The effect of quarantine due to Covid-19 pandemic on seizure frequency in 102 adult people with epilepsy from Apulia and Basilicata regions, Southern Italy

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A B S T R A C T

Objective: following the COVID-19 pandemic, a quarantine was imposed to all of regions Italy by 9th March until 3rd May 2020. We investigated the effect of COVID-19 infection and quarantine on seizure frequency in adult people with epilepsy (PwE) of Apulia and Basilicata regions, Southern Italy.
Methods: This is an observational, retrospective study based on prospective data collection of 102 successive PWE. The frequency of seizures was evaluated during pre-quarantine (January- February), quarantine (March––April), and post–quarantine period (May-June), while PwE were divided into A) cases responding to treatment with $\leq$ 1 seizure per year; B) cases responding to treatment with 2–5 seizure per year; C) cases with drug-resistant epilepsy with $\leq$ 4 seizures per month; D) cases with drug-resistant epilepsy with 5–10 seizures per month. PwE underwent several self-report questionnaires regarding therapeutic compliance, mood, stress and sleep during quarantine period.
Results: Approximately 50 % of PwE showed seizure frequency changes (22.55 % an increase and 27.45 % a reduction) during quarantine. Seizure frequency significantly ($p < 0.05$) increased in PwE responding to treatment with $\leq$ 1 seizure per year, while significantly ($p < 0.05$) reduced in PwE with drug-resistant epilepsy with 5–10 seizures per month. The data was not influenced by therapeutic adherence, sleep and depression. The analysis of anxiety showed a moderate level of anxiety in PwE responding to treatment with < 1 seizure per year, while moderate stress was perceived by all PwE. Seizure frequency changes were related to quarantine, but not to COVID-19 infection. In fact, unlike other regions of Italy, particularly Northern Italy, Apulia and Basilicata regions were less affected by COVID-19 infection, and almost all PwE recognized the quarantine as a stressful event. Emotional distress and anxiety due to social isolation, but also the relative reduction of triggers for epileptic seizures were the most important factors for changes in seizure frequency.
Conclusions: Our study adds to the growing concern that the indirect effects of COVID-19 pandemic will far outstrip the direct consequences of the infection.

1. Introduction

In February 2020, Italy became the epicenter for coronavirus disease (COVID-19) infection in Europe. By 9th March 2020, 7.375 laboratory-confirmed cases of Covid-19 infection and 366 deaths had been observed in Italy [1], therefore as a public health response, on that date, an isolation and a community quarantine were imposed to all of regions

Italy until 3rd May. The term "quarantine", in public health practice, refers to the separation of people who have been exposed to an infectious disease, with the shutdown of businesses, schools and public places with physical distancing in all regions. Instead, the term "isolation" refers to the separation of people who are known to be infected [2]. If quarantine and isolation can be seen as two important measures that allow to prevent and to minimize the effect of infectious disease

diffusion, on the other hand they can also be unpleasant experiences. The loss of freedom, the uncertainty over disease status, and also boredom might generate dramatic effects [3]. Previous studies have described an increased risk of seizure susceptibility due to social isolation stress in both human and rodents [4]. In people with epilepsy (PwE), social isolation stress has important effects on the quality of life, severity of disease and social functioning [5]. In addition, few studies characterized the impact of a uniformly recognized stressful acute event (i.e., the 9/11/2001 terror attack; the 1991 Gulf War; the evacuation in February 1995 during a flood in Holland) on PwE [6–8]. Seizure exacerbation emerged in a small proportion of exposed PwE, but in a higher proportion of cases stressed and directly affected by the events.

We investigated the effect of COVID-19 infection and quarantine on seizures in adult PwE (≥18 years) of Apulia and Basilicata regions, Southern Italy, followed-up by our epilepsy center. We specifically estimated the frequency of seizures during Covid-19 pandemic quarantine and two months before and after quarantine. Finally, we evaluated possible variations associated with therapeutic compliance, stress, mood, and sleep during quarantine.

2. Methods

We included a retrospective consecutive cohort of PwE evaluated to our epilepsy center from January 1 st to March 8th 2020. A case was eligible for inclusion if the PwE was 18 years or older, fulfilled the diagnosis of epilepsy according to the current criteria of International League Against Epilepsy (ILAE) [9], compiled a detailed seizure diary and could release a written informed consent. Then, we excluded PwE with age < 18 years, inability to keep a seizure calendar, with intellectual disability or serious medical disorders and who refused to fill out the questionnaires. Successively, the patients were prospectively followed-up during COVID-19 pandemic quarantine (from March 9th to May 3rd 2020) and two months after (from May 4th to July 4rd 2020). Therefore, PwE were evaluated in three main period: pre-quarantine period (January- February), quarantine period (March–April), post--quarantine period (May-June). Moreover, to explore the entire epilepsy spectrum and according to their seizure frequency and treatment response, PwE were divided into four groups: A) cases responding to treatment with ≤ 1 seizure per year; B) cases responding to treatment with 2–5 seizure per year; C) cases with drug-resistant epilepsy with ≤ 4 seizures per month; D) cases with drug-resistant epilepsy with 5–10 seizures per month. Finally, eligible PwE underwent several self-report questionnaires regarding therapeutic compliance (Morisky Scale) [10], mood (Generalized Anxiety Disorder – GAD-7, Patient Health Questionnaire – PHQ9, Neurological Disorder Depression – NDDI-E) [11–13], stress (Impact of Events Scale-Revised – IES-R, Perceived Stress Scale – PSS-10) [14,15], and sleep (Epworth Sleepinees Scale – ESS, Insomnia Severity Index – ISI) [16,17], during quarantine period. PwE were subjected to standardized telephonic or via telemedicine interview and each questionnaire was self-administered. Seizure frequency was documented by seizure diaries compiled by PwE. Questionnaires and seizure diaries were mailed to our epilepsy center.

The data from PwE was tabulated and included a) demographic and general information: age, gender, residence, school attendance, job, driving; b) details of the epilepsy features, particularly age at seizure onset; seizure type; epilepsy type; response to the therapy, drug-resistant epilepsy, number of AEDs; history of epilepsy surgery; c) seizure frequency, changes in treatment, cluster seizures and status epilepticus before, during and after quarantine period; c) COVID-19 infection in PwE and parents; d) data from questionnaires.

2.1. Statistical analysis

Clinical and demographical cases' features were reported as frequency and percentages or as mean mean ± standard deviation with a 95 % confidence range for continuous variables and as percentage for the categorical and discrete variables. Group comparisons were performed using the software Statistical Package for Social Sciences version 24 (SPSS-IBM). The calculation of the Spearman's Rho correlation coefficient and Kendall Tau β coefficient was carried out in order to evaluate the correlation degree between the variables. The Kolmogorov-Smirnov test was used to assess the hypotheses of data's normality. Finally, the data was analyzed through t-Student test, ANOVA, test and Chi-square test. P value<0.05 were considered for statistical significance.

3. Results

The sample consisted of 102 PwE (F 54.90 %; mean age: 36.24 ± 14.87; age range 18–81 years). In particular, group A 26 cases, group B 25 cases; group C 25 cases, group D 26 cases.

Table 1 summarizes the demographic features of PwE. No cases were affected by COVID-19. PwE recognized the quarantine as a stressful event, while only one case from group A referred as subjective stress perception the fear of COVID-19 infection.

Fig. 1 shows seizure frequency during the three periods. In particular, pre-quarantine period (January-February): mean: 14.94 ± 38.99 seizures (range 0–280); quarantine period (March-April): mean:

Table 1
Demographic features.

Variable	Mean ± SD or Number (%) (range)
Number of Patients	102
Gender (F/M)	56/46 (54.9 %/49.1)
Age (y)	36.24 ± 14.87 (18−81)
Education	
Primary School	7
Secondary School	25
High School	54
University	16
Driving Licences	29
Concurrent medical diseases	34 (33.34 %)
Region/Province	
Apulia	96
Foggia	33 (32.58 %)
Barletta-Andria-Trani	19 (18.88 %)
Bari	24 (32.58)
Brindisi	5 (4.9 %)
Lecce	7 (6.96 %)
Taranto	8 (7.94 %)
Basilicata	6
Potenza	4 (3.99 %)
Matera	2 (1.91 %)
COVID-19 Infection	
Patients	0
Parents	2
Age at Onset Epilepsy (y)	19.3 ± 20.19 (1−80)
Duration of Epilepsy (y)	16.88 ± 14.78 (1−47)
Epilepsy (type, etiology)	
Focal	77 (75.49 %)
Genetic	3 (3.90 %)
Structural	38 (49.35 %)
Unknown	36 (46.75 %)
Generalized	25 (24.51 %)
Genetic	24 (96 %)
Unknown	1 (4%)
Drug Responsive Epilepsy	51
< 1seizure/year	26
≥ 1 seizure1/year	25
Drug Resistant Epilepsy	51
< 4 seizures/month	25
≥ 4 seizures/month	26
Number of AEDs	
1	31 (30.39 %)
2	44 (43.19 %)
3	18 (17.65 %)
4	8 (7.84 %)
5	1 (0.98 %)

F: female. **M:** male. **y:** years. **AEDs:** antiepileptic drugs. **DS:** standard deviation.
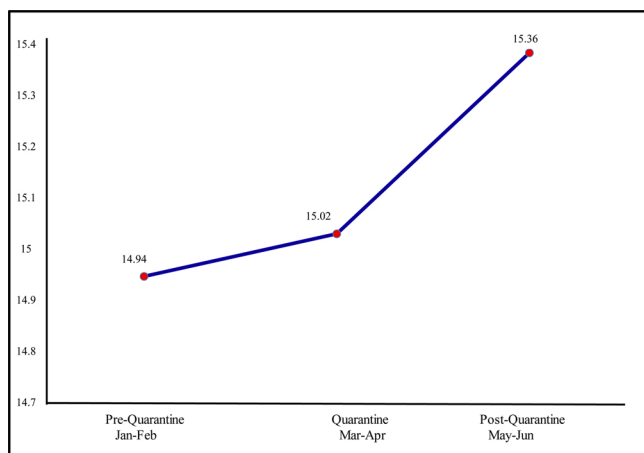
Fig. 1. seizure frequency during pre-quarantine (January-February), quarantine and post – quarantine periods.

15.02 ± 39.53 seizures (range 0–251); post – quarantine period (May-June): mean: 15.36 ± 37.87 seizures (range 0–240).

Approximately 50 % of PwE presented seizure frequency changes: 23 cases (22.55 %) showed an increase, while 28 cases (27.45 %) reported a reduction of frequency.

According to Spearman's Rho correlation coefficient, a statistically significant correlations ($p < 0.01$) emerged between seizures frequency of pre-quarantine and quarantine periods. Moreover, a statistically significant correlations ($p < 0.01$) resulted between seizures frequency of pre-quarantine and post-quarantine periods, and quarantine and post-quarantine periods.

Comparing mean values, there weren't significant differences among values of each period ($p > 0.05$), while the differences among pre-quarantine and post-quarantine showed p value = 0.064.

In group A, 2 cases (7.69 %) showed an increase of seizure frequency, while 24 (92.31 %) showed no variation in seizure frequency

In group B, 3 cases (12 %) showed an increase of seizure frequency, while 10 (40 %) reported a reduction in seizure frequency.

In group C, 10 cases (40 %) showed an increase of seizure frequency, while 9 (36 %) reported a reduction in seizure frequency.

In group D, 9 cases (30.76 %) showed an increase of seizure frequency, while 8 (34.62 %) reported a reduction in seizure frequency (Fig. 2).

Statistical significant correlations were disclosed in group A ($p < 0.01$ Rho of Spearman), group B ($p < 0.01$ Rho of Spearman) and
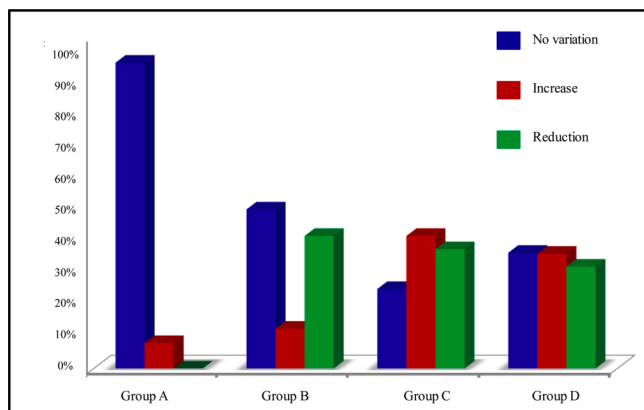
group D ($p < 0.05$ Pearson) during the pre-quarantine and quarantine period. Seizure frequency significantly ($p < 0.05$ Pearson) increased in group A, while significantly ($p < 0.05$ Pearson) reduced in group D.

Table 2a–2c summarizes the data from questionnaires, while Fig. 3 shows GAD-7 and PSS-10 in general sample, and in sample with increase of seizure frequency. GAD-7 showed an average of 5.62 ± 4.78 (range 0–21) in all patients, while in group A was 6.30 ± 5.19 (range. 0–20, mode 5), i.e. considered compatible with moderate anxiety and with statistical significant correlation (p value < 0.03 Pearson). Moreover, in all cases PSS-10 mean value was 13.45 ± 6.27 (range 2–28, mode 14), compatible with moderate stress perceived by the patients. In group A, PSS-10 was 14.69 ± 6.48 (range 2–28, mode 12) during the quarantine, i.e. compatible with moderate stress, but without statistical significant correlation. The data were not influenced by sleep, depression, and, finally, therapeutic adherence because Morisky Scale showed high adherence (9.16 ± 1.90) during quarantine period.

4. Discussion

As regards stress, most of the previous studies usually have evaluated the nature of the stressful event, but not the patient stress perception and its probable response to stress. In addition, few studies, often on limited populations, have studied the impact of environmental stressful events on PwE. In 1994, Neufeld et al. [6] assessed the relationship between stress and Gulf War experience in about 100 adult PwE, particularly when Israelis were under stress from the threat of Scud missile attacks. 8 cases reported an increase in the frequency of seizures, while 4 cases had seizures directly related to the sounding of an alarm. In 1998, Swinkels et al. [7] evaluated the influence on the seizure frequency in PwE of a forced evacuation during a flooding in the Netherlands in 1995. 30 evacuees were evaluated and among those, 8 cases showed an increase and 1 a decrease in seizure frequency. In 2005, Klein et al. [8] studied the effect of emotional stress related to the 09/11/2001 terror attack on seizures in 66 PwE that lived in the area directly involved in the terror attack, evaluating the average monthly changes in seizure frequency between the three months before 09/11 and the month after 09/11. 12 % of PwE referred seizures worsening during the month after 09/11 and the exacerbation was higher in 50 % of PwE directly affected by the event. In Italy, recently two studies evaluated the role of COVID-19 infection in PwE. The first by Assenza et al. [18] administered a 48-item online survey to 456 PwE from different Italian regions affected by quarantine COVID-19 related infection and identified 13 % of the patients that, according to their self-reported seizure frequency, had improved during the quarantine period. The second study by Cabona et al. [19] investigated epilepsy course during COVID-19 infection from the Epilepsy Centers of three hospitals of Northern Italian Regions (Liguria and Lombardia). Of a total of 189 cases, 18 patients reported seizure changes during the COVID-19 period: 16 cases showed a change

Fig. 2. seizure frequency changes in four groups of patients: group A) patients responding to treatment with ≤ 1 seizure per year; group B) patients responding to treatment with 2-5 seizure per year; group C) patients with drug-resistant epilepsy with ≤ 4 seizures per month; group.

Table 2a
General Sample: 102 patients.

TEST	Mean	Standard Deviation	Minimum Value	Maximum Value	Mode
MORISKY SCALE	9.16	1.90	4	11	11
GAD-7	5.63	4.78	0	21	0
PHQ-9	5.73	4.73	0	19	0
NDDI-E	8.61	3.48	0	21	6
IES-R	16.84	14.71	0	54	0
PSS-10	14.85	7.58	2	28	11
ISI	4.80	4.90	0	21	0
ESS	4.48	322	0	20	4

GAD-7: Generalized Anxiety Disorder; **PHQ9**: Patient Health Questionnaire; **NDDI-E**:Neurological Disorder Depression; **IES-R**: Impact of Events Scale-Revised;
PSS-10: Perceived Stress Scale; **ESS**: Epworth Sleepinees Scale;
ISI: Insomnia Severity Index.

Table 2b

Sample with increase of seizure frequency: 23 cases (22.55 %).

TEST	Mean	Standard Deviation	Minimum Value	Maximum Value	Mode
MORISKY SCALE	9.61	1.70	6	11	11
GAD-7	6.30	5.19	0	20	5
PHQ-9	5.65	4.57	0	16	2
NDDI-E	8.61	3.33	0	15	6
IES-R	21.92	18.47	0	57	6
PSS-10	14.69	6.48	2	28	12
ISI	5.45	5.21	0	21	0
ESS	4.87	3.71	0	20	4

GAD-7: Generalized Anxiety Disorder; **PHQ9**: Patient Health Questionnaire; **NDDI-E:**Neurological Disorder Depression; **IES-R**: Impact of Events Scale-Revised;
PSS-10: Perceived Stress Scale; **ESS:** Epworth Sleepinees Scale;
ISI: Insomnia Severity Index.

Table 2c

Sample with reduction of seizure frequency: 28 cases (27.45 %).

TEST	Mean	Standard Deviation	Minimum Value	Maximum Value	Mode
MORISKY SCALE	9.25	2.01	4	11	11
GAD-7	4.41	3.34	0	12	0
PHQ-9	3.19	3.03	0	10	0
NDDI-E	8.39	2.83	6	14	6
IES-R	13.33	12.13	0	38	0
PSS-10	12.43	6.01	3	25	14
ISI	4.32	5.24	0	17	0
ESS	3.52	2.65	0	10	1

GAD-7: Generalized Anxiety Disorder; **PHQ9**: Patient Health Questionnaire; **NDDI-E:**Neurological Disorder Depression; **IES-R**: Impact of Events Scale-Revised;
PSS-10: Perceived Stress Scale; **ESS:** Epworth Sleepinees Scale;
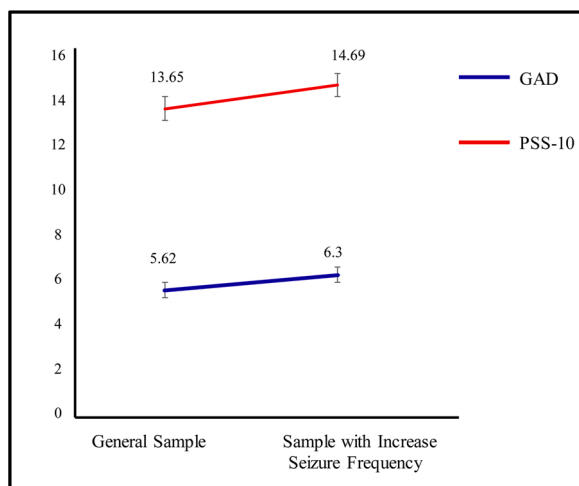**ISI:** Insomnia Severity Index.

Fig. 3. GAD and PSS-10 values in general sample, and in sample with increase of seizure frequency.

in seizure frequency (an increase in 8 and a decrease in 8), while 2 PwE reported a change in seizure semiology. The PwE changes showed comparable levels of preoccupation, suggesting that such frequency variation had little or no psychologic impact on this patients' cohort.

Our study from adult PwE of two Southern Italian Regions (Apulia and Basilicata) showed that approximately 50 % of cases presented seizure frequency changes (22.55 % an increase and 27.45 % a

reduction) during quarantine COVID-19 related infection. In particular, seizure frequency significantly increased in group A (i.e., cases responding to treatment with ≤ 1 seizure per year), while significantly reduced in group D (i.e. cases with drug-resistant epilepsy with 5–10 seizures per month). All data were not influenced by therapeutic adherence, sleep and depression. Instead, the analysis of anxiety showed a moderate level of anxiety in group A, while moderate stress was perceived by all cases. No comparison was possible with the period before quarantine, as we did not have the data. Moreover, seizure frequency changes were related to quarantine, but not to COVID-19 infection. In fact, unlike other regions of Italy, particularly Northern Italy, Apulia and Basilicata regions were less affected by COVID-19 infection, and our cases recognized the quarantine as a stressful event, while only one patient from group A referred as subjective stress perception the fear of COVID-19 infection. A possible interpretation of results might be that quarantine, with a relative reduction of triggers for epileptic seizures, may have caused a reduction in frequency in patients with drug-resistant epilepsy. Conversely, the moderate level of anxiety related to quarantine may have caused a frequency increase in PwE responding to treatment with ≤ 1 seizure per year. Finally, the persistent seizure frequency changes in post-quarantine period may be related to gradually, but not fully, reduction of strict restrictions in space, time and intensity.

The strength of our study is consecutive patient recruitment, the seizure frequency evaluated by an accurate seizure diary, and the evaluation of the entire epilepsy spectrum according to seizure frequency and treatment response compared to previous Italian studies.

The limitations are the retrospective design and the pre-post analysis subjected to several biases. Moreover, we considered the variable quarantine and COVID 19 infection, without evaluation of other possible causes of changes in seizure frequency and without analysis of psychiatric and other comorbidities before the quarantine period. Finally, seizure frequency variability over time is a well-known data and comparing the frequency of seizures occurring during the period of lockdown with only two pre-lockdown months may be in part insufficient.

In conclusion, the current COVID-19 pandemic can influence the seizure frequency in PwE. Emotional distress and anxiety due to social isolation, but also the relative reduction of triggers for epileptic seizures were the most important factors for changes in seizure frequency. Our study adds to the growing concern that the indirect effects of COVID-19 pandemic will far outstrip the, still terrible, direct consequences of the infection.

CRediT authorship contribution statement

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgments

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