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ORIGINAL ARTICLE

The impact of COVID-19 in Dravet syndrome: A UK survey

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Abstract

Objectives: To understand the risks, impact and outcome of COVID-19 in people affected by Dravet Syndrome (DS).

Materials and Methods: An anonymous cross-sectional online survey was conducted between June 17 and July 13, 2020, addressed to families of people with DS.

Results: A total of 116 responses were collected, from families of children (n = 86; 74%) and adults (30; 26%) with DS. The majority (106; 91%) were shielded at the family home during lockdown. Symptoms compatible with COVID-19 were reported in 22 (19%) individuals. Only four individuals with symptoms had a PCR swab test, none of which was positive. Only one symptomatic person had antibody testing (but not swab testing), which was positive. One person had repeatedly positive swab tests whilst in hospital for renal failure, but had no typical symptoms of COVID-19. In 50% of people with DS who developed possible or probable COVID-19 symptoms, seizure worsening was reported, in terms of increased seizure frequency or duration or both. Medical attention was required in 9/22 (41%), all of whom were children.

Conclusions: In this cohort of people with DS, we observed an infection rate, determined by compatible symptoms, of 19%, with no deaths and benign outcome in most cases despite the underlying complex epilepsy although children often required medical attention. Early adoption of preventative measures, including testing of symptomatic individuals, regular surveillance for people living in residential care facilities, and shielding of individuals with comorbidities increasing the risk of severe outcome, may limit the impact of COVID-19.

KEYWORDS
epilepsy, infections, seizures

1 | INTRODUCTION

The COVID-19 pandemic, which to date has caused over 2,000,000 deaths worldwide, continues to grow, with hundreds of thousands of new infection cases every day. Understanding risk factors for the severe forms of the disease, and identifying people more vulnerable to the risks of infection, are crucial steps for appropriate clinical management and prevention strategies. There are an increasing number of clinical studies for COVID-19, but our current understanding in relationship to seizures and epilepsy remains limited by the relative lack of cohort studies, especially in people with pre-existing seizures and epilepsy.

Dravet Syndrome (DS), is one of the most common developmental and epileptic encephalopathies (DEEs), with early onset of seizures and developmental issues. Fever is one of most common precipitants for seizures.[1] Severe peri-ictal hypoxaemia can complicate seizures in DS.[2] People with DS have a high burden of morbidity and risk of premature mortality, mainly epilepsy-related.[3]

In an unprecedent catastrophic event such as the SARS-CoV-2 pandemic, people with epilepsy have faced multiple challenges, including the risk of infection itself but also indirect effects related to their comorbidities, reduced access to treatment and health-care services and stress.[4] In the UK, shielding and additional support have been recommended for people with specific medical conditions that have been established or considered to be associated with greatest risk of severe illness from COVID-19, that is clinically 'extremely vulnerable' status. In the UK, epilepsy broadly is not included in this category, but people can also be classed as clinically extremely vulnerable, based on clinical judgement and an assessment of their needs.[5] Additional guidance in people with severe epilepsies is needed.

Here we present a survey of people with DS and their carers, to understand the risks, impact and outcome on one of the most severe epilepsy syndromes.

2 | METHODS

This study was a cross-sectional survey open between June 17 and July 13, 2020, conducted by Dravet Syndrome UK (DSUK), an independent patient advocacy group (Charity Number 1128289). DSUK emailed a survey (template available in Supporting Information) to their registered families, who have at least one child or adult with a confirmed and verified diagnosis of DS and who had consented to be contacted by email. Families were invited to complete the survey anonymously with the stated purpose of improving clinical understanding of COVID-19 in people with DS in the UK. Families were advised that the results would be shared with DSUK's medical advisory board and made public subject to consultation with DSUK's medical advisory board. Families were given details of DSUK's data handling policy and also given a contact email address at DSUK for any questions arising. No personal information is included in this report of the results of the survey. Variables in the survey included: age, habitual place of residence, residence during lockdown, 'extremely vulnerable' status during lockdown, pre-existing respiratory symptoms, swallowing difficulties, spine abnormalities, need for self-isolation to contact with anyone with COVID-19 symptoms, manifestation of COVID-19 symptoms and/or testing for COVID-19, changes in seizure frequency and/or length associated with COVID-19, other neurological or non-neurological complications associated with COVID-19, medical attention/interventions required for COVID-19.

Fisher's exact test or Pearson χ^2, as appropriate, were used for association tests. Statistical significance was set at a p-value <0.05. Statistical analysis was performed using Stata/IC V.11.1 (Stata, Texas, USA).

3 | RESULTS

A total of 116 responses were collected, from families of children (n = 86; 74%) and adults (30; 26%) with DS, from various parts of the UK and one from Ireland. Age ranges were as follows: under 5 years (n = 23), 5–11 (n = 32), 12–17 (n = 31), 18–24 (n = 16), 25–34 (n = 11), 35–44 (n = 3). The majority (106; 91%) were shielded at the family home during lockdown, whilst a few people with DS remained at their residential home (9; 8%) and one DS person stayed at the family business (1%). 'Extremely vulnerable' status for risk of severe forms of COVID-19 was given to 50 (43%) people with DS, whilst 47 (40%) were not and no request was made, 10 (9%) were not despite a request having been made by the GP or neurologist, and 9 (8%) families were uncertain about the declared vulnerability status of their child. At least three DS people without 'extremely vulnerable' status have been shielding anyway.

Comorbidities potentially increasing the risk of COVID-19 complications were reported in some people with DS; these included a tendency to respiratory problems, for example history of recurrent chest infections, in 28 (24%); swallowing difficulties, for example percutaneous endoscopic gastrostomy (PEG) in 25 (22%); spinal abnormalities, for example scoliosis, curved or twisted spine, in 33 (29%), ranging from mild (n = 24) to severe (n = 2). Statistical analysis did not reveal significant association between any of these comorbidities and presentation of COVID-19 symptoms.

Contact with people who displayed COVID-19 symptoms, necessitating self-isolation, was reported for 10 DS people (9%), and six of these 10 subsequently developed symptoms themselves.

Symptoms compatible with COVID-19 were reported in 22 (19%) DS individuals, including high temperature (17;, 15%), new continuous cough (9; 8%), difficulty in breathing (5; 4%), shortness of breath (4; 3%), sore throat (4; 3%), chills (3; 3%), repeated shaking with chills (3; 3%), muscle pain (3; 3%), headache (3; 3%), new loss of taste or smell (2; 2%), abdominal pain (2; 2%), and other gastrointestinal symptoms (5; 4%). In some people with DS, it was obviously difficult to assess the presence of some symptoms, such as pain or loss of taste or smell. Five people had only isolated high temperature without other symptoms, similar to their habitual episodes of chest infections in most cases. Only four individuals with symptoms had a PCR swab test, none of which was positive; none of the other symptomatic people had a swab test. Only one symptomatic person (symptoms included new continuous cough, high temperature, repeated shaking with chills, muscle pain, headache, sore throat, new loss of taste or smell) had antibody testing (but not swab testing), which was positive. One person had a number of hospitalizations during lockdown due to severe renal failure requiring dialysis; he did not have any symptoms of COVID-19 but had repeated swab tests whilst in hospital, which were positive on three occasions over about seven weeks: the infection was not considered relevant to his clinical presentation as he tested positive for the first time three weeks after he had been admitted with renal failure. The cause of renal failure was attributed to polytherapy for his epilepsy. Six other

TABLE 1 Summary of clinical presentation and required treatment in the 22 children (<18 years) and adults (≥18 years) who had symptoms compatible with COVID-19.

Children	Age range (years)	Symptoms	Medical attention required	COVID–19 testing	Change in seizure pattern
	Under 5	Difficulty breathing	Required resuscitation, ventilation, and antibody treatment in hospital	No	Increased frequency and duration
	Under 5	High temperature, shortness of breath	Treated with oxygen in hospital	Negative PCR swab	Increased frequency
	Under 5	High temperature, repeated shaking with chills, sore throat, cough	Attended emergency department, no treatment required	No	Increased frequency and duration, including longer postictal recovery
	Under 5	High temperature, gastrointestinal symptoms	Required ventilation in hospital	No	Increased frequency and duration
	Under 5	New continuous cough, high temperature	No	No	No
	5–11	New continuous cough, high temperature, repeated shaking with chills, muscle pain, headache, sore throat, new loss of taste or smell	Treated with oxygen at home	Positive for antibodies	Increased frequency (responded to clobazam increase)
	5–11	High temperature, generally unwell for a week	No	No	No
	5–11	New continuous cough, high temperature, difficulty breathing, muscle pain, sore throat	Treated with oxygen at home	No	No
	5–11	High temperature	Was already on non-invasive ventilation with BiPAP ventilator, was treated with antibiotics and oxygen at home	No	No
	5–11	Headache, new loss of taste or smell	No	Negative PCR swab	No
	5–11	High temperature	No	No	No
	5–11	New continuous cough, high temperature	No	No	No
	5–11	New continuous cough, high temperature, shortness of breath, difficulty breathing, repeated shaking with chills	Treated with oxygen and intravenous antibiotics in hospital	No	Increased frequency and duration
	12–17	Gastrointestinal	No	Negative PCR swab	Unknown
	12–17	High temperature and sore throat	No	No	Increased frequency
	12–17	New continuous cough and flu-like symptoms	No	No	Increased frequency
	12–17	New continuous cough, high temperature, shortness of breath, difficulty breathing, muscle pain, headache, abdominal pain and other gastrointestinal symptoms, ear pain, post-infectious neurological and psychological symptoms (diagnosed with PANS/ PANDAS)	Yes, oxygen saturation monitored at home; no treatment required	No	No
	12–17	High temperature	No	No	Unknown
	12–17	High temperature	No	No	Increased frequency

(Continues)

TABLE 1 (Continued)

Children	Age range (years)	Symptoms	Medical attention required	COVID-19 testing	Change in seizure pattern
Adults	18–24	High temperature	No	Negative PCR swab	No
	18–24	New continuous cough, high temperature	No	No	Increased frequency and duration
	25–34	New continuous cough, high temperature, shortness of breath, difficulty breathing, gastrointestinal symptoms, red eyes	No	No	Increased frequency

Abbreviations: BiPAP, Bilevel Positive Airway Pressure); PANDAS, paediatric autoimmune neuropsychiatric disorder associated with streptococcal infections; PANS, paediatric acute-onset neuropsychiatric syndrome.

asymptomatic people had negative swab tests. One asymptomatic person was admitted to hospital due to a seizure and had an antibody test which was negative.

Of the people with DS with COVID-19 symptoms, during the illness five had more frequent and longer seizures (of these, in one also a longer postictal recovery was described), six had more frequent seizures without change in seizure length, and nine had no changes in seizure frequency or length; there was no information provided for two (Table 1). Interestingly, the person asymptomatic for COVID-19 who repeatedly tested positive on swab testing was reported to have reduced seizure frequency at the time of testing.

One young person with DS, aged 12–17 years, had various symptoms including new continuous cough, high temperature, shortness of breath, difficulty breathing, muscle pain, headache and ear pain, abdominal pain and other gastrointestinal symptoms, but did not have swab or antibody testing. This individual experienced post-infectious neurological and psychological symptoms and was diagnosed with paediatric acute-onset neuropsychiatric syndrome (PANS)/paediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS). It is difficult to establish the cause with certainty.

In 9/22 (41%) people with DS and COVID-19 symptoms, medical attention was required because of their clinical symptoms of infection, either at home (n = 4) or in a hospital setting (n = 5) including intensive care (n = 2), oxygen administration and/or ventilation (n = 6), intravenous antibiotic treatment (n = 1) or just monitoring of oxygen saturation (n = 2) (Table 1).

There was no significant difference in the prevalence of symptoms between children and adults (19, 22%, in children vs 3, 10%, in adults, $p = 0.115$). However, we note that all the individuals who developed more severe symptoms requiring medical attention were children (four under age 5 years, four aged 5–11 years, one aged 12–17). There was no difference between the individuals who required medical attention and the ones who had milder forms, with respect to the following comorbidities: scoliosis ($p = 0.310$), swallowing difficulties ($p = 372$) and tendency to develop respiratory illnesses such as recurrent chest infections ($p = 0.474$).

From the open comment section (most relevant comments summarized in Table 2), additional points emerged, including parental anxiety related to shielding and risks of carers and other family members contracting the infection, anxiety related to hospital attendance, lack of support during shielding, difficulties during lockdown with changes in routine affecting mood and behaviour. On the other hand, one family reported a positive effect of the lockdown with their child being happy with the parents being the only carers and receiving support from a mental health nurse, psychologist and psychiatrist through frequent video calls, and another family reported reduced seizure frequency during lockdown possibly due to reduced infections and stress normally related to school attendance.

In one case, it was reported that the use of clobazam for increased seizure frequency was an effective treatment measure.

TABLE 2 Most relevant comments related to shielding, reported from the open comment section (reported as original comments, anonymized).

Original comments
As a parent I am experiencing anxiety as shielding due to end in August. We have a care agency supporting the 24/7 care needs our daughter has, and I'm also very worried about the risks that having carers come in presents to our daughter and us as a family. My other children are expected to resume school in Sept, as am I as I work in school and I'm terrified about the risks this presents.
Been in lockdown since 4th of March no carers or respite. But carers slowly coming back in wearing full ppe.
We have kept daughter as isolated as possible during lockdown, and continue to do so, to protect her health; whilst balancing out her and our wellbeing need and taking occasional respite support and some brief visits to school during July. We have had one Carer helping who has remained in our bubble as best we can. We feel this careful but pragmatic approach has worked for us. We are opening up gradually but remain cautious.
Feel totally let down from people that are supposed to support us, no care workers, no disability social worker contactable, no help, absolutely exhausted.
Just far more behavioural issues due to lockdown and change routine.
Seizure control good. Do not see GP or specialist. Was refusing to leave house for months before lockdown so has not been upset by it in fact has been happy with her parents as sole Carers!!! Mental health nurse, psychologist and psychiatrist in frequent telephone and video contact. We stopped PAs [personal assistants] coming before lockdown.

4 | DISCUSSION

This survey reports 22/116 (19%) individuals with DS who presented with respiratory and other symptoms during the pandemic, though the symptoms were not necessarily specific for COVID-19. The main limitation of the survey is the lack of testing which makes it difficult to establish the actual risk or presence of infection and related outcomes.

Most families have been shielding even if their child with DS was not given 'extremely vulnerable' status, and this may have contributed to prevention of infection. A few individuals with DS had been in contact with people who displayed COVID-19 symptoms, necessitating self-isolation, and the majority of them subsequently developed symptoms themselves. Symptoms were severe enough to require hospitalization in six individuals (5%), with admission to intensive care for ventilation in two. The presence of comorbidities, including susceptibility to respiratory infections, dysphagia, and spinal abnormalities, was not significantly associated with the presentation of COVID-19 symptoms. However, the statistical analysis was limited by the small sample size.

In 50% of people with DS who developed possible or probable COVID-19 symptoms, seizure worsening was reported, in terms of seizure frequency or duration or both, but no episodes of status epilepticus or other complications were described. A few families described a similar pattern of seizure exacerbation to the one that their children would have during any concurrent respiratory infection. In one person with DS, sequelae of neurological and psychiatric symptoms were reported, and a diagnosis of PANS/PANDAS was made. Again, lack of testing represents a major limitation to ascription of causality. No other post-infectious complications were reported.

Interestingly, of the five individuals who had a swab test, the only one who tested positive (on three occasions) had no COVID-19 symptoms despite severe renal failure requiring dialysis (and now awaiting kidney transplant). This is in keeping with the observation of asymptomatic individuals even among vulnerable people with epilepsy and other comorbidities.[6] In our long-term care facility for adults with epilepsy, we recently reported two people with DS who tested positive on a PCR swab test: one required hospitalization but only had mild respiratory symptoms and has now fully recovered; the other was asymptomatic, although subjective symptoms such as loss of taste or smell could not be assessed due to cognitive impairment; neither had significant seizure deterioration.[6]

The impact of COVID-19 in epilepsy is not fully established yet, with only a few retrospective studies reporting neurological symptoms, which do not always include seizures, in the context of severe acute respiratory syndrome due to COVID-19.[7-18] Data on the impact of COVID-19 in people with pre-existing epilepsy is also limited.[19-21] The impact of COVID-19 in the most severe forms of epilepsy such as DEEs and other genetic epilepsies is even less well established.[22]

Whilst there was no difference in the age of individuals who had symptoms compatible with COVID-19, we note as an observation that all those who required medical attention were children (the majority below the age of 12 years). In a cross-sectional study of 48 critically ill children affected by COVID-19 and admitted to North American paediatric intensive care units, an uncharacterized 'neurological presentation' was reported in two children, and three had 'seizures' as pre-existing comorbidity; this study showed that rates of COVID-related severe illness and mortality in children are lower than in adults.[8] In the paediatric population, there are a small number of children who present with a Kawasaki-like disease, also known as toxic shock syndrome, which includes persistent fever, single or multi-organ dysfunction, headache, and meningeal signs; no seizures have been reported to date associated with this Kawasaki-like disease.[9,10] No such presentation was reported in our cohort. This observation should be interpreted with caution due to the small sample size and the possibly different threshold for parents to seek medical attention for younger children.

Limitations in our study include the small sample size, the retrospective design of the survey, and the lack of data on infection status and immunity due to limited testing having been performed. There is no information available on the occurrence of similar symptoms in previous years; therefore, for most subjects who developed symptoms the association with COVID-19 infection remains purely

speculative. This was not a controlled study, which would be difficult to justify. We should also note that our cohort mostly included children and young adults and this age distribution may have contributed to the benign outcome observed in all cases.

Most families in our survey were or have been shielding even when not medically advised to do so, and although this may have contributed to prevention of infection, there was anecdotal evidence of social and psychological issues related to shielding (Table 1). Shielding may represent an important factor for prevention of infection, and general practitioners and epilepsy specialists could consider inclusion in the 'extremely vulnerable group' of people with DS who have comorbidities that may increase the risk of severe outcomes. On the other hand, if the latter are not present, there is no evidence currently that people with DS are at increased risk of severe outcomes from COVID-19, and shielding in these circumstances seems unjustified and may carry adverse psychosocial consequences. Tolerance of shielding may vary significantly across people with DS, and we do not know its longer term consequences on mood and behaviour. The impact on caregivers has also not been clearly established yet. Given the clinical spectrum of severity in DS, a holistic risk/benefit assessment of shielding should be conducted on an individual basis, including health and social care needs. The physical and mental wellbeing of families and carers should also be considered in such an assessment.

Testing at least of symptomatic people, and regular surveillance for people living in residential care homes, is a crucial factor to reduce the spread of infection, and thus limiting the impact of the pandemic in vulnerable people.[6]

Although from our study we cannot establish what preventative factors may have been present, we observed an infection rate, determined by compatible symptoms, of 19%, with no deaths and benign outcome in most cases despite the underlying complex condition. We could cautiously conclude that DS may not put affected individuals at increased risk of severe outcomes, compared with those with other health conditions,[23] assuming that shielding and other infection prevention and controls are put in place.

Should there be a further wave of infection, we recommend prompt testing of symptomatic individuals, and regular surveillance for people living in residential care facilities. Declaration of 'extremely vulnerable status' and shielding should be considered on an individual basis, following assessment of comorbidities that may increase the risk of severe outcomes. We do not know what adverse effects there may be of prolonged or repeated shielding, and such consequences need consideration. There is no treatment for COVID-19 yet. A number of studies are investigating potential therapeutic targets. Vaccination seems the most promising strategy, with 33 candidate vaccines under clinical evaluation.[24] Although vaccination is often a precipitating factor of seizure onset in DS,[25] there is now established evidence that vaccination-associated earlier seizure onset does not alter disease course in DS.[26,27] Subsequent vaccinations do not significantly affect clinical and cognitive outcome,[28] whilst the risk of subsequent vaccination-associated seizures seems to be vaccine-specific.[27]

In conclusion, our study provides additional evidence that risk of severe outcomes of COVID-19 in people with DS may not be not significantly increased, although medical attention may still be required. However, prospective studies are lacking.

ETHICS STATEMENT

We abided by national regulations in the UK where the survey was undertaken. Data handling information was provided at the start of the survey and detailed in the following link: https://www.dravet.org.uk/privacy-policy/. This meets the information and consent requirements for survey data sharing, as stated in the UK Data Service regulation (https://www.ukdataservice.ac.uk/manage-data/legal-ethical/consent-data-sharing/surveys.aspx). No personal information is included in this report of the results of the survey.

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CONFLICT OF INTEREST

None of the authors have competing interests to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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