Genetic epilepsies and COVID-19 pandemic: Lessons from the caregiver perspective

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LETTER

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To the Editors:

The COVID-19 pandemic represents an unprecedented international crisis with significant health, economic, and social consequences. This scenario has forced the medical community to face new practical and ethical challenges that require rapid responses. Early data show a variety of neurological manifestations in a significant proportion of patients with SARS-CoV-2 infection,[1,2] although there is little documentation of the effects on people with epilepsy.[2,3] In this study, we assess the impact of the COVID-19 pandemic in a particularly vulnerable population: individuals with genetic developmental and epileptic encephalopathies (DEEs) and their caregivers. Although children appear to present milder COVID-19 manifestations,[4] patients with DEEs present an increased susceptibility to certain triggers related to viral infections and respiratory comorbidities, are at risk of missing medical follow-up and emergency assistance due to health care resource allocation focus on COVID-19 patients, and are exposed to broader sociopsychological impact related to lockdown. Therefore, this study evaluates the impact of the pandemic on patients with genetic DEEs and their caregivers in Spain, one of the current hotspots of the pandemic.

This study was a cross-sectional survey open between April 7 and April 11, 2020, 23-27 days after national lockdown was established in Spain. Participants were caregivers of DEE patients with proven or suspected genetic origin, recruited through patient advocacy groups, using internet-based sources. They were asked to fill out a structured questionnaire. Informed written consent was obtained from each caregiver. This methodology, previously used for Dravet syndrome and other neurodevelopmental diseases,[5] permits collecting larger samples for rare conditions. Statistical analysis was performed with R v3.6.2.

A total of 277 responses from caregivers were collected, covering several different conditions. The most frequent genetic diagnoses were as follows: *SCN1A*, *CDKL5*, *STXBP1*, *KCNQ2*, *PCDH19*, and *SYNGAP1* (see Table 1). DEEs of suspected genetic origin with negative genetic findings were reported by 36.8%. Mean age was 12.4 years; 58.1% were female. Fifteen patients (5.5%) were reported to present typical COVID-19 symptoms. Only seven of them were tested with SARS-CoV-2 polymerase chain reaction, with a positive result in three cases. The type of DEE of these three patients was Dravet syndrome, *STXBP1* encephalopathy, and DEE without genetic diagnosis. All of them had mild symptoms, and none needed hospitalization or showed either seizure or behavioral worsening. Because of the high rate of mild or asymptomatic cases in pediatric populations, we also asked whether there had been confirmed COVID-19 cases in people with close contact with the patient. That was the case in 30 (10.8%).

Overall, 39 (14.1%) and 87 (30.3%) cases reported seizure frequency increase or behavioral deterioration during the lockdown, respectively. In addition, there was one case of status epilepticus and nine patients who experienced some degree of neurological regression. Caregivers reported a series of partly overlapping factors that could contribute to seizure or behavioral deterioration: (1) new onset symptoms of anxiety (68.6%) or depression (69.7%) in caregivers, (2) inability to reach their neurologist using telemedicine resources (62.8%), (3) living in homes without a terrace or yard (62.8%), (4) economic problems (62.4%), (5) loss of regular stimulation and physical therapies (51.8%), (6) avoidance of seeking medical advice for serious health issues in the emergency department due to fear of COVID-19 (20.6%), (7) cancelation of essential medical appointments (18.5%), and (8) difficulties finding their antiseizure medication (ASM) at a pharmacy (8.3%). Some of these factors might be affected by the oversaturated health care system, mainly in the Spanish regions with the highest incidence of COVID-19 (Madrid or Catalonia), where 55.5% of the survey responders live.[6] To explore the association between these factors and epilepsy or behavior worsening we performed bivariate (see Table 1) and multivariate analysis. Multivariate logistic regression showed that the main variables associated with seizure increase were age ($P = .034$) and difficulties finding ASM ($P = .05$), whereas the main variables associated with behavioral deterioration were type of epilepsy ($P = .015$), living in a home without a terrace or yard ($P = .009$), and caregivers' anxiety ($P < .001$).

TABLE 1 Changes in epilepsy and behavior according to type of genetic epilepsy and other relevant variables during the pandemic

	Stable epilepsy	Epilepsy worsening	*P*	Stable behavior	Behavioral worsening	*P*
Type of genetic epilepsy						
Dravet syndrome	50 (94.3)	3 (5.7)	—	37 (69.8)	16 (30.2)	—
CDKL5 deficiency disorder	19 (90.5)	2 (9.5)	—	18 (85.7)	3 (14.3)	—
STXBP1 encephalopathy	15 (75)	5 (25)	—	17 (85)	3 (15)	—
KCNQ2 encephalopathy	14 (100)	0 (0)	—	7 (50)	7 (50)	—
PCDH19-related epilepsy	11 (91.7)	1 (8.3)	—	11 (91.7)	1 (8.3)	—
SYNGAP1 disorder	8 (100)	0 (0)	—	3 (37.5)	5 (62.5)	—
Other genetic DEEs[a]	39 (83)	8 (17)	—	30 (63.8)	17 (36.2)	—
DEEs without genetic diagnosis	82 (80.4)	20 (19.6)	—	70 (68.6)	32 (31.4)	—
Total	238 (85.9)	39 (14.1)	.117	193 (69.7)	84 (30.3)	.038
Other relevant variables						
Current age	10 (6.1)	12 (6.2)	.088	10 (6.1)	10 (6.1)	.575
COVID-19 in patient[b]	11 (73.3)	4 (26.7)	.137	11 (73.3)	4 (26.7)	.9
COVID-19 in close contacts[b]	21 (70)	9 (30)	.021	17 (56.7)	13 (42.3)	.093
COVID-19 high-incidence region	125 (82.7)	26 (17.3)	.084	101 (66.9)	50 (33.1)	.251
Cancelation of relevant medical visits	38 (74.5)	13 (25.5)	.01	30 (58.8)	21 (41.2)	.058
Difficulties finding ASM at pharmacy	15 (65.2)	8 (34.8)	.008	16 (69.6)	7 (30.4)	.968
Home without terrace or yard	146 (83.9)	28 (16.1)	.21	113 (65.3)	60 (34.7)	.03
New onset anxiety	158 (83.2)	32 (16.8)	.051	115 (60.8)	74 (39.2)	<.001

Note: Quantitative variables are expressed as median (interquartile range), qualitative variables as frequency (%).

Abbreviations: ASM, antiseizure medication; DEE, developmental and epileptic encephalopathy.

[a]Other genetic diagnoses with more than one case were: *SCN8A* and *GNAO1* (n = 5 each), *SCN2A* (n = 4), and *CACNA1A*, *TSC1*, and *SCN9A* (n = 3 each).

[b]COVID-19 cases are suspected or confirmed in patients, confirmed in contacts.

In conclusion, although more research is needed and a cross-sectional design has obvious limitations, patients with DEEs and their caregivers face multiple challenges during the COVID-19 pandemic that might lead to worse seizure and psychological outcomes in this population. According to our results, these would be related to both the direct impact on the patients of the COVID-19 infection and the lockdown, and indirectly to health system barriers (so-called "secondary harm"[7]) and sociopsychological and economic burdens of the caregiver.

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CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this letter is consistent with those guidelines.

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