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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
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

Giuseppe d’Orsi a,*, Francesca Mazzeo a, Domenico Ravidà b, Maria Teresa Di Claudio a, Annarita Sabetta a, Alessandra Lalla a, Stefania Sbrizzi c, Carlo Avolio a

a Epilepsy Centre – S.C. Neurologia Universitaria, Policlinico Riuniti, Foggia, Italy
b Istituto Pediatrico della Svizzera Italiana, Ente Ospedaliero Cantonale, Bellinzona, Switzerland
c Department of Physical Medicine and Rehabilitation, Policlinico Riuniti, University of Foggia, Italy

ARTICLE INFO

Keywords:
Quarantine
COVID-19 infection
Epilepsy
Seizure frequency
Stress

ABSTRACT

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 ≤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. 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 ≤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 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 1st 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 4th 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 with 2–5 seizure per year; B) cases responding to treatment with 1 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.

2.1. Statistical analysis

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: 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.

Finally, the data was analyzed through t-Student test, ANOVA, test and Chi-square test. P value < 0.05 were considered for statistical significance.

### 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 Licenses                | 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 (3.00 %)                       |
| Structural                      | 38 (49.35 %)                     |
| Generalized                     | 36 (46.75 %)                     |
| Unknown                         | 25 (24.51 %)                     |
| Drug Responsive Epilepsy        | 24 (96 %)                        |
| < 1 seizure/year                | 26                               |
| ≥ 1 seizure/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.
Approximately 50% of PwE presented seizure frequency changes: 23 cases (22.55%) showed an increase, while 28 cases (27.45%) reported a reduction in seizure 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).

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 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 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

| TEST       | Mean | Standard Deviation | Minimum Value | Maximum Value | Mode |
|------------|------|--------------------|---------------|---------------|------|
| MORISKY    | 9.16 | 1.90               | 4             | 11            | 11   |
| SCALE      |      |                    |               |               |      |
| 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 | 3.22               | 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 Sleepiness Scale; ISI: Insomnia Severity Index.
Clinical Neurology and Neurosurgery 203 (2021) 106592

Table 2b
Sample with increase of seizure frequency: 23 cases (22.55 %).

| TEST       | Mean   | Standard Deviation | Minimum Value | Maximum Value | Mode |
|------------|--------|--------------------|---------------|---------------|------|
| MORISKY    | 9.61   | 1.70               | 6             | 11            | 11   |
| SCALE      |        |                    |               |               |      |
| 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    |

Table 2c
Sample with reduction of seizure frequency: 28 cases (27.45 %).

| TEST       | Mean   | Standard Deviation | Minimum Value | Maximum Value | Mode |
|------------|--------|--------------------|---------------|---------------|------|
| MORISKY    | 9.25   | 2.01               | 4             | 11            | 11   |
| SCALE      |        |                    |               |               |      |
| 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; PHQ-9: Patient Health Questionnaire; NDDI-E: Neurological Disorder Depression; IES-R: Impact of Events Scale-Revised; PSS-10: Perceived Stress Scale; ESS: Epworth Sleepiness 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

Giuseppe d’Orsi: Study concept and design, Acquisition of data, Analysis and Interpretation. Francesca Mazzeo, Maria Teresa Di Claudio, Annarita Sabetta, Carlo Avolio: Acquisition of data, Analysis and Interpretation. Domenico Ravidà, Francesca Mazzeo, Stefania Sbrizzi: Statistical analysis.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgments

We are grateful to all the 102 people with epilepsy of our center who actively participated in study, despite the distance and the difficulties of the period.
References

[1] H. Sjödin, A. Wilder-Smith, S. Osman, Z. Farroq, J. Rochlov, Only Strict Quarantine Measures Can Curb the Coronavirus Disease (Covid-19) Outbreak in Italy, 2020. www.eurosurveillance.org.

[2] W.E. Parmet, M.S. Sinha, Covid-19-the law and limits of quarantine, New England J. Med. Surg. Collat. Branches Sci. 382 (15) (2020) e28, https://doi.org/10.1056/NEJMpa2004211.

[3] A. Giubilini, T. Douglas, H. Maslen, J. Savulescu, Quarantine, isolation and the duty of easy rescue in public health, Develop. World Bioeth. 18 (2017) 182–189.

[4] S. Amiri, A. Shirzadian, A. Mirzaian, M. Imran-Khan, M.R. Balaet, N. Kordjazy, A. R. Delpour, S.E. Mehr, Involvement of the nitricergic system in the proconvulsant effect of social isolation stress in male mice, Epilepsy Behav. 41 (2014) 158–163.

[5] J. McCagh, J.E. Fisk, G.A. Baker, Epilepsy, psychosocial and cognitive functioning, Epilepsy Res. 66 (2009) 1–14.

[6] M.Y. Neufeld, M. Sadeh, D.F. Cohn, A.D. Korczyn, Stress and epilepsy: the Gulf war experience, Seizure 3 (1994) 135–139.

[7] W.A.M. Swinkels, M. Engelsman, D.G.A. Kasteleijn-Nolst Trenite, G.J. Baal MGm de Haan, G. Oosting, Influence of an Evacuation in February 1995 in the Netherlands on the Seizure Frequency in Patients with Epilepsy: A controlled study, Epilepsia (39) (1998) 1203–1207.

[8] P. Klein, L. van Pansel, Effect of stress related to the 9/11/2001 terror attack on seizures in patients with epilepsy, Neurology 64 (2005) 1815–1816.

[9] R.S. Fisher, C. Acevedo, A. Arzimanoglou, A. Bogacz, J.H. Cross, C.E. Elger, et al., ILAE official report: a practical clinical definition of epilepsy, Epilepsia. 55 (April 4) (2014) 475-482, https://doi.org/10.1111/epi.12550.

[10] S.J. Moon, W.Y. Lee, J.S. Hwang, Y.P. Hong, D.S. Morrisky, Accuracy of a screening tool for medication adherence: a systematic review and meta-analysis of the Morisky Medication Adherence Scale-8, PLoS One (12) (2017) e0187139.

[11] M.A. Ruiz, E. Zamorano, J. García-Campayo, A. Pardo, O. Freire, J. Rejas, Validity of the GAD-7 scale as an outcome measure of disability in patients with generalized anxiety disorders in primary care, J. Affect. Disord. 128 (2011) 277–286.

[12] R. Kocalevent, A. Hinz, E. Brähler, Standardization of the depression screener patient health questionnaire (PHQ-9) in the general population, Gen. Hosp. Psychiatry 35 (2013) 551–555.

[13] A. McGonigal, J.A. Micoaulaud Franchi, N. Villeneuve, A. Lepine, M. Viellard, M. Milh, Screening for depression in youth with epilepsy: the NDDI-E-Y, Epilepsia 59 (2018) 1999–2000.

[14] K.K. Wu, K.S. Chan, The development of the Chinese version of impact of event Scale-revised (IIES-R), Soc. Psychiatry Psychiatr. Epidemiol. 38 (2003) 94–98.

[15] E.H. Lee, B.Y. Chung, C.H. Suh, J.Y. Jung, Korean versions of the perceived Stress Scale (PSS-14, 10 and 4); psychometric evaluation in patients with chronic disease, Scand. J. Caring Sci. 29 (2014) 183–192.

[16] C.M. Morin, G. Belleville, L. Bélanger, H. Ivers, The insomnia severity index: psychometric indicators to detect insomnia cases and evaluate treatment response, Sleep 34 (2011) 601–608.

[17] M. Skinner TC, J. Clarke, P. Eastwood, R.S. Bucks, Can we get more from the Epworth Sleepiness Scale (ESS) than just a single score? Sleep Breath. 17 (2012) 763–769.

[18] G. Assenza, L. Lanzante, F. Brigo, A. Coppola, G. Di Gennaro, V. Di Lazzaro, et al., Epilepsy care in the time of COVID-19 pandemic in Italy: risk factors for seizure worsening, Front. Neurol. 3 (11) (2020) 737, https://doi.org/10.3389/fneur.2020.00737.

[19] C. Cabona, F. Deleo, L. Marinelli, D. Audenino, D. Arnaudi, F. Rossì, R. Di Giacomo, et al., Epilepsy course during COVID-19 pandemic in three Italian epilepsy centers, Epilepsy Behav. 25 (112) (2020) 107375, https://doi.org/10.1016/j.yebeh.2020.107375.