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EPILEPSY IN TIME OF COVID-19. A SURVEY-BASED STUDY

RUNNING TITLE: Epilepsy and COVID-19 pandemic.

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ABSTRACT

Objectives: Collateral damage may occur in epilepsy management during the coronavirus (COVID-19) pandemic. We aimed to establish the impact of this pandemic on epilepsy patients in terms of patient-reported seizure control and emerging symptoms.

Materials & Methods: Cross-sectional study including consecutive patients assessed by telephone contact in an epilepsy clinic during the first month of confinement. Demographic and clinical characteristics were recorded and a 19-item questionnaire was systematically completed. Data regarding the impact of confinement, economic effects of the pandemic, and subjective perception of telemedicine were recorded. Additional clinical data were obtained in patients with a COVID-19 diagnosis.

Results: Two-hundred and fifty-five patients were recruited: mean age 48.2 ± 19.8 years, 121 (47.5%) women. An increase in seizure frequency was reported by 25 (9.8%) patients. Sixty-eight (26.7%) patients reported confinement-related anxiety, 22 (8.6%) depression, 31 (12.2%) both, and 72 (28.2%) insomnia. Seventy-three (28.6%) patients reported a reduction in economic income. Logistic regression analysis showed that tumor-related epilepsy etiology [OR=7.36 (95% CI 2.17-24.96)], drug-resistant epilepsy [OR=3.44 (95% CI 1.19-9.95)], insomnia [OR=3.25 (95% CI 1.18-8.96)], fear of epilepsy [OR=3.26 (95% CI 1.09-9.74)], and income reduction [OR=3.65 (95% CI 1.21-10.95)] were associated with a higher risk of increased seizure frequency. Telemedicine was considered satisfactory by 214 (83.9%) patients. Five patients were diagnosed with COVID-19, with no changes in seizure frequency.

Conclusions: The COVID-19 pandemic has effects in epilepsy patients. Patients with tumor-related, drug-resistant epilepsy, insomnia, and economic difficulties are at a higher risk of increased seizure frequency. Telemedicine represents a suitable tool in this setting.

KEYWORDS: Seizures, coronavirus, pandemics, epilepsy, quality of life

INTRODUCTION

In late December 2019, the health authorities of Wuhan City (Hubei province, China) reported a series of pneumonia cases of unknown etiology. Shortly thereafter, the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the etiologic agent causing coronavirus disease (COVID-19).¹ This infectious disease rapidly advanced to become a pandemic, as declared by the World Health Organization (WHO) on 11 March, 2020,² and at the time of writing of this article, there are more than two million cases worldwide.³ Spain is one of the most highly affected countries, with nearly 200,000 total cases and 20,000 deaths.⁴

The COVID-19 pandemic is a challenge for healthcare systems around the world. It is an exceptional health emergency that is generating an enormous health and socio-economic impact. The pandemic has led governments to impose stringent measures on the population such as mandatory home confinement to contain the spread of the infection. Among European countries, Spain is second only to Italy in terms of extreme pressure on the healthcare system.⁵ The huge demand for hospital and out-of-hospital resources to treat these patients has led to reorganization of the entire healthcare infrastructure and its workers, and this has inevitably affected healthcare for other conditions, including epilepsy.

In epilepsy patients, the pandemic has led to postponement of outpatient visits, cancellation of epilepsy-related tests, such as electroencephalograms (EEG) and magnetic resonance imaging (MRI) studies, and even difficulties in attending emergency situations due to saturation of the healthcare services. In this context, communications technology is undergoing a revolution, with telemedicine being a useful emerging alternative to facilitate medical care in chronic patients.^{6,7,8}

Chronic health conditions such as hypertension, diabetes, and cardiovascular disease have been identified as risk factors for developing severe Covid-19.^{9,10} However, the relationship between epilepsy and COVID-19, and the effects of the pandemic on epilepsy patients have been scarcely investigated to date. Patients with epilepsy face a unique situation at this time, and some may be at risk of breakthrough seizures not only due to COVID-19 itself, but also to the effects of home confinement and collapse of the healthcare services.

This study provides the results of a cross-sectional survey of patients from a specialized Epilepsy Unit at a Spanish tertiary hospital and reference center for patients with COVID-19. The aim of the study was to establish the impact of the pandemic on epilepsy patients in terms of seizure

control and other key indicators, and to determine their subjective perception of telemedicine as a remote resource in this exceptional setting.

METHODS

Study design and participants

This is a cross-sectional study conducted in a specialized Epilepsy Unit including patients assessed by the outpatient clinic between 16 March and 17 April 2020. Following the guidelines described in the Vall d'Hebron Hospital contingency plan, all patients with an outpatient visit scheduled before the Spanish Government's state of alarm declaration on 13 March 2020 were assessed by telephone visit. The study conforms with World Medical Association Declaration of Helsinki and it was approved by the Vall d'Hebron Research Institute Clinical Research Ethics Committee [PR(AG)2018-2020]. Patients 17 years of age and older with a definite diagnosis of epilepsy according to the International League Against Epilepsy (ILAE) criteria¹¹ were consecutively included in the study. All patients included gave oral consent for participation. The presence of psychogenic non-epileptic seizures only, paroxysmal neurological symptoms of an uncertain or non-epileptic nature, acute symptomatic seizures without a strict epilepsy diagnosis, and inability to complete the questionnaire by patients or their caregivers were considered exclusion criteria. All patients were attended by a trained epileptologist in a telephone visit, in which seizure frequency, treatment-related adverse events and other emerging symptoms were assessed as a routine outpatient evaluation. Information regarding epilepsy syndromes, current antiepileptic drug (AED) treatment, average baseline seizure frequency and drug resistance was obtained from the medical records. All epilepsies were classified according to the current ILAE classification.¹² The Modified Rankin scale (mRS) score¹³, presence of dysphagia, and demographic data, including current living and employment situation, were assessed. The presence of intellectual disability was also recorded, defined as neurodevelopmental disorders involving significant limitations in both intellectual functioning and in adaptive behavior, according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5).¹⁴

Telephone survey description

After the routine clinical telephone visit, a neurologist administered a 19-item questionnaire to all participants. The survey was administered directly to patients, or to their caregivers in those with intellectual disability, dementia, or other conditions which, in the neurologist's opinion, made

them unable to answer the questions. The 19 items included were mainly closed-ended questions for which patients had a choice of answers. The last question was open-ended and patients were able to provide additional comments or suggestions related to the survey, the pandemic, or the confinement measures if they so desired. The questionnaire had five sections related to the following: 1) effects of the isolation measures taken by the patient or their families/caregivers; 2) effects of the government-imposed confinement on seizure frequency, AED treatment, emergency room consultations, delays in testing, and emergence of anxiety/depression symptoms and sleep disturbances, as perceived and self-reported by the patients. Changes in seizure frequency were estimated based on the average baseline seizure frequency and seizure count during the confinement period. Severity and impact of anxiety and depression symptoms were evaluated by the neurologist, and were interpreted as emerging symptoms when considered clinically significant. Patients were also asked what their worst fear was at the moment; 3) economic impact of the pandemic on the patients' usual income; 4) subjective perception of telephone visits during the pandemic. Finally, 5) patients were questioned about symptoms compatible with COVID-19. Those with a possible or confirmed diagnosis of COVID-19 were then asked about their seizure frequency during the disease, need for hospital or intensive care unit (ICU) admission, treatments received, progress of the disease, and possible changes in AED treatment. If necessary, medical records were reviewed to obtain detailed information regarding the treatments received and clinical outcome. The presence of fever, cough, myalgia or arthralgia and associated fatigue without dyspnea or clinical/radiological signs of pneumonia were considered mild COVID-19-compatible symptoms.¹⁵ A self-reported 50% or higher increase with respect to the patient's baseline seizure frequency, obtained from the medical records, or the development of unprovoked seizures in previously seizure-free patients were considered increased seizure frequency.

Statistical analysis

Descriptive and frequency statistical analyses were obtained and comparisons were made using the IBM SPSS Statistics 22.0 software. Categorical variables are reported as frequencies (percentages) and continuous variables as the mean $\pm$ standard deviation (SD) or median and interquartile range [IQR], as appropriate. Statistical significance in comparisons between the variables studied and increased seizure frequency were assessed using Pearson's chi-square test for categorical variables (except when at least one expected frequency in the contingency table was less than 5, in which case the Fisher exact test was used), the Student *t* test in comparisons with age, and the Mann-

Whitney *U* test in comparisons with the number of antiepileptic drugs and the mRS. Variables associated with a *p*-value <0.1 in the univariate analysis were entered in a forward stepwise multiple logistic regression model as independent variables to identify factors independently associated with an increase in seizure frequency. Odds ratios (ORs) and 95% confidence intervals (CIs) are shown in the final model. A bar chart was designed to show the probability of a seizure frequency increase according to the cumulative number of independently associated factors. *P*-values <0.05 were considered statistically significant.

RESULTS

During the period of study, 335 patients were assessed by telephone contact with the Epilepsy Clinic and 255 of them were included in the analysis. The details of the enrollment process are shown in Figure 1.

Mean age of the patients included was 48.2 ± 19.8 years, and 121 (47.5%) were women. Most patients had focal epilepsy (*n*=223; 87.5%), and 56 (22%) patients had a diagnosis of drug-resistant epilepsy. The most frequent focal epilepsy subtype was temporal lobe epilepsy (*n*=101; 44.9%), followed by frontal (*n*=60; 26.7%), parietal (*n*=9; 4%), and posterior quadrant (*n*=9; 4%). Forty-six patients (20.4%) had focal epilepsy with undetermined epileptic foci. The demographic and clinical characteristics of the sample are summarized in Table 1.

Impact of confinement and isolation measures

Twenty-five (9.8%) patients reported an increase in seizure frequency relative to their baseline status since the start of confinement, whereas 11 patients (4.3%) reported a reduction in seizure frequency. Among those with an increase, five patients (20%) consulted in the emergency department because of seizures, three (12%) considered consulting but did not for fear of SARS-CoV-2 contagion, two (8%) contacted the emergency phone line and were advised to stay home, and one patient (4%) tried to contact the emergency line, but found it saturated.

A delay in performance of epilepsy-related tests occurred in 37 patients (14.5%). Routine EEG was the test most often delayed (*n*=11; 29.7%), followed by MRI (*n*=9; 24.3%), and video-EEG monitoring (*n*=8; 21.6%). Seven patients (2.7%) reported difficulties obtaining their medication supply in the pharmacy, six (85.7%) because their prescription had expired and one (14.3%) because the medication was not available.

Confinement-related anxiety and depression were reported by 68 (26.7%) and 22 (8.6%) patients, respectively, and 31 patients (12.2%) reported having both anxiety and depression symptoms since the start of confinement. Regarding sleep disturbance, 72 patients (28.2%) reported insomnia and 22 patients (8.6%) reported that their usual sleep schedules had changed. Eighteen patients (7.1%) stated that they were sleeping for a longer period per day than usual due to the confinement measures (Figure 2).

Seventy-three patients (28.6%) stated that the usual family income had decreased because of the confinement-related restrictions. When asked about their worst fear at the time of the interview, 90 patients (35.3%) answered that their worst fear was contracting COVID-19 infection and 37 (14.5%) responded that it was epilepsy. Sixty-one patients (23.9%) had no particular fear at the time, and 37 patients (14.5%) were unable or refused to answer. Thirty patients (11.8%) expressed other fears, the most common being duration of confinement (n=6; 2.4%), neoplastic disease (n=6; 2.4%), and their relatives' health (n=4; 1.6%).

Eighteen patients (7.1%) had to remain under isolation inside their homes to protect themselves or their relatives from contagion. In 21 patients (8.2%), at least one relative with whom they usually live had to be under isolation measures, most often their mother (n=8; 3.1%) or husband/wife (n=6; 2.4%). Among these, five (23.8%) were the patient's principal caregiver. Three patients (1.2%) had to move to a different home because of a suspected case in the family.

Several factors were associated with increased seizure frequency during the confinement period. A tumor-related etiology ($p=0.011$), drug-resistant epilepsy ($p=0.001$), the presence of anxiety ($p=0.028$) or insomnia ($p=0.001$), the fear of epilepsy ($p=0.002$), and a reduction in economic income ($p=0.018$) were significantly associated with increased seizure frequency (Table 2).

On multivariate analysis, a tumor-related etiology (OR=7.36, 95% CI 2.17-24.96), drug-resistant epilepsy (OR=3.44, 95% CI 1.19-9.95), fear of epilepsy (OR=3.26, 95% CI 1.09-9.74), insomnia (OR=3.25, 95% CI 1.18-8.96), and income reduction (OR=3.65, 95% CI 1.21-10.95) were independently associated with increased seizure frequency. The combinations of these factors provided a cumulative probability estimate of increased seizure frequency (Figure 3).

Perception of telemedicine during the pandemic

When asked about their perception of the usefulness of telephone visits during confinement, 124 patients (48.6%) stated they were very satisfied, and 90 (35.3%) were quite satisfied. Seven patients (2.7%) reported that the visits were unsatisfactory, and some refused to answer (n=34; 13.3%). None of the clinical factors were predictive of a better opinion of telemedicine in this setting.

For future follow-ups, 97 (38%) patients considered it useful to conduct telephone visits, while 93 (36.5%) preferred face-to-face visits. Fifty-five patients (21.6%) said they did not prefer one of these options over the other, and nine patients (3.5%) refused to answer. Interestingly, five patients (2%) spontaneously mentioned that they would like to try a video call option.

In the analysis of clinical factors potentially predictive of a better perception of telemedicine in the future, patients with a greater fear for COVID-19 felt positive about conducting telephone visits (49.2% had expressed this fear vs. 30.1% of patients who preferred face-to-face visits; $p=0.037$). A non-significantly higher percentage of patients with drug resistant-epilepsy preferred face-to-face visits (28% vs. 18.4% of those preferring telemedicine visits; $p=0.081$).

COVID-19 in epilepsy patients

Five patients (2%) had a diagnosis of SARS-CoV-2 infection based on PCR detection in a nasal and/or oropharyngeal smear, and all of them required hospital admission. None received mechanical ventilation, and two patients (0.78% of the total sample) died. All five patients received their usual AED treatment, and no changes in seizure frequency were reported. Details on COVID-19 disease in these patients are provided in Table 3.

Twenty-three patients (9%) reported symptoms compatible with mild COVID-19, but had no confirmatory diagnostic test. None of these patients received specific COVID-19 treatment. Nineteen of them (82.6%) reported no changes in seizure frequency, while four patients (17.4%) reported increased frequency. Twenty-one (91.3%) of the possible COVID-19 patients remained under the same AED treatment, and two (8.7%) had treatment changes, one because of a prescription change due to increased seizure frequency and one because of missed AED doses.

Patients with confirmed COVID-19 infection had a higher mean mRS score (3, IQR 2.5-4 vs. 1, IQR 1-2; $p=0.005$) than patients with mild symptoms suggestive of COVID-19 without a confirmed laboratory diagnosis, and there was a higher percentage of men (100% vs. 30.4%;

p=0.008) and ADL-dependent patients (80% vs. 17.4%; p=0.015). In addition, confirmed COVID-19 patients were older (mean age 62.5±24.5 vs. 46.3±22.8; p=0.165) and had a higher percentage of vascular etiologies (40% vs. 10%; p=0.099), but the differences did not reach statistical significance.

DISCUSSION

This study assesses the impact of the COVID-19 pandemic on epilepsy patients with regard to seizure control, emerging symptoms, and other key indicators. The results show that nearly 10% of patients experienced an increase in seizure frequency during the confinement measures, almost half of them reported having anxiety and/or depression symptoms, and nearly 30% experienced insomnia in this context. Some information is available on the impact of the pandemic on several medical specialties,¹⁶ but there is scarce evidence on how it affects patients with chronic neurological disorders, such as epilepsy. Our results provide an overview of the consequences of the confinement measures and restructuring of the healthcare system.

Our sample is a real-life cohort of patients attended in an epilepsy clinic. All patients were assessed by a trained epileptologist, and the epilepsy diagnosis and classification were accurately performed in each case. The percentage of treatment-refractory epilepsy patients was similar to the expected rate in the general epilepsy population,¹⁷ and patients with intellectual disability and dependence for daily living activities were included. Hence, the sample is diverse and representative of the usual patient profile assessed in a tertiary hospital epilepsy clinic.

We found several collateral effects of the pandemic in this sample of patients. A delay in epilepsy-related tests occurred in 15% of patients. However, this value may be underestimated, as patients with a first unprovoked seizure who were not as yet formally diagnosed with epilepsy were excluded from the analysis. It is likely that examinations were delayed in new-onset seizures during the lockdown. The percentage of patients reporting difficulties with their medication supply was found to be low. The survey was conducted between four and six weeks after the start of confinement measures and no drug supply problems have been reported in Spain to date, although this is a potential problem to keep in mind for the long-term that depends on the particularities of pharmaceutical regulation in each country.

Almost 30% of patients experienced a negative economic impact related to the pandemic and confinement measures, and this factor was independently associated with an increase in seizure

frequency. This is an intriguing finding and a cause for concern. Epilepsy patients are known to be at higher risk of employment difficulties and sociodemographic vulnerability,^{18,19} and the socioeconomic impact of the pandemic could have devastating consequences in the epilepsy population worldwide.

A high percentage of epilepsy patients experienced anxiety and depression symptoms, as well as insomnia during the confinement measures. Almost half the patients in our study reported one or more of these symptoms, in line with recent evidence from west China showing that severe psychological distress occurred in epilepsy patients during COVID-19 outbreak²⁰. The magnitude of these manifestations cannot be accurately assessed in a survey analysis, but they provide an approximation of the overall psychological burden of the situation in this population. Anxiety and insomnia were also independently associated with an increase in seizure frequency. This gives an indication of the negative effect these symptoms may have on the overall health state of epilepsy patients, a concept that has been proposed by previous evidence²¹. Sleep deprivation is a known precipitating factor for seizures, and our results are in the line with those reported in the literature, where psychiatric comorbidities have been identified as risk factors for seizure recurrence and pharmacoresistance.^{17,22,23}

Nearly one in every ten epilepsy patients reported an increase in seizure frequency since the start of confinement measures. This result deserves special attention from clinicians, as a significant number of patients may be at risk of breakthrough seizures during this exceptional situation. Tumor-related and drug-resistant epilepsy, the presence of insomnia, and income reductions were identified as independent risk factors for worsening seizure frequency. The two particular types of epilepsy mentioned represent a more difficult-to-treat patient population²⁴. Also, drug-resistant epilepsy has been associated with severe psychological distress during the pandemic²⁰, and our results highlight the need for special attention to these patients. Moreover, a reduction in economic income, in itself, can be a major source of anxiety, depression and insomnia, and therefore, a stress-precipitating factor. Interestingly, the fear of epilepsy was also associated with an increase in seizures. This can be understood as adequate insight on the patients' part about their disease and its control, and it should be taken into account when patients seek medical attention.

On the other hand, a small proportion of patients reported a reduction in seizure frequency during the confinement period. This is an interesting finding, which could represent a spontaneous fluctuation for some patients, but also indicates that a certain beneficial effect of confinement

measures could exist in some particular cases, in terms of schedule and lifestyle regularity and reduction in work stress. However, this small number of patients does not allow making assumptions in this matter, and the negative impact seems to prevail in the overall population of our study, in line with recent literature²⁵.

The presence of three or more of the risk factors identified here elevated the risk of a seizure frequency increase to 40%, and to our knowledge, no further data related to this issue are available. These findings might be useful to identify the most vulnerable patients in this particular setting who could require closer monitoring.

The use of communication technology to provide medical information has been investigated in chronic diseases and in epilepsy,^{26,27} and the unprecedented situation we are currently facing offers a unique scenario in which telemedicine has become an essential tool. According to the recently provided recommendations, telehealth should be prioritized if possible in the current situation,⁷ and in fact our patients had an overall positive opinion of telephone visits during the pandemic. It is likely that the use of more developed tools (i.e. video call) offers a more profitable use of telehealth, since visual contact can help decrease anxiety and concerns regarding health problems.

Regarding COVID-19 itself, five patients in our sample had confirmed SARS-CoV-2 infection. This represents a small proportion of patients included in the cohort. However, there was some bias in COVID-19 detection, as confirmatory diagnostic testing was not indicated in cases with mild symptoms, and many patients with mild symptoms did not consult with the health services. All five confirmed cases required hospitalization, and two patients had a fatal outcome. Epilepsy has not been identified as a risk factor for developing severe COVID-19.^{9,10}

The five confirmed cases in our sample had a higher rate of previous disability and tended to be older than the mild cases, thus suggesting that they had other major risk factors for developing severe COVID-19. Men are also reported to be at higher risk of a poor outcome,²⁸ and all five of our confirmed cases were men. The two deaths reported occurred in patients who were older than 70 years, with previous disability and several comorbidities predisposing to a severe COVID-19. Conclusions cannot be stated with such a small number of confirmed COVID-19 in our sample, but these findings suggest that severe and fatal COVID-19 was probably related to several baseline clinical risk factors other than epilepsy itself in these patients. None of these patients experienced worsening of seizure frequency, in line with a recently published multicenter study in which no

evidence was found to establish a higher risk of acute symptomatic seizures in patients with COVID-19.²⁹

This study has some limitations. The survey design inevitably implies that the data reported are subjective, particularly the presence of emerging symptoms such as anxiety and depression, which could not be quantified by standardized measurement tools. Also, changes in seizure frequency could not be evaluated by an accurate seizure diary given the study design during this period. In addition, the universal application of confinement measures and the diversity of patients and epilepsy types included prevents rigorous comparison with a normal situation, and some outcome measures might represent the natural course of the disease in particular cases. However, the study provides compelling new evidence on early collateral consequences of the COVID-19 pandemic in epilepsy patients. Further longitudinal, and multicenter studies are needed to establish these effects with more precision at the long term.

CONCLUSION

The COVID-19 pandemic and the confinement measures to control it can have an impact on patients with epilepsy. A significant number of patients experienced an increase in seizure frequency, and a high percentage reported anxiety, depressive symptoms, and insomnia. Tumor-related and drug-resistant epilepsy, the presence of insomnia, and a reduction in economic income were found to be risk factors for increased seizure frequency. Telemedicine emerged as a useful tool that was well accepted by patients to offer clinical assessment and mitigate the effects of physical distancing during confinement.

CONFLICT OF INTEREST STATEMENT

E. Fonseca declares research funding and speaker fees from UCB Pharma, Esteve laboratorios, Eisai Inc and Sanofi Genzyme. L. Abaira declares research funding and speaker fees from UCB Pharma, BIAL Pharmaceutical, Eisai Inc., Sanofi Genzyme and Esteve laboratorios. E. Santamarina declares research funding and speaker fees from UCB Pharma, BIAL Pharmaceutical, Eisai Inc. Arvelle and Esteve laboratorios. I. Seijo-Raposo declares research funding from UCB Pharma, Neuraxpharm and GW pharmaceuticals. M. Toledo declares research funding and speaker fees from UCB Pharma, BIAL Pharmaceutical, Eisai Inc., Sanofi, Arvelle and Esteve laboratorios. M Quintana, S. Lallana and JL. Restrepo have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

After publication, anonymized data supporting the findings of this study are available from the corresponding author upon reasonable request from any qualified investigator.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues concerning ethical publication and affirm that this report is consistent with those guidelines.

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Table 1. Demographic and clinical characteristics of epilepsy patients included in the study

Age, years, mean $\pm$ SD (range)	48.2 $\pm$ 19.8 (17 – 94)	
Sex, n (%)	Male	134 (52.5)
	Female	121 (47.5)
Type of epilepsy, n (%)	Focal	223 (87.5)
	Generalized	30 (11.8)
	Unclassifiable	2 (0.8)
Etiology, n (%)	Unknown	76 (29.8)
	Genetic [†]	34 (13.3)
	Vascular	33 (12.9)
	Tumor	29 (11.4)
	Perinatal anoxia	17 (6.7)
	Mesial temporal sclerosis	15 (5.9)
	Post-traumatic	13 (5.1)
	Infectious disease	11 (4.3)
	Malformations of cortical development	10 (3.9)
	Inflammatory/Autoimmune	5 (2)
	Post-anoxic encephalopathy	4 (1.6)
	Toxic/Metabolic	3 (1.2)
	Other	5 (2)
Intellectual disability, n (%)	47 (18.4)	
Dysphagia, n (%)	20 (7.8)	
mRS, n (%)	0	25 (9.8)
	1	94 (36.9)
	2	67 (26.3)
	3	41 (16.1)
	4	26 (10.2)
	5	2 (0.8)
Dependence for ADL, n (%)	70 (27.5)	
Number of AEDs, n (%)	0	5 (2)
	1	126 (49.4)
	2	74 (29)
	3	36 (14.1)

	4	14 (5.5)
Drug-resistant epilepsy, n (%)	56 (22)	
Usual place of residence, n (%)	Own home	162 (63.5)
	Parents' or caregiver's home	82 (32.2)
	Nursing home	10 (3.9)
	Other	1 (0.4)
Current activity, n (%)	Unable to work	88 (34.5)
	Employed	68 (26.7)
	Retired	53 (20.8)
	Unemployed	20 (7.8)
	Student	20 (7.8)
	Homemaker	6 (2.4)
Person responding to the survey, n (%)	Patient	160 (62.7)
	Family/Caregiver	95 (37.3)

†Genetic generalized epilepsy (formerly referred to as idiopathic generalized epilepsy) was considered a genetic etiology. ADL, activity of daily living; AEDs, antiepileptic drugs; mRS, modified Rankin scale; SD, standard deviation

Table 2. Demographic and clinical factors in patients with and without an increase in seizure frequency and significant differences between groups in the univariate analysis. Each clinical variable is represented as the percentage of patients who experienced an increase in seizure frequency (“Yes”) and those who did not (“No”). The clinical factors associated with increased seizures were tumor-related etiology with respect to other etiologies, drug-resistant epilepsy, the presence of anxiety and insomnia during confinement, fear of epilepsy, and an income reduction.
*Variables with statistically significant differences.

Demographic and clinical factors		Increased seizure frequency during confinement		p-value
		No (n=230)	Yes (n=25)	
Age, years, mean $\pm$ SD		48.7 $\pm$ 19.9	43.7 $\pm$ 19.2	0.228
Sex, female		105 (45.7%)	16 (64%)	0.081
Type of epilepsy	Generalized	29 (12.6%)	1 (4%)	0.081
	Focal	200 (87%)	23 (92%)	
	Unclassifiable	1 (0.4%)	1 (4%)	
Epilepsy foci	Temporal	91 (45.3%)	10 (41.7%)	0.903
	Frontal	53 (26.4%)	7 (29.2%)	
	Parietal	9 (4.5%)	0 (0%)	
	Posterior quadrant	8 (4%)	1 (4.2%)	
	Unknown	40 (19.9%)	6 (25%)	
Etiology	Unknown	70 (30.6%)	6 (24%)	0.011
	Tumor*	21 (9.1%)	8 (32%)	
	Vascular	33 (14.3%)	0 (0%)	
	Malformations of cortical development	8 (3.5%)	2 (8%)	
	Infectious disease	11 (4.8%)	0 (0%)	
	Mesial temporal sclerosis	13 (5.7%)	2 (8%)	
	Inflammatory/Autoimmune	3 (1.3%)	2 (8%)	
	Toxic/Metabolic	2 (0.9%)	1 (4%)	
	Post-traumatic	12 (5.2%)	1 (4%)	
	Genetic	32 (13.9%)	2 (8%)	

	Other	5 (2.2%)	0 (0%)	
	Perinatal anoxia	16 (7%)	1 (4%)	
	Post-anoxic encephalopathy	4 (1.7%)	0 (0%)	
Intellectual disability		42 (18.3%)	5 (20%)	0.789
Dysphagia		17 (7.4%)	3 (12%)	0.427
mRS		2 (1-3)	2 (1-2.5)	0.637
Dependence for ADLs		64 (27.8%)	6 (24%)	0.684
Number of AEDs		1 (1-2)	2 (1-3)	0.090
Drug-resistant epilepsy*		44 (19.1%)	12 (48%)	0.001
Anxiety*		84 (37.3%)	15 (60%)	0.028
Depression		46 (20.4%)	7 (28%)	0.381
Insomnia[†]		58 (25.7%)	14 (56%)	0.001
Worst fear	None	60 (30.8%)	1 (4.3%)	0.002
	Epilepsy*	28 (14.4%)	9 (39.1%)	
	COVID-19	82 (42.1%)	8 (34.8%)	
	Other	25 (12.8%)	5 (21.7%)	
Reduced income*		61 (26.9%)	12 (50%)	0.018

ADLs, activity of daily living; AEDs, antiepileptic drugs; mRS, modified Rankin scale.

Table 3. Clinical features of confirmed COVID-19 cases in epilepsy patients

Case	1	2	3	4	5
Sex, age (years)	Male, 38	Male, 82	Male, 83	Male, 74	Male, 33
Epilepsy diagnosis	GGE	Focal, vascular	Focal, vascular	Focal, vascular	Focal, infectious
Comorbidities	RBBB, recurrent nephritic colic	Vascular risk factors, hearth failure, stroke, COPD	Vascular risk factors, atrial fibrillation, ischemic heart disease, stroke, chronic renal failure	Vascular risk factors, pacemaker, chronic renal failure, SAH	Neurocysticercosis
Dysphagia	No	Yes	Yes	No	No
mRS	3	4	4	3	2
COVID-19 symptoms	Fever, cough, headache, cough, odynophagia	Cough, dyspnea, fever	Cough, dyspnea, fever	Cough, dyspnea, fever	Cough, fever
X-ray	Left lung infiltrate	No infiltrates	Right basal infiltrate	Bilateral infiltrates	Bilateral infiltrates
COVID-19 treatment	AZM + DRV/c + HCQ	AZM + LPV/r + HCQ	AZM + LPV/r + HCQ	No treatment due to potential interactions	No treatment due to potential interactions
Death	No	No	Yes	Yes	No

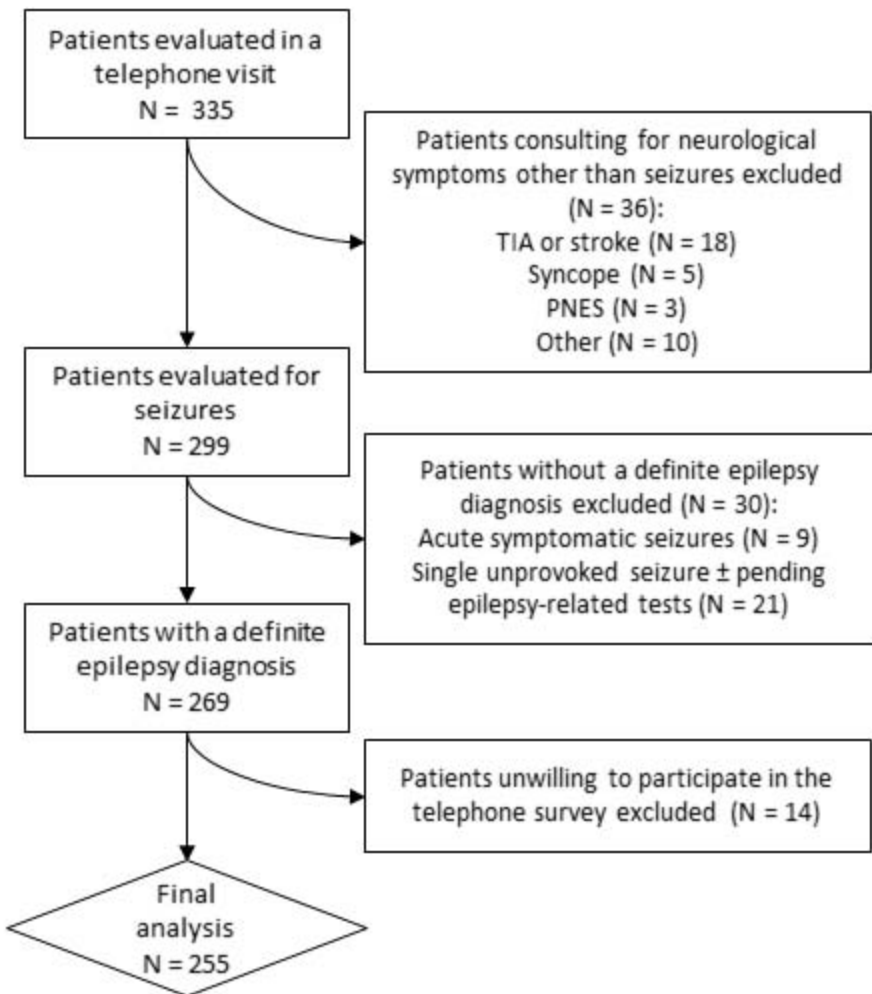
AZM, azithromycin; COPD, chronic obstructive pulmonary disease; DRV/c, darunavir/cobicistat; GGE, genetic generalized epilepsy; LPV/r, lopinavir/ritonavir; mRS, modified Rankin scale; RBBB, right bundle branch block; SAH, subarachnoid hemorrhage

FIGURE LEGENDS

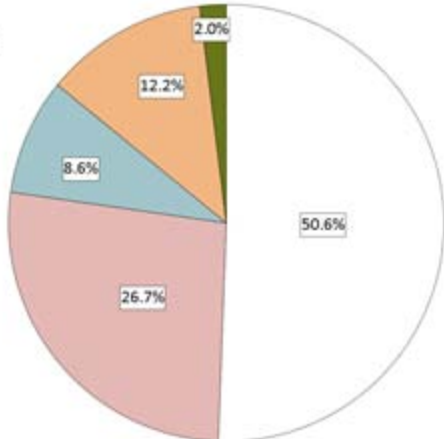
Figure 1. Flow chart of the patient recruitment process. PNES, psychogenic non-epileptic seizures; TIA, transient ischemic attack.

Figure 2. Confinement-related emerging symptoms. A) proportion of patients reporting anxiety and depressive symptoms in the telephone survey. B: proportion of patients reporting sleep disturbances in the telephone survey. N/A: not applicable.

Figure 3. Probability of increased seizure frequency depending on the cumulative association of 5 risk factors (tumor-related etiology, drug-resistant epilepsy, fear for epilepsy, insomnia and reduction of economic income). The bars represent groups of patients divided according to their number of accumulated risk factors (0, 1, 2 and ≥ 3 risk factors). Error bars show the 95% CI. None of the patients with no risk factors reported an increase in seizure frequency, whereas the group with 3 or more risk factors showed the highest percentage of increased seizure frequency (40%).

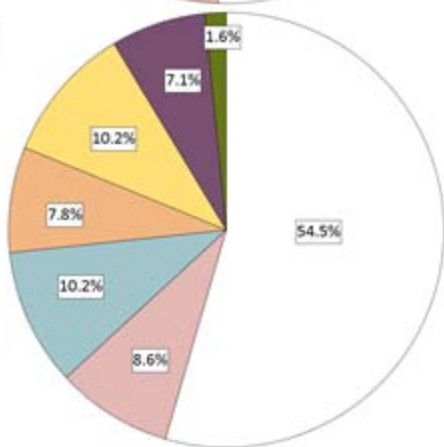


A



- None
- Anxiety
- Depression
- Both
- N/A

B



- None
- Schedule changes
- Conciliation insomnia
- Maintenance insomnia
- Insomnia of both types
- Increased daily hours of sleep
- N/A

