Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Epilepsy & Behavior 112 (2020) 107396

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Influence of the COVID-19 outbreak in people with epilepsy: Analysis of a Spanish population (EPICOVID registry)

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ARTICLE INFO

Article history:
Received 13 June 2020
Revised 3 August 2020
Accepted 6 August 2020
Available online 7 September 2020

Keywords:
COVID-19
SARS-CoV-2
Coronavirus
Epilepsy
Seizure
Neurology

ABSTRACT

Background: The aim of this study was to have a better understanding of the influence of the coronavirus disease 2019 (COVID-19) pandemic in people with epilepsy (PWE) and to assess whether there have been changes in seizure control during the current COVID-19 outbreak, exploring the possible causes thereof.
Methods: This is an observational, retrospective study based on prospective data collection of 100 successive patients who attended an epilepsy outpatient clinic either face-to-face or telephonically during the months of the COVID-19 outbreak and national state of emergency.
Results: One hundred patients were included, 52% women, mean age 42.4 years. During the COVID-19 period, 27% of the patients presented an increase of >50% of seizure frequency. An increase of stress/anxiety (odds ratios (OR): 5.78; $p = 0.008$) and a prior higher seizure frequency (OR: 12.4; $p = 0.001$) were associated with worsening of seizures. Other risk factors were exacerbation of depression, sleep deprivation, less physical activity, and history of epilepsy surgery. Three patients had status epilepticus (SE) and one a cluster of seizures. Likewise, 9% of patients improved their seizure control. Reduction in stress/anxiety (OR: 0.05; $p = 0.03$) and recent adjustment of antiepileptics (OR: 0.07; $p = 0.01$) acted as protecting factors.
Conclusions: A high proportion of PWE suffered a significant worsening of their seizure control during the months of the COVID-19 pandemic. Emotional distress due to home confinement was the main factor for the change in seizure control. Promoting physical activity and adequate sleep may minimize the potential impact of the pandemic in PWE. Ensuring correct follow-up can prevent decompensation in those PWE at high risk.

1. Introduction

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) has rapidly spread worldwide, being considered a pandemic in March 2020. In the first few months of the COVID-19 outbreak, some studies have emphasized the neurological manifestations of COVID-19 [1,2]. Seizures are a neurological complication that can be produced by SARS-CoV-2; however, they do not seem to be frequent, happening in about 0.5% or even less of patients with COVID-19 [1–3]. Typically, these seizures are acute symptomatic and may be triggered by different factors: fever, hypoxemia/hypercapnia, severe illness, systemic inflammatory overresponse, COVID-19 treatments, and central nervous system direct invasion by SARS-CoV-2 may all play a role.

It is unclear whether or not the consequences of the COVID-19 pandemic influence people with epilepsy (PWE). Normally, these patients are very sensitive to different factors such as physical or emotional disturbances or environmental and lifestyle changes. Many factors can increase the risk of seizures, i.e., illness and fever, stressful events, sleep deprivation, changes in antiepileptic drugs (AED), use of proconvulsive treatments, to name a few. Some are unavoidable during a sociosanitary crisis like that currently being experienced. Spain is one of the most affected countries worldwide, up to May 21, 2020, a total of 233,037 cases of COVID-19 and 27,940 deaths have been officially reported by the national authorities [4]. Because of the rapid increase of infections, the Spanish Government enacted a national state of emergency on March 14, 2020, limiting public mobility and compelling home confinement and social isolation [5]. This national lockdown, in addition to the direct effects of COVID-19, have dramatically altered the lifestyle and normal routines of the entire Spanish population. Therefore, in addition to the risk of neurological involvement that COVID-19 itself has, during the pandemic, different circumstances may negatively impact on seizure control in PWE.

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https://doi.org/10.1016/j.yebeh.2020.107396
1525-5050/

Some studies have evaluated the status of PWE during previous epidemic outbreaks [6] and other natural catastrophes [7], finding a worsening of seizure control in an important proportion of this group. A recent study analyzed the impact of the current COVID-19 pandemic in patients with genetic encephalopathies and their caregivers, finding a worsening of seizure control in 14% of the patients during the lockdown period [8]. Despite it not being a representative sample of the population with epilepsy, it evidences the challenge that the current sociosanitary crisis generates for PWE.

To explore whether there have been changes in seizure control in PWE due to the current outbreak of COVID-19 and to assess the possible causes thereof, we have analyzed 100 successive PWE who attended the Epilepsy Outpatient Clinic of a tertiary hospital in Spain during the COVID-19 outbreak and national lockdown.

2. Methods

An observational, retrospective study was conducted in a tertiary center (Albacete University General Hospital) in the province of Albacete (Castilla-La Mancha, Spain). One hundred successive PWE were recruited from those attended at the Epilepsy Outpatient Clinic between May 17 and June 7, 2020, during both face-to-face visits and telephonic consultations. All patients were diagnosed with epilepsy according to the current criteria [9] and had at least one seizure during the last five years, fulfilling the definition of active epilepsy [10]. Patients with episodes highly suggestive of nonepileptic paroxysmal events (syncope, psychogenic nonepileptic seizures, etc.) that could not be clearly differentiated from their seizures were excluded. If the patient had an intellectual disability, the interview was conducted in conjunction with their caregivers.

Patients were asked to answer a predefined survey during the visit (see questionnaire in Supplementary Material). Demographic data such as age, sex, epilepsy duration, epilepsy type and lateralization, etiology, intellectual disability, neuroimaging alterations, drug-resistant epilepsy, number of AED, history of epilepsy surgery, and changes in treatment within the previous 3 months were reviewed. Seizure frequency during the period corresponding to the national state of emergency (from March 14, 2020, onward) was recorded and compared with seizure frequency during the previous six months. Seizure frequency was recorded in number of seizures per month according to patients' calendars of seizures, and posteriorly classified in three options: seizure frequency increase, seizure frequency decrease, or no changes in seizure frequency. We searched for possible cases of status epilepticus (SE) or sudden unexpected death in epilepsy (SUDEP). We considered a significant change in seizure frequency those differences of more than 50% compared with the previous period. Different questions about their lifestyles and routines during the quarantine and social isolation (changes in mood such as sadness/depression and stress/anxiety, work, diet, alcohol consumption, rest and sleep, and adherence to antiepileptic treatment) were asked. Changes in the follow-up from their primary care health center and hospital outpatient clinics were assessed. During the state of alert, our Neurology Department opened a telephone line and an email for patients, in order for patients to contact their neurologist if they deemed it necessary. Unannounced consultations (either face-to-face, telephonic, and email) with Neurology outpatient clinics, patient visits to their health center, emergency department (ED), and admissions to hospital or intensive care units (ICU) for any reason were reviewed. Those patients who reported avoiding the ED or appointments with a general practitioner (GP) or specialist were registered, as well as those who experienced a delay in their epilepsy appointment. The registered factors related to COVID-19 included infection (confirmed by reverse transcription-polymerase chain reaction (rt-PCR) analyses of throat swab samples or by serum antibodies) or compatible symptoms of the patient or in a family member with whom they live. Severity of COVID-19 was defined according to the 2007 Infectious Diseases Society of America/American Thoracic Society criteria [11] into mild or severe disease. National lockdown-related features such as possibility to reach their pharmacy, medication shortages, possibility of attendance at work, occupational centers, or schools were recorded.

This study was conducted in accordance with the Declaration of Helsinki and local governmental regulations and was approved by the local ethics committee. Written informed consent was obtained from each study participant.

2.1. Statistical analysis

The statistical analysis was performed using the SPSS software, version 25 (SPSS, Chicago, IL). A descriptive analysis of the variables collected was performed: the qualitative variables were expressed as a percentage and the quantitative variables using mean ± standard deviation (SD) or median-interquartile range (IQR) whether or not they had a normal distribution. An analysis of the main factors associated with the significant changes of the number of seizures was performed: the ratios were compared using the Chi squared test, quantitative variables were compared using the Student's t test or the U Mann–Whitney test when appropriate. Finally, a multivariate analysis using binary logistic regression was performed. The confidence intervals (CI) and odds ratios (OR) were calculated. In all cases, p values less than 0.05 were considered as statistically significant. The size of the sample was calculated based on an expected variation of seizure frequency in 10–25% of the patients included, as observed in previous studies [6–8]. Assuming a percentage of data loses of 10%, our sample should be at least of 90 PWE. Besides this, assuming the possibility that the references used do not represent our population of PWE, we decided to increase the sample up to 100 patients.

3. Results

One hundred patients were included, 52% women, mean age 42.4 years (range: 15–85). The timeline of visits and its relationship with the different phases of the national state of emergency and epidemiological evolution of the pandemic in Spain [4,12] can be seen in Fig. 1. No differences were observed between patients included in different phases of confinement. Thirty-nine patients were seen face-to-face in the Neurology Clinic, and 61 were visited telephonically. The demographic characteristics are described in Table 1. Of the 19 patients with generalized epilepsy, seven were idiopathic generalized epilepsies (IGE) (three juvenile myoclonic epilepsy, three juvenile absence epilepsies, one IGE with only generalized tonic–clonic seizures), eight were epileptic encephalopathies (one genetic epilepsy with febrile seizures plus [GEFS+], four Lennox–Gastaut syndromes, two Dravet syndromes, one West syndrome), and the other four were other generalized syndromes. Of 73 focal epilepsies, 34 were from the left hemisphere, 21 from the right, and 18 from unknown lateralization; 26 were temporal, 30 frontal, six posterior quadrant, and 11 from unknown foci.

During the COVID-19 period, 11 patients had a lower seizure frequency compared with the prior six months, 60 patients had the same seizure frequency, and 29 patients had a higher seizure frequency. Seizure control worsened significantly in 27% of the patients, and it improved significantly in 9%. Overall, 39% of patients were seizure-free for at least six months before the COVID-19 outbreak, in four of them (10.3%), seizures recurred during the pandemic. No SUDEP occurred during the study period. Only 1 case had positive tests (both rt-PCR of throat swabs and antibodies in blood test) for COVID-19 (Table 2), being asymptomatic for the infection, which was diagnosed during a hospital admission due to a cluster of seizures (see below). In Tables 2 and 3, the most relevant clinical features are described.

The following risk factors were statistically associated with a significant worsening of seizure control: exacerbation of stress/anxiety (21 [77.8%] vs 21 [28.8%], OR: 8.67, 95% CI: 3.07–24.50; $p < 0.001$), sadness/depression (15 [55.6%] vs 20 [27.4%], OR: 3.31, 95% CI: 1.32–8.29; $p = 0.01$), sleep deprivation (16 [59.3%] vs 15 [20.5%], OR: 5.62, 95% CI:

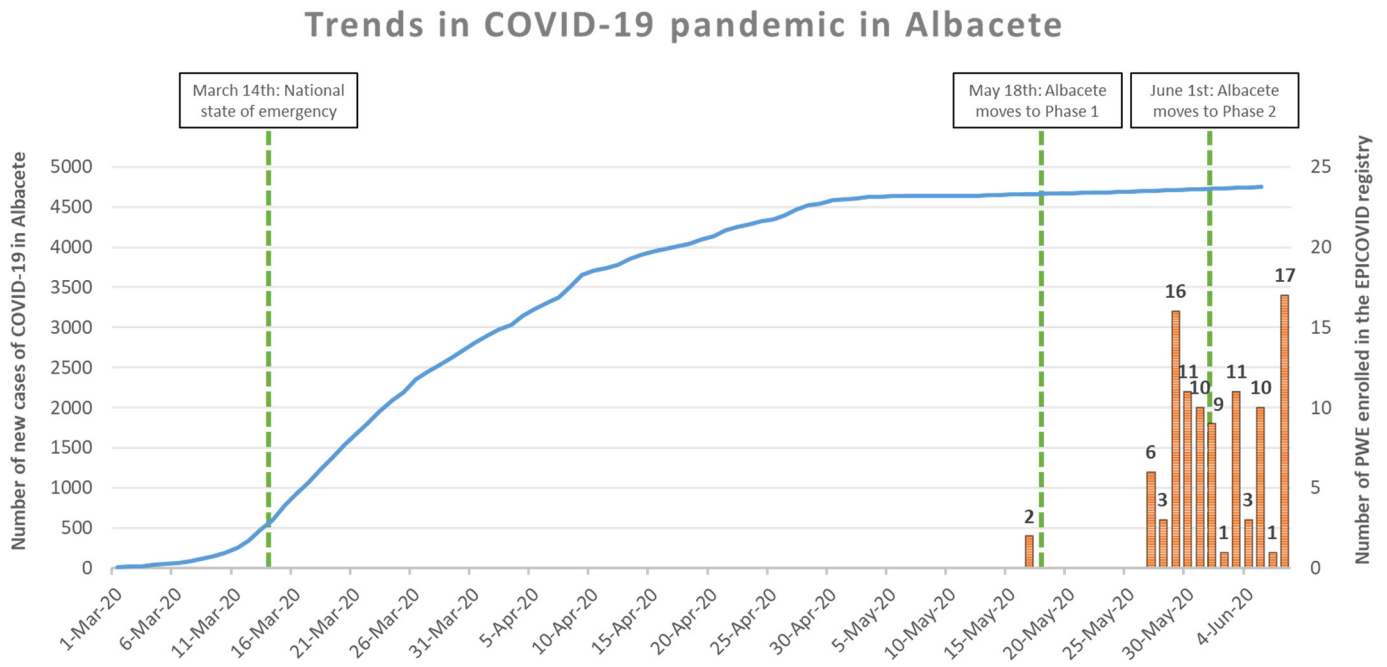

Fig. 1. Evolution of the COVID-19 pandemic in Albacete and PWE inclusions in the EPICOVID registry. Trend of the pandemic in the city of Albacete, Spain, represented by the number of pooled cases of COVID-19 diagnosed in Albacete (blue line) [4]. Relevant changes due to local confinement occurred on March 14th (state of alarm and national lockdown), May 18th (the city of Albacete moves to phase 1 of confinement de-escalation), and June 1st (the city of Albacete moves to phase 2 of confinement de-escalation) [12]. The EPICOVID registry was opened on May 15th. Two people with epilepsy (PWE) were included during the lockdown, 46 during phase 1, and 52 during phase 2 of confinement de-escalation. No differences were observed between patients included in different phases of confinement.

2.16–14.61; $p < 0.001$), doing less physical exercise (18 [66.7%] vs 25 [34.2%], OR: 3.84, 95% CI: 1.51–9.98; $p = 0.004$), and history of epilepsy surgery (4 [14.8%] vs 1 [1.4%], OR: 12.5, 95% CI: 1.32–117.74; $p = 0.006$). The median of seizure frequency during the previous six months was higher in those patients who had a significant increase of seizure frequency during the pandemic compared with those who did not: 2 (IQR: 0.3–6) vs 0.25 (IQR: 0–2.25), $p = 0.008$. There was no relationship among those with COVID-19 symptoms, having drug-resistant epilepsy, delays to the visits with the epileptologist, recent changes in AED, or who avoided going to an emergency room with an increase of seizure frequency. Neither having problems going to a pharmacy nor difficulty finding their AED, attending school/occupational center, nor logistical adjustments to working arrangements were associated with changes in seizure control. A multivariate analysis using a binary logistic regression model was performed, including sex, history of epilepsy surgery, seizure frequency in the previous 6 months, stress/anxiety increase, sadness/depression increase, sleep deprivation, and doing less physical exercise. Only suffering higher stress/anxiety and having a prior higher seizure frequency were independently associated with a significant increase of seizure frequency in the multivariate analysis (OR: 5.78, 95% CI: 1.57–21.28, $p = 0.008$ and OR: 12.14, 95% CI: 2.6–56.74, $p = 0.001$, respectively). Those patients whose seizure control deteriorated consulted more frequently with the neurologist without prior appointment ($p = 0.001$), visited an ED (OR: 4.76, 95% CI: 1.36–16.63; $p = 0.009$), and were more frequently admitted to hospital (OR: 12.52, 95% CI: 1.33–117.74; $p = 0.006$).

Table 1
Demographic characteristics.

	All (n = 100)	Sz worsening >50% (n = 27)	Sz improvement >50% (n = 9)
Sex (woman)	52	18	4
Age (years) (mean ± SD)	42.4 ± 16.4	42 ± 14.9	41.5 ± 16.7
Epilepsy duration (years) (mean ± SD)	19.8 ± 16	20.3 ± 16.6	24 ± 21.4
Epilepsy type			
Generalized	19	3	1
Focal	73	23	5
Unknown	8	1	3
Etiology of epilepsy			
Genetic	17	3	2
MCD	10	4	0
Cerebrovascular	7	2	1
Tumoral	15	5	1
HS	6	2	1
Unknown	36	8	4
Other	9	3	0
Alterations in MRI	50	16	3
Cognitive impairment	30	7	2
Drug-refractory epilepsy	61	18	3
Number of AED (median, IQR)	2, 2–3	2, 2–3	2, 1–3
Epilepsy surgery			
Resective	5	4**	0
VNS	5	2	0

Statistical significance: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.
AED: antiepileptic drugs. HS: hippocampal sclerosis. IQR: interquartile range 25–75. MCD: malformation of cortical development. MRI: magnetic resonance imaging. OR: odds ratio. Sz: seizure. SD: standard deviation. VNS: vagus nerve stimulator.

Four patients were admitted to hospital during the study period because of seizures. Three patients had SE and one a cluster of focal seizures with and without impaired awareness. Of the patients with SE, one presented with a focal without impairment of consciousness SE, another with a focal with impaired consciousness SE, and the third case had a generalized convulsive SE that required admission to the ICU. None of these three patients had either antibody against SARS-CoV-2 in blood tests nor SARS-CoV-2 RNA upon rt-PCR analysis of throat swab samples. By contrast, the patient admitted because of a cluster of seizures had positive rt-PCR and serological tests for SARS-CoV-2 but was clinically asymptomatic, and blood tests and chest X-ray were normal.

Regarding patients who significantly improved their seizure control during the pandemic ($n = 9$), the following factors were protectors in our study: an improvement in AED adherence (2 [22.2%] vs 0 in nonimprovement groups, OR: 0.71, 95% CI: 0.03–0.15; $p < 0.001$), a decrease of stress/anxiety (3 [33.3%] vs 8 [8.8%], OR: 0.19, 95% CI:

Table 2
Clinical features during COVID-19 pandemic.

	Sz worsening >50% (n = 27) n (%)	Sz improvement >50% (n = 9) n (%)	No significant Sz changes (n = 64) n (%)
Sz frequency 6 months prior lockdown (mean Sz/month ± SD)	12.9 ± 38.7	1.9 ± 1.8	19.9 ± 131.8
Sz frequency during lockdown (mean Sz/month ± SD)	34.1 ± 68.9	0 ± 0	16.6 ± 104.8
Seizure-free at least 6 months prior lockdown	4 (14.8%)	0	35 (54.7%)
AED changes <3 months prior lockdown	5 (18.5%)	4 (44.4%)*	10 (15.6%)
COVID-19 symptoms			
Mild	5 (18.5%)	2 (22.2%)	8 (12.5%)
Severe	0	0	0
COVID-19 confirmed			
rt-PCR	1 (3.7%)	0	0
SARS-CoV-2 serum antibodies	1 (3.7%)	0	0
Admission to ED	7 (25.9%)**	2 (22.2%)	3 (4.7%)
Admission to hospital	4 (14.8%)**	1 (11.1%)	0
Admission to ICU	1 (3.7%)	0	0
Urgent telephonic consult with GP	7 (25.9%)	2 (22.2%)	12 (18.8%)
Urgent telephonic consult with neurologist	10 (37%)***	0	6 (9.4%)
Avoid going to ED or consult with GP or specialist	4 (14.8%)	2 (22.2%)	9 (14.1%)
Epilepsy visit delay	13 (48.1%)	6 (66.7%)	35 (54.7%)

Statistical significance: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.
AED: antiepileptic drugs. COVID-19: coronavirus disease 2019. ED: emergency department. GP: general practitioner. ICU: intensive care unit. rt-PCR: reverse transcription-polymerase chain reaction. SARS-CoV-2: severe acute respiratory syndrome coronavirus type 2. Sz: seizure.

0.04–0.92; p = 0.02), and AED modifications within the three previous months (4 [44.4%] vs 15 [16.5%], OR: 0.24, 95% CI: 0.06–0.9; p = 0.04). Seizure frequency during the preceding period was not associated with seizure control improvement. The rest of the demographic, clinical, and lifestyle variables were not associated with better seizure control. A multivariate analysis using a binary logistic regression model was performed, including type of epilepsy, AED adherence improvement, recent changes in AED, sadness/depression decrease, stress/anxiety decrease, and sleep improvement. Only AED changes within the previous three months (OR: 0.07, 95% CI: 0.008–0.53; p = 0.01) and a decrease of stress/anxiety (OR: 0.05, 95% CI: 0.004–0.707; p = 0.03) were statistically associated with an improvement in seizure control in the multivariate analysis.

On the other hand, 42 patients stated having more stress/anxiety during the pandemic and another 11 reported having less stress/anxiety than previously. For those reporting higher levels of anxiety during the pandemic, the following variables were statistically associated: history of epilepsy surgery (n = 5; p = 0.007), sadness/depression (n = 32; p = 0.229), and sleep deprivation (n = 27; p = 0.015). By contrast, intellectual disability acted as a protecting factor for anxiety (OR: 0.38, 95% CI: 0.15–0.98, p = 0.04). Exacerbation of stress/anxiety and sadness/depression were associated with home confinement and social isolation (n = 21 and n = 15, respectively), the COVID-19 sociosanitary crisis (n = 3 and n = 2, respectively), both (n = 13), or other reasons (n = 5 both cases).

4. Discussion

A high proportion of PWE had a worsening of their seizure control during the COVID-19 pandemic. In our study, 27% of patients had an increase in their seizure frequency of more than 50% compared with

Table 3
Relevant lifestyle changes during COVID-19 pandemic.

		Sz worsen >50% (n = 27) n (%)	Sz improvement >50% (n = 9) n (%)	No significative Sz changes (n = 64) n (%)
Stress/anxiety	Less than normal	0	3 (33.3%)*	8 (12.5%)
	Same as normal	6 (22.2%)	4 (44.4%)	37 (57.8%)
	More than normal	21 (77.8%)***	2 (22.2%)	19 (29.7%)
Sadness/depression	Less than normal	0	2 (22.2%)	6 (9.4%)
	Same as normal	12 (44.4%)	7 (77.8%)	38 (59.4%)
	More than normal	15 (55.6%)*	0	20 (31.3%)
Alcohol consumption	Less than normal	5 (21.7%)	2 (22.2%)	5 (7.8%)
	Same as normal	22 (78.3%)	6 (66.7%)	58 (90.6%)
	More than normal	0	1 (11.1%)	1 (1.6%)
Alimentation	Less than normal	4 (14.8%)	0	3 (4.7%)
	Same as normal	18 (51.9%)	7 (77.8%)	52 (82.2%)
	More than normal	5 (18.5%)	2 (22.2%)	9 (14.1%)
Sleep	Less than normal	16 (59.3%)***	2 (22.2%)	13 (20.3%)
	Same as normal	8 (29.6%)	3 (33.3%)	38 (59.4%)
	More than normal	3 (11.1%)	4 (44.4%)	13 (20.3%)
Exercise	Less than normal	18 (66.7%)**	3 (33.3%)	22 (34.4%)
	Same as normal	6 (22.2%)	5 (55.6%)	36 (56.3%)
	More than normal	3 (11.1%)	1 (11.1%)	6 (9.4%)
AED adherence	Worse than normal	0	0	0
	Same as normal	27 (100%)	7 (77.8%)	64 (100%)
	Better than normal	0	2 (22.2%)***	0
Problems finding pharmacy		1 (3.7%)	1 (11.1%)	1 (1.6%)
Problems finding AED		1 (3.7%)	0	5 (7.8%)

Statistical significance: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.
AED: antiepileptic drugs. Sz: seizure.

that in the preceding months. Nonetheless, the reason for this seizure exacerbation was not due to COVID-19 infections but rather to other factors that emerged during the pandemic. In studies conducted by Aledo-Serrano et al. [8] and Lai et al. [6], around 15% of the patients saw their seizure control worsen. In the study of Lai et al. [6] during the SARS epidemic, an important proportion of patients missed follow-up with their medical provider and did not receive medication, which was the main factor for seizure exacerbation. In our environment during the pandemic, only six patients (in two of which seizure control worsened) referred problems finding their AED, which indicates that although trade routes were altered, our region was not affected by medication shortages during the lockdown. At the same time, all the patients continued to take their medication with the same or better adherence (probably home confinement contributed to good adherence to treatment), leading us to believe that the cause of seizure control deterioration was not attributable to medication issues.

In our study, patients who worsened from their disease did so mainly because of higher stress and anxiety, and those who improved had significantly less stress compared with that in the previous months. Thus, emotional distress was the most important factor for seizure control in our population, and in most of the patients in whom stress worsened (42% of patients), this was due to confinement at home (50% of cases). Another study compared psychological distress between PWE and healthy controls during the COVID-19 outbreak [13]. People with epilepsy showed significantly higher levels of psychological distress than healthy controls, with the diagnosis of drug-resistant epilepsy being one of the main predictors of higher stress levels. In our sample, being drug-resistant was not associated with changes in stress levels, but all patients who had a history of epilepsy surgery reported stress exacerbation. Higher stress was also associated, in our population, with sleep alterations, which is a well-known seizure risk factor. Finally, physical activity deserves a mention. Home confinement due to the COVID-19 pandemic can also have negative effects on lifestyle routines such as diet or physical activity [14]. In the current study, 31% of patients reported a reduction in physical activity during the pandemic. Moreover, a reduction of physical exercise during quarantine was associated with worsening of seizure frequency, but since the multivariate analysis did not support this, probably emotional distress influenced both variables. Physical exercise has a positive effect on anxiety and depression in PWE [15,16], and its potential benefits in epilepsy are supported by an increasing body of evidence [17,18]. Based on the above, encouraging PWE to carry out more physical exercise during the COVID-19 pandemic can minimize the impact on mood disturbances and seizure decompensation that this period can potentially produce.

As with previous coronaviruses and other respiratory viruses [19,20], SARS-CoV-2 potentially demonstrates neurotropism [21,22]. Several studies have stressed the neurological manifestations of COVID-19 [1,2]. Acute symptomatic seizures and SE in COVID-19 seems infrequent [1–3], albeit recently several cases of SE due to COVID-19 have been published [23–25], all of which had positive rt-PCR for SARS-CoV-2 but only one case had a prior diagnosis of epilepsy. In our series, four patients were hospitalized because of worsening of seizures, three in SE, which is substantially more than we are used to seeing in our Center. None of our three cases had a clear cause for the SE, and all three had a negative rt-PCR for SARS-CoV-2. However, one patient in our series was admitted to hospital due to clusters of seizures and had a positive rt-PCR for SARS-CoV-2. Since the patient was clinically asymptomatic, the relevance of COVID-19 in the cluster of seizures remains unknown.

Theoretically, PWE are not at greater risk of having COVID-19 or for developing a severe form of the disease, except for those with autoimmune epilepsy under immunosuppressive treatment [26]. However, whether or not seizures, AED, or epilepsy itself comprise some risk of immunosuppression is still under discussion [27]. According to the national seroprevalence study in Spain, in our city, Albacete, around 11.7% of the inhabitants have been infected with SARS-CoV-2 [28]. In our hospital's COVID-19 series [1], 21 of 841 (2.5%) patients admitted to hospital with COVID-19 had a history of epilepsy. Of these, 8 (2.4%) had a severe COVID-19 and 13 (2.5%) a mild SARS-CoV-2 infection, suggesting a lack of association between COVID-19 severity and epilepsy. In the current study, 15% of patients reported having had some symptom compatible with mild COVID-19, but only one patient tested positive for SARS-CoV-2 (either rt-PCR or antibodies for SARS-CoV-2). However, only 16 patients were tested for the disease, the other 84 were unaware of their infection status. The proportion of patients reporting compatible COVID-19 symptoms was higher in the group of PWE in whom seizures worsened (24%), though this was not statistically significant.

People with epilepsy can suffer consequential detriment to their epilepsy care during events such as the current COVID-19 pandemic. An important problem PWE face is that going to emergency rooms could expose them to SARS-CoV-2. The Epilepsy Foundation recommends avoiding emergency rooms for PWE as much as possible in order to reduce the risk of contracting COVID-19 and, instead, contact their doctor's office if they feel that they have to be seen urgently [29]. Of our sample, 12 patients went to an ED during the main months of the COVID-19 outbreak in our country for different reasons, not always related to epilepsy, and 11 avoided going to an emergency room despite feeling that it was necessary to do so. During this period, 17% of our patients tried to contact their neurologist, only one of whom did not succeed, reflecting the rapid reaction of our department to this extraordinary situation. By contrast, more than half of patients suffered delays to their epilepsy consultation, which could have had a negative impact in certain cases. Currently, countries worldwide are allocating the majority of their resources for healthcare to fight against the COVID-19 outbreak. During the worst moments of the COVID-19 crisis in Spain, our Public Health System, including our own hospital, was completely overwhelmed. Neurologists from our department were redeployed to care teams for patients with COVID-19, thereby leading to cancelations of nonurgent outpatient appointments and admissions for video-electroencephalographic monitoring. Probably, this situation hindered the best possible care for those patients with worsened seizure control. One of the factors associated with an improvement in seizure control was to have modified AED in the previous months, evidencing that a regular follow-up, with early detection of aggravations and proper AED adjustments, result in a clear benefit for PWE.

Finally, our study suggests that during confinement, the diagnosis and control of emotional distress and the prompt detection of a worsening in seizure control or decompensation of comorbidities should be considered crucial, in order to initiate an early treatment when needed. Maintaining a normal follow-up in outpatient clinics can help to achieve these objectives, but in a pandemic like the current one, the appointments can suffer delays and cancelations, and going to the hospital in person implies a high risk of infection. Telematic outpatient visits in epilepsy may be a valuable resource in these cases (in the present study, more than half of the visits were done telephonically), which has also been proposed by other authors [26,29–32]. In addition, we propose to open an option of remote contact so that patients can contact their physician if needed (e.g., by phone and/or email), to provide a rapid response if the first symptoms of decompensation of seizures or comorbidities appear.

4.1. Study limitations

The main limitation of the study is the absence of a validated scale or instrument to measure the changes in the subjective variables, such as anxiety or depression. A more extensive evaluation of these or other variables may have allowed a better understanding of the evolution of PWE during the COVID-19 outbreak. The pandemic context of the study strongly influenced in data acquisition. In addition, the social and healthcare situation changed rapidly during the weeks of the study, which may have influenced the perception of those PWE visited in different phases of confinement. The study is retrospective, with all the limitations associated with these studies.

5. Conclusions

The current COVID-19 pandemic has a major influence on PWE. A high proportion of PWE had a significant worsening on their seizure control during the months of the pandemic. Emotional distress and anxiety due to home confinement and social isolation were the most important factors for changes in seizure frequency. Encouraging PWE to do more physical activity and promoting adequate sleep can minimize the potential impact on mood disturbances and seizure exacerbation that the current pandemic has caused. Ensuring correct follow-up of these patients can prevent decompensations in those at high risk of worsening from their seizures. Therefore, telephonic consultations may be a valuable resource during the COVID-19, or indeed any outbreak.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2020.107396.

References

[1] Romero-Sánchez CM, Díaz-Maroto I, Fernández-Díaz E, Sánchez-Larsen Á, Layos-Romero A, García-García J, et al. Neurologic manifestations in hospitalized patients with COVID-19: the ALBACOVID registry. Neurology. 2020 published online ahead of print.
[2] Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 2020 published online ahead of print.
[3] Lu L, Xiong W, Liu D, Liu J, Yang D, Li N, et al. New onset acute symptomatic seizure and risk factors in coronavirus disease 2019: a retrospective multicenter study. Epilepsia. 2020 published online ahead of print.
[4] Centro Nacional de Epidemiología. Situación y evolución de la pandemia de COVID-19 en España. Available at https://cnecovid.isciii.es/covid19/. [Accessed 28 May 2020].
[5] Real Decreto 463/2020, de 14 de marzo, por el que se declara el estado de alarma para la gestión de la situación de crisis sanitaria ocasionada por el COVID-19, BOE. 2020(num. 67):25390–400 Available at https://www.boe.eseli/es/rd/2020/03/14/463. [Accessed 20 May 2020].
[6] Lai SL, Hsu MT, Chen SS. The impact of SARS on epilepsy: the experience of drug withdrawal in epileptic patients. Seizure. 2005;14:557–61.
[7] Swinkels WAM, Engelsman M, Kasteleijn-Nolst Trenite DGA, Baal MG, de Haan GJ, Oosting J. Influence of evacuation in February 1995 in the Netherlands on the seizure frequency in patients with epilepsy: a controlled study. Epilepsia. 1995;39:1203–7.
[8] Aledo-Serrano Á, Mingorance A, Jiménez-Huete A, Toledano R, García-Morales I, Anciones C, et al. Genetic epilepsies and COVID-19 pandemic: lessons from the caregiver perspective. Epilepsia. 2020;00:1–3.
[9] Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014;55:475–82.
[10] Forsgren L, Beghi E, Õun A, Sillanpää M. The epidemiology of epilepsy in Europe — a systematic review. Eur J Neurol. 2005;12:245–53.
[11] Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44:S27–72.
[12] de Sanidad de España Ministerio. Plan para la Transición hacia una nueva normalidad. Available from: https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov-China/documentos/PlanTransicionNuevaNormalidad.pdf. [Accessed 15 July 2020].
[13] Hao X, Zhou D, Li Z, Zeng G, Hao N, Li E, et al. Severe psychological distress among patients with epilepsy during the COVID-19 outbreak in southwest China. Epilepsia. 2020 published online ahead of print.
[14] Vancini RL, de Lira CAB, Andrade MS, Arida RM. CoVID-19 vs. epilepsy: it is time to move, act, and encourage physical exercise. Epilepsy Behav. 2020 published online ahead of print.
[15] Arida RM, de Almeida AC, Cavalheiro EA, Scorza FA. Experimental and clinical findings from physical exercise as complementary therapy for epilepsy. Epilepsy Behav. 2013;26:273–8.
[16] Elger CE, Johnston SA, Hoppe C. Diagnosing and treating depression in epilepsy. Seizure. 2017;44:184–93.
[17] Nakken KO, Bjørholt PG, Johannesen SL, Loyning T, Lind E. Effect of physical training on aerobic capacity, seizure occurrence, and serum level of antiepileptic drugs in adults with epilepsy. Epilepsia. 1990;31:88–94.
[18] Arida RM, Cavalheiro EA, da Silva AC, Scorza FA. Physical activity and epilepsy: proven and predicted benefits. Sports Med. 2008;38:607–15.
[19] Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol. 2020 published online ahead of print.
[20] Bohmwald K, Gálvez NMS, Ríos M, Kalergis AM. Neurologic alterations due to respiratory virus infections. Front Cell Neurosci. 2018;12:386.
[21] Paniz-Mondolfi A, Bryce C, Grimes Z, Gordon RE, Reidy J, Lednicky J, et al. Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). J Med Virol. 2020 published online ahead of print.
[22] Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, et al. A first case of meningitis/encephalitis associated with SARS-coronavirus-2. Int J Infect Dis. 2020 published online ahead of print.
[23] Balloy G, Mahé PJ, Leclair-Visonneau L, Péréon Y, Derkinderen P, Magot A, et al. Non-lesional status epilepticus in a patient with coronavirus disease 2019. Clin Neurophysiol. 2020 published online ahead of print.
[24] Vollono C, Rollo E, Romozzi M, Frisullo G, Servidei S, Borghetti A, et al. Focal status epilepticus as unique clinical feature of COVID-19: a case report. Seizure. 2020;78:109–12.
[25] Somani S, Pati S, Gaston T, Chitlangia A, Agnihotri S. De novo status epilepticus in patients with COVID-19. Ann Clin Transl Neurol. 2020 published online ahead of print.
[26] French JA, Brodie MJ, Caraballo R, Devinsky O, Ding D, Jehi L, et al. Keeping people with epilepsy safe during the COVID-19 pandemic. Neurology. 2020 published online ahead of print.
[27] Beghi E, Shorvon S. Antiepileptic drugs and the immune system. Epilepsia. 2011;3:40–4.
[28] Pollán M, Pérez-Gómez B, Pastor-Barriuso R, Oteo J, Hernán MA, Pérez-Olmeda M, et al, ENE-COVID Study Group. Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study. Lancet. 2020 published online ahead of print.
[29] Epilepsy Foundation. COVID-19 and epilepsy/managing epilepsy during the covid-19 Crisis. Available from https://www.epilepsy.com/learn/covid-19-and-epilepsy/managing-epilepsy-during-covid-19-crisis. [Accessed 1 June 2020].
[30] Punia V, Nasr G, Zagorski V, Lawrence G, Fesler J, Nair D, et al. Evidence of a rapid shift in outpatient practice during the COVID-19 pandemic using telemedicine. Telemed J E Health. 2020 published online ahead of print.
[31] Hatcher-Martin JM, Adams JL, Anderson ER, Bove R, Burrus TM, Chehrenama M, et al. Telemedicine in neurology: telemedicine work group of the American Academy of Neurology update. Neurology. 2020;94:30–8.
[32] Patterson V, Bingham E. Telemedicine for epilepsy: a useful contribution. Epilepsia. 2005;46:614–5.