The impact of COVID-19 in Dravet Syndrome: a UK survey

Simona Balestrini[1], Galia Wilson[2], Claire Eldred[2], Helen Evans[2], Sanjay M Sisodiya[1]

[1] Department of Clinical and Experimental Epilepsy, UCL Queen Square Institute of Neurology, London, UK, and Chalfont Centre for Epilepsy, Chalfont St. Peter, UK.

[2] Dravet Syndrome UK (DSUK), Registered Charity Number 1128289, member of Dravet Syndrome European Federation (DSEF)

Abstract

Aim. The aim of this survey was to understand the risks, impact and outcome of COVID-19 in people affected by Dravet Syndrome.

Method. An anonymous cross-sectional online survey was conducted between June 17 and July 13, 2020, addressed to families of people with Dravet Syndrome.

Results. A total of 116 responses were collected, from families of children (n=86; 74%) and adults (30; 26%) with Dravet Syndrome. 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.

Interpretation. In this cohort of people with Dravet Syndrome, 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. 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.

Introduction

The COVID-19 pandemic, which to date has caused over 800,000 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 (Dravet et al, 2005). Severe peri-ictal hypoxaemia can complicate seizures in DS (Kim et al, 2018). People with DS have a high burden of morbidity and risk of premature mortality, mainly epilepsy-related (Shmuely et al, 2016).

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 (Huang et al, 2020). 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, i.e. clinically 'extremely vulnerable' status. Epilepsy 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 (https://www.gov.uk/government/publications/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19#definition). 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.

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 Supplementary Data) 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. 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 chi^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).

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. 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, e.g. history of recurrent chest infections, in 28 (24%); swallowing difficulties, e.g. percutaneous endoscopic gastrostomy (PEG) in 25 (22%); spinal abnormalities, e.g. 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 with 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 hospitalisations 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: the infection was not considered relevant to his clinical presentation. Six other 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. 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 10/22 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=6) including intensive care (n=2), oxygen administration and/or ventilation (n=6), intravenous antibiotic treatment (n=1) or just monitoring of oxygen saturation (n=3).

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).

From the open comment section (most relevant comments summarised in Table 1), 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.

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 hospitalisation 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 (Balestrini et al, 2020). 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 hospitalisation 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 (Balestrini et al, 2020).

The impact of COVID-19 in epilepsy is not fully established yet. A retrospective study in Wuhan of 214 hospitalized patients with severe acute respiratory syndrome due to COVID-19, reported one case with occurrence of a convulsive seizure; impaired consciousness and acute stroke were the most common neurological symptoms (Mao et al, 2020). In a cross-sectional study of 48 critically ill children affected by COVID-19 and admitted to North American paediatric intensive care units, an uncharacterised '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 (Shekerdemian et al, 2020). In the paediatric population, there are a small but growing 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 (Riphagen et al, 2020; Verdoni et al, 2020). Another retrospective multicentre study conducted in China including 304 children and adults hospitalized during the acute phase of COVID-19 infection did not report an increased risk of acute symptomatic seizures or status epilepticus (Lu et al, 2020), despite these having been reported anecdotally (Abdulsalam et al, 2020; Anand et al, 2020; Dugue et al, 2020; Elgamasy et al, 2020; Hepburn et al, 2020; Karimi et al, 2020; Moriguchi et al, 2020; Vollono et al, 2020).

Data on the impact of COVID-19 in people with pre-existing epilepsy is also limited. A cross-sectional study conducted in Spain suggested a higher risk of contracting COVID-19 and of

disease-related fatality in people with epilepsy, although the sample size was very small (Cabezudo-García et al, 2020). An online survey conducted in Italy showed seizure worsening in 67/456 (18%) people with epilepsy, mainly in those taking a higher number of antiseizure medications (ASMs) and with sleep disturbances (Assenza et al, 2020), which may both be markers of a more severe epilepsy. Another survey conducted in Saudi Arabia reported seizure frequency increase in 46/156 (29.5%) people with epilepsy, which again seemed associated with a higher number of ASMs, sleep changes, but also with higher baseline seizure frequency, non-adherence to treatment, and increase in self-reported stress (Alkhotani et al, 2020).

The impact of COVID-19 in the most severe forms of epilepsy such as DEEs and other genetic epilepsies is even less well established. A cross-sectional survey conducted in Spain and including 277 caregivers of people with DEEs (mean age 12.4 years) documented seizure frequency increase in 39 (14%) and behavioural deterioration in 87 (30%) cases during the lockdown, and these were associated with various factors including difficulties in accessing medications, living in homes without outside space, and caregivers' anxiety. Three people with DEE, including one with DS, tested positive for SARS-CoV-2 infection; all had mild symptoms, and none required hospitalisation or had clinical deterioration (Aledo-Serrano et al, 2020).

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. This was not a controlled study, which would be difficult to justify.

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 (Balestrini et al, 2020).

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 (Clark et al, 2020), 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 (World Health Organization, 2020). Although vaccination is often a precipitating factor of seizure onset in DS (Tro-Baumann et al, 2011), there is now established evidence that vaccination-associated earlier seizure onset does not alter disease course in DS (McIntosh et al, 2010; Verbeek, et al, 2015). Subsequent vaccinations do not significantly affect clinical and cognitive outcome (Zamponi et al, 2014), whilst the risk of subsequent vaccination-associated seizures seems to be vaccine-specific (Verbeek et al, 2015).

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. However, prospective studies are lacking.

Table 1. Most relevant comments related to shielding, reported from the open comment section (reported as original comments, anonymised).

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.

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