrictive attitudes prior to COVID-19 tended to correlate with individuals with frequent febrile episodes ( $P = 0.029$ )—no correlations were found with low/high frequency of seizures. During lockdown, 192 (88%) responders declared that they modified the protective measures based on official recommendations adding facemasks in more than half. Facemasks were mainly used for caregivers. The majority (81%) of responders implemented also additional decontamination procedures when returning indoors. Decontamination procedures were used by 100 families (81%) washing the uncovered parts with water and soap (57%) or with hydro alcoholic solutions (17%), and 26% took showers every time they turned home from outside. All the family members used facemasks in half of cases (54%), the caregiver alone used them in 33% of cases, and

**TABLE 1** Summary of the main questions of the survey (English version) detailing the different sections

Questions	Answers
<i>Section I: Demographic information of the responder</i>	
1.1 In which country do you live?	Answers Section I <sup>a</sup>
1.2 Region:	
1.3 City:	
1.4 Respondent to the survey:	1.4-a Mother 1.4-b Father 1.4-c Caregiver/other family member 1.4-d Tutor/educator (if patients are isolated in specialized centers)
<i>Section II: Demographic information of the individual with Dravet Syndrome</i>	
2.1 Gender:	2.1-a Male 2.1-b Female
2.2 Age: months/years	
2.3 Age of diagnosis of DS: months/years	
2.4 Prior to quarantine/isolation the individual with Dravet syndrome attended:	2.4-a School 2.4-b Institute/residential center for people with disabilities 2.4-c Work environment/day center 2.4-d Other (if other please specify)
2.5 Do you live in a country that has announced containment restrictions?	2.5-a Yes 2.5-b No
<i>Section III: Use protective measure /contact before and during the containment/quarantine</i>	
3.1 Did you use before COVID-19 particular measures to protect your child from infections and contagious diseases?	3.1-a Yes 3.1-b No
3.2 How would you evaluate these measures compared to measures undertaken for COVID-19?	3.2-a More restrictive 3.2-b Equally restrictive 3.2-c Less restrictive 3.2-d I do not know
3.3 Have you changed the means you used to protect the individual suffering from Dravet syndrome?	3.3-a Yes 3.3-b No

(Continues)

TABLE 1 (Continued)

Questions	Answers
3.4 Did you follow the recommendation of using face masks?	3.4-a Yes 3.4-b No
3.5 If you answer yes to 3.4, please answer the following: who is wearing it?	3.5-a The patient with Dravet syndrome 3.5-b The caregiver 3.5-c Both, the patient and the caregiver 3.5-d Everybody in the family
3.6 Did you use specific decontamination measures for the family members of the individuals with Dravet when coming back home after a time spent outside home?	3.6-a Yes 3.6-b No
3.7 If you answer yes to 3.6, please answer the following: which measures did you use	3.7-a By washing the exposed parts with alcohol solutions 3.7-b By washing the exposed parts with soap and water 3.7-c By taking a shower
3.8 Have remote contact been organized by the institutions/schools that the individual with DS attended before to provide educational activities?	3.8-a Yes 3.8-b No
3.9 If you answered no to 3.8, please answer the following: would you have liked to have a continuous contact with the educational team?	3.9-a Not at all 3.9-b Slightly 3.9-c Moderately 3.9-d Much 3.9-e Very much
3.10 Have remote contacts been organized by the advocacy groups in your country?	3.10-a Yes 3.10-b Not at all
<i>Section IV: Individual with DS and contagion with COVID-19</i>	
4.1 Has the individual with Dravet syndrome had contact* with people with tested positive to COVID-19?	4.1-a Yes 4.1-b No 4.1-c I don't know
4.2 If you answer yes to 4.1, please answer the following: with whom?	4.2-a Other patients in the center or the rehabilitation site 4.2-b People providing care, rehabilitation or education (caregiver, doctor, nurse therapist, educator, etc) 4.2-c Family members 4.2-d Other (if other space for specify)

(Continues)

TABLE 1 (Continued)

Questions	Answers
4.3 Did the individual with Dravet syndrome have fever during isolation (with or without COVID-19)?	4.3-a Yes 4.3-b No
4.4 If you answer yes to 4.3, please answer the following: how high?	4.4-a $\leq 37.5^{\circ}\text{C}$ 4.4-b $37.6\text{-}38.5^{\circ}\text{C}$ 4.4-c $38.6\text{-}39.5^{\circ}\text{C}$ 4.4-d $\geq 39.5^{\circ}\text{C}$
4.5 Did she/he presented other symptoms?	4.5-a Yes 4.5-b No
4.6-4.14 (list of the symptoms reported at the time of the study for COVID-19 with Y/N)	
4.15 Was she/he tested for COVID-19?	4.15-a Yes 4.15-b No
4.16 If you answer yes to 4.15, please answer the following: was she/he COVID-19 positive?	4.16-a Yes 4.16-b No
4.17 Was she/he hospitalized—not just for COVID-19?	4.17-a Yes 4.17-b No
4.18 If you answer yes to 4.17, please answer the following: was she/he in intensive care?	4.18-a Yes 4.18-b No
<i>Section V: Symptoms related to DS before and during COVID-19 and organization of care</i>	
5.1 In the previous three months before the pandemic, what was the mean frequency of seizures per month?	5.1-a 0 5.1-b 1 5.1-c 2 5.1-d 3 5.1-e 4 5.1-f 5 5.1-g 6 5.1-h 7 5.1-i 8 5.1-l 9 5.1-m 10 5.1-n $> 10$
5.2 How can you describe the seizures' frequency of the person with DS?	5.2-a Improved 5.2-b Stable 5.2-c Worsened 5.2-e Other (if other space for specify)
5.5 Did the patient with DS need Emergency Room?	5.5-a Yes 5.5-b No

(Continues)

TABLE 1 (Continued)

Questions	Answers
5.6 If you answer yes to 5.5, please answer the following: did they have the same availabilities as before?	5.6-a Better than usual 5.6-b As always 5.6-c Worse than usual
5.7 I If you answer yes to 5.5, please answer the following: how would you evaluate the waiting time to the consultation at the emergency room?	5.7-a Better than usual 5.7-b As always 5.7-c Worse than usual
5.8 Did you have a scheduled medical visit (consultation) with the specialist of the individual with DS during this lockdown period?	5.8-a Yes 5.8-b No
5.9 If you answer yes to 5.8, please answer the following: please check what applies best for this visit	5.9-a It was done onsite as planned with special permission 5.9-b It was done over the phone 5.9-c It was done via video conference 5.9-d It was postponed to a defined date 5.9-e It was postponed without a defined date
5.10 If it 5.9-d or 5.9-e “was postponed”, please answer the following: would you have like to have this visit through a video conference or a phone?	5.10-a Yes 5.10-b No
5.11 (this question was available just for the responders that answered to the previously “5.11” question) Why?	Free text
5.12 Have you had problems with the availability/reachability of the medicines of the individual with DS?	5.12-a Yes 5.12-b No
5.13 If you answer yes to 5.12, please answer the following: was it resolved and how?	5.13-a There was a simple delay and drugs have already arrived 5.13-b The specialist had to intervene 5.13-c Other (if other space for specify)
5.14 Was the individual with Dravet syndrome participating in a clinical trial for Dravet syndrome/epilepsy-specific drugs during this lockdown?	5.14-a Yes

(Continues)

TABLE 1 (Continued)

Questions	Answers
5.15 How was this trial organized during this period? Choose what fits best the situation of the individual with DS	5.15-a Everything is being done as planned 5.15-b Visits were postponed and medication was sent home 5.15-c Visits were postponed and relative/caregiver had to go to the hospital to pick up the medication 5.15-d We had to exit definitely the trial 5.15-e Trial has been temporarily interrupted
5.16 Is the individual with Dravet syndrome participating in a clinical trial for COVID-19-specific drugs/antibodies during this period?	5.16-a Yes 5.16-b No
5.17 (If 5.16 Yes) Which one?	free text
5.18 How would you evaluate the behavior changes of the individual with DS?	5.18-a Improved 5.18-b Stable 5.18-c Worsened 5.18-e Other (if other space for specify)
5.19 Have you been offered remote psychological support for the individual with Dravet syndrome and/or for your family members/caregiver/educator?	5.19-a Yes 5.19-b No
5.20 If you answer yes to 5.19, please answer the following: what mean was used for the psychological support?	5.20-a Phone 5.20-b Video conference 5.20-c Text (email, Whatsapp, sms...)
5.21 If you answer yes to 5.20, please answer the following: how much did you consider it useful?	5.21-a not at all useful 5.21-b Poorly useful 5.21-c Quite useful 5.21-d Very much useful
5.22 If you answer no to 5.19, please answer to the following: would you have liked to have such a support?	5.19-a Yes 5.19-b No
<i>Section VI: Evaluation of future televisits and contacts</i>	<i>Answers Section VI°</i>
6.1 Do you think that televisits could also be useful in the future?	6.1-a Yes 6.1-b No 6.1-c Maybe 6.1-d In case of emergency 6.1-e Other (precise)

(Continues)

**TABLE 1** (Continued)

Questions	Answers
6.2 What would you prefer as a mean for a televisit?	6.2-a telephone interview + ad hoc questionnaire 6.2-b video conference 6.2-c By email 6.2-d other modes (precise)
6.3 Do you believe in the advantages of a televisit? (reducing travel time, reduced travel expenses, etc).	6.3-a Yes 6.3-b No 6.3-c Maybe 6.3-d Other (precise)
6.4 Additional comments and/or suggestions for your doctor/therapist/patient advocacy organization/etc	Free text

**TABLE 2** Characteristics of patients: patients' gender, the parent who answered the survey, the country of residence and age at clinical diagnosis of DS

	Number	Percentage
Responder	171	75%
Mother	56	24%
Father	2	1%
Other familiars/caregivers	—	—
Tot.	229	100%
Gender	118	52%
Male	111	48%
Female	—	—
Tot.	229	100%
Country	205	90%
Europe	71	31%
Spain	50	22%
France	48	21%
Italy	19	8%
Croatia	17	10%
Other EU	24	7%
Extra UE	—	—
Tot.	229	100%
DS clinical diagnosis (age)	54	29%
Before 1 y	150	68%
Within 3 y	51	23%
Between 3 and 10 y	18	8%
After 10 y	—	—
Tot.	229	100

both the caregiver and the individual with DS in 11%. Only a few families used the facemask only for the individuals with DS (2%).

Only one patient in this series with respiratory symptoms and fever had a positive test to COVID-19, presenting fever but without exacerbation of seizures.

Contact with the reference medical team was possible in about half of patients. Of the 107 patients with clinic appointments previously scheduled for the period of lockdown, appointments were fulfilled onsite for 12 patients (11%), conducted remotely (phone/video call) for 39 (36%), and postponed for 56 (52%). Most of those with postponed appointments would have welcomed a phone/video call with their referring physicians during lockdown.

Over half of responders (53%) had confidence in remote contact and clinical evaluation and were supportive toward regular use of remote consultations, even post-COVID-19. Video was considered key for remote communications by 55% of responders; 42% highlighted that video could be a quick and effective method of communication during such emergencies.

Most responders (58%) agreed that remote consultations could have advantages over regular ones, mainly in reduced travel and waiting rooms time. During lockdown, few families (9 families, 4%) needed emergency care that was obtained as prior to pandemics.

Regarding seizures' frequency and behavior changes during lockdown, 14 responders answered "do not know" to if any changes occurred. Among the remaining 205 responders, seizures' frequency was considered stable by most (79%), few reported an increase in seizure frequency (11%), and 10% perceived an improvement. Behavior changes were reported as worsened by 37%, stable in 57%, and improved in 6% of responders.

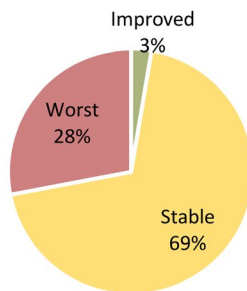
We found no significant correlation between the worsening of the behavior and the age groups except for a trend with the adolescents group as behavior worsening was reported in 32%, 39%, 42%, and 31% of the 4 age groups (preschool (<6 years), middle childhood (6-12 years, inclusive), adolescent (13-20 years, inclusive), and adults ( $\geq 21$  years)), respectively.

Association between seizures' frequency and behavior changes was significant, with the majority of individuals reported with worsened epilepsy having also worsened behavior (91%) ( $P < 0.001$ ) (Figure 1). However, behavior worsened also in 69% of patients with stable epilepsy and in 3% of patients with improved epilepsy. Furthermore, 11 (27.5%) of the 40 patients who did not experience seizures during the 3 months prior and during the lockdown was reported to have a behavior worsening (Figure 1).

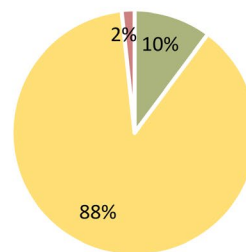
Only 21 families (9.6%) reported receiving psychological support (12 from France, 6 from Spain, and 3 from Ex-EU responders). Four families received psychological support via email or short message service (SMS), 3 by video call, and 14 by phone call. Half of families were unsatisfied with the psychological remote support. Out of 198 families (90.4%)

### A. Behaviour change correlated to seizure frequency changes

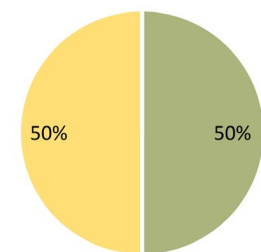
Individuals with an increased seizure frequency  
n=75



Individuals with a stable seizure frequency  
n=118

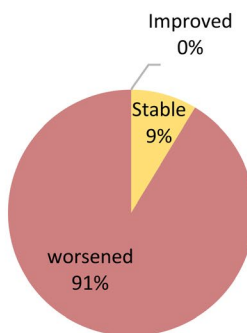


Individuals with decreased seizure frequency  
n=12

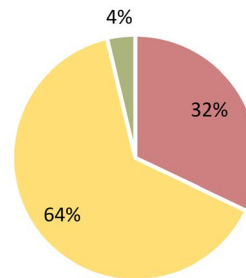


### B. Seizure frequency change correlated to behaviour changes

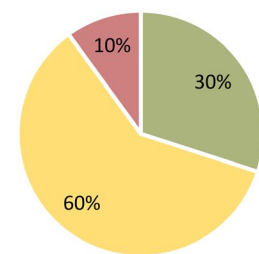
Patient with worsened behaviour  
n=23



Patient with no behaviour change  
n=162



Patient with improved behaviour  
n=20



**FIGURE 1** Association between behavior changes and seizures' frequency and between seizures frequency behavior changes. Pts, patients

who were not offered psychological support, half stated that they would have welcomed it.

Twenty percent of responders (16 in Italy, 15 in Spain, 4 in France, 1 in Croatia, and 8 in other EU or Ex-EU) represented patients involved in clinical trials during lockdown. No patient had to stop the investigational treatments, and scheduled visits were postponed for 64% of them. Investigational treatments were delivered at home or to institutions accessible to families and close to their homes.

## 4 | DISCUSSION

Several studies have analyzed the burden of COVID-19 on patients with epilepsy<sup>11,12</sup>; we believe this is the first to study patients with DS and their families. Epilepsy was relatively stable during lockdown, while behavior disorders worsened. Half of clinic appointments were postponed, and remote contact with families was variable. Families would have appreciated greater use of remote consultations with their medical teams. Remote consultations were largely considered a worthwhile future option

for similar situations or routinely to decrease travel and waiting-room times.

Our data indicate that caregivers of patients with DS already use protective measures against transmission of infections; only one in five responders declared that they increased the protective measures during the COVID-19 pandemic. The main change was related to an increase use of facemasks use and decontamination procedures when coming back home. Facemasks were used by the whole family and by the caregivers in the majority of cases. The individual with DS only in some of the cases was wearing a mask. This might be explained by the difficulty to have individuals with intellectual disability and behavior disorders to accept facemasks. The difficulty to keep the facemasks was an important issue for individuals with DS as this negatively impacted their community activities when it was available and their capacity to regain their institutions and schools. Prior to COVID-19, restriction and use of protective measures established by the families were higher in patients experiencing frequent febrile episodes. This was an expected result as the frequency of status epilepticus induced by fever and febrile illness remains the major burden in the patients' group with frequent febrile episodes. This



might explain the child care arrangement for children with DS with in many reports an impact on the parents carrier as they choose to avoid community child care modes at least in the first years of age were the febrile events and possible consequent status and long lasting seizures are frequent.<sup>13</sup>

Behavior disorders worsened in over one-third of patients, in almost all children with worsened seizures' frequency, but also with stable or improved seizures' frequency. Despite a trend in correlation to the adolescents, there was no significant relation with the different age groups and this worsening was reported in all 4 groups. Staying at home with additional time to rest/sleep and with fewer demanding activities might have been expected to improve behavior. Worsening in behavior might have been related to the lack of daily activities and rehabilitations programs for patients with DS during lockdown in addition to extreme isolation even in their familiar nucleus. Emerging evidence on school or work-therapy activities suggests that patients with DS better managed epilepsy and behavior when rehabilitative-educational support is constant. This might favor a better support of such activities against overprotection measures and isolation. This, however, should be balanced by the specific situation of each child and family helping to design the most adapted and personalized program. Finally, we did not detail in our survey the behavior disorders' subtypes but we focused only on the changes, so we cannot specify the most impacted underlying behavior disorders. Many families perceived psychosocial support as insufficient—only 21 of 219 families received such support. We speculate that phone or remote psychological support ought to be implemented to provide professional assistance to patients and caregivers. Indeed, telemedicine was generally perceived as supportive for patients and families. Although not the ideal medical solution and its usage varied across countries, telemedicine perhaps helped mitigate the isolation of patients and families. Protocols for telemedicine should be established in preparation for future similar situations, emergency consultations, or in the case of the patient living far from the reference hospital.

Finally, we explored the effect of lockdown on participation in ongoing clinical trials. Reorganization of clinical trials seemed timely, since continuation of investigational treatments was preserved for all participants. To ensure both safety for patients and continuity of provision of drugs, the Food and Drug Administration (FDA)<sup>14</sup> and the European Medicines Agency (EMA)<sup>15</sup> advocated the use of telemedicine and virtual consultations during the COVID-19 pandemic. COVID-19 has perhaps accelerated a long-standing request from PAGs (patients' advocacy groups) for the adoption of remote consultations. Indeed, such televisits might be adopted for some of the routine visits. This would reduce travel times and their consequent physical and financial costs, ultimately improving the quality of life of both patients and caregivers.

## 5 | CONCLUSIONS

Although the COVID-19 pandemic and lockdown presented difficulties for patients with DS and their families, prior adoption of protective measures against general infection might have contributed to avoiding high levels of contagion within this population. Lockdown restrictions did not change the epileptic condition of patients but worsened the behavior disorders. Structured protocols, regular remote consultations, online psychological support, and the possibility of emergency contacts with the medical teams—not only during special circumstances, but also as a settled system in addition to the classical in presence clinics—would be highly welcomed by the families of patients with DS. Patients' advocacy groups could be valuable partners with physicians, regulatory agencies, and industries for the initiation, coordination, and implementation of specific protocols to be followed for clinical trials during future emergency situations or to help future patients and families friendly trials.

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## CONFLICT OF INTEREST

The authors have nothing to declare in relation to this manuscript. This manuscript did not receive any additional fund. 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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