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Brief Communication

Correlates of psychological distress in epileptic patients during the COVID-19 outbreak

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ABSTRACT

Introduction: Following the severe consequences of the coronavirus disease 2019 (COVID-19) outbreak, on March 9th, 2020 the Italian Government implemented extraordinary measures to limit viral transmission, including restrictive quarantine measures. Psychological distress represents the seizure-precipitating factor most often reported by patients with epilepsy. To date, no studies have analyzed the role played by the different dimensions of psychological distress quarantine-induced in patients with epilepsy.

Materials and Methods: We included a total of 40 patients, 18 suffered from generalized, and 22 from focal epilepsy. The patients previously seen in the outpatient clinic during the pre-lockdown period between January and February 2020 were reevaluated after the lockdown period. Psychological distress was evaluated by using the three subscales of Impact of Event Scale-Revised (IES-R). Finally, we employed logistic regression analyses to explore the demographic and clinical features associated to high scores on IES-R.

Results: Patients with higher scores on IES-R Intrusion and IES-R Avoidance subscales demonstrated an increased number of epileptic attacks compared to prelockdown period. Multivariate logistic regression analyses showed that a specific subgroup of patients (i.e., older, female with more anxious symptoms) are at higher risk of increased seizure frequency.

Conclusions: Our study confirmed that the frequency of epileptic seizures increased during lockdown when compared to pre-lockdown period. The early identification of patients more vulnerable to worsening is crucial to limit the risk of requiring hospital or clinical treatment during the COVID-19 outbreak.

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1. Introduction

Epilepsy is a disease characterized by a spontaneous recurrence of unprovoked seizures. It is one of the most common chronic neurological conditions, with a prevalence rate of 0.7–1.0%, and higher incidence among elderly people and children [1]. Although in the majority of patients, seizures can be triggered by various endogenous and exogenous factors, psychological distress (e.g., traumatic psychological experiences) represents the seizure-precipitating factor most often reported by patients with epilepsy [2]. In late 2019, a pneumonia cluster of unknown origin was identified in Wuhan, China. A novel coronavirus termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was isolated from human cases and its genetic sequence shared publicly in early January 2020. The disease caused by SARS-CoV-2, named coronavirus disease 2019 (COVID-19), quickly spread to all Chinese provinces and to several other countries worldwide. Therefore, on 11 March 2020 the World Health Organization announced that the COVID-19 outbreak had reached pandemic levels [3]. The COVID-19 pandemic has created unprecedented challenges for medical healthcare systems worldwide. Italy has been the first Western country heavily affected by COVID-19 outbreak and has used rigorous global containment and quarantine efforts to limit infection diffusion [4]. Notwithstanding the need for such containment measures for guaranteeing public health and safety, COVID-19 outbreak and social lockdown may be appraised as a psychological distressing event causing negative side effects on general [5] as well as on neurological populations such as epileptic patients [6]. To our knowledge, few studies, only in the Asian population, [7–9] have recently investigated the association between the development of outbreak-related distress and a seizure exacerbation. However, to date no one has analyzed the role played by

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the different dimensions of psychological distress and its correlation with demographic and clinical features in patients with epilepsy from Western countries. Therefore, the aims of this study were: (a) to compare epileptic seizure frequency during the last pre-lockdown visit between January and February 2020 versus its frequency after the lockdown period of March and April 2020; (b) to explore the potential role played by different dimensions of psychological distress during outbreak; and (c) to identify the demographic and clinical features of high-risk patients to provide them with more adequate support. To achieve these aims, we analyzed differences in terms of epilepsy outcome both in the overall sample and in subsamples of patients stratified according to level (high/low) of experienced psychological distress related to COVID-19 outbreak and social lockdown. Moreover, we profiled the main demographic and clinical features of patients experiencing more marked psychological distress.

2. Materials and methods

2.1. Subjects

We screened patients from a longitudinal cohort followed by the Outpatient Epilepsy clinic of the First Division of Neurology at the University of Campania "Luigi Vanvitelli" (Naples, Italy). Of 90 progressive patients, we enrolled a total of 40 patients, 18 suffered from generalized, and 22 from focal epilepsy. The inclusion criteria were (a) a complete medication adherence to antiepileptic drugs (AE) and (b) a satisfactory global cognitive status to avoid any bias in administering the neuropsychological battery. Fifty patients refused to participate in the study. The patients previously seen in our outpatient clinic during the pre-lockdown period between January and February 2020, as part of an ongoing research protocol, were re-evaluated after the lockdown period of March and April 2020. Clinical details regarding the adherence to AE treatment, the use/abuse of alcohol and the occupational state during outbreak were collected by phone-interviews. Then, patients were asked to fill-out and return by email specific scales assessing the psychological impact of the event. Two experienced psychologists (M.S. and V.S.E.) explained project details to the patients by phone-calls. Psychological distress was evaluated using the Impact of Event Scale-Revised (IES-R) one of the most widely used self-report tool within the trauma literature [10,11]. This scale includes three subscales tapping intrusion (e.g., repeated thoughts about the event), avoidance (e.g., effortful attempts not to think about the event), and hyperarousal (e.g., anger, irritability, hypervigilance, difficulty concentrating) measures related to traumatic event. Anxious and depressive symptoms were assessed using Hospital Anxiety and Depression Scale (HADS) [12]; sleep disturbances were measured by Insomnia Severity Scale (ISI) [13].

The local Ethics Committee supervised and approved all procedures, in accordance with the Declaration of Helsinki. According to the recent statement from the Italian Medicines Agency (AIFA) (www.aifa.gov.it) regarding COVID-19 emergency-related studies, informed consent was obtained by email from all participants.

2.2. Statistical analysis

We used the Wilcoxon signed-rank test (Z) to show the differences in the number of epileptic seizures between pre-lockdown and post-lockdown periods for overall sample.

To explore the impact of psychological distress related to COVID-19 outbreak on the frequency of epileptic seizures, we compare the number of epileptic seizures between pre-lockdown and lockdown periods in subsamples of patients with high (i.e., experiencing high psychological distress related to COVID-19 outbreak) or low (i.e., experiencing low psychological distress related to COVID-19 outbreak) scores on IES-R Intrusion, IES-R Hyperarousal, and IES-R Avoidance subscales. In this regard, the three IES-R subscales were split into two parts (i.e. high and low) according to the median value, because no cut-off values have been provided so far.

Finally, we employed three separate logistic regression analyses (forward stepwise) to explore the demographic and clinical features associated with high scores on IES-R Intrusion, IES-R Hyperarousal, or IES-R Avoidance. All analyses were performed using SPSS version 21, with p value <0.05 considered statistically significant.

3. Results

We report the descriptive statistics in Table 1.

During the outbreak, no patients modified the adherence to AE treatment, the use of alcohol, or their occupational state. Regarding occupational state, 32 patients did not report any change since they were either students or unemployed. Eight of them had worked from home (i.e. "smart-working"). None of the patients was diagnosed with COVID19 or reported a close contact to COVID19 patients.

As for the overall sample, the number of epileptic attacks was significantly higher at lockdown (Mdn = 0.5; interquartile range or IQR = 11.0) than at pre-lockdown (Mdn = 0.0; interquartile range or IQR = 8.0), $Z = -1.9$, p-value = 0.04. The same pattern of results was observed for patients with high scores on IES-R Intrusion and IES-R Avoidance subscales (Table 2).

Multivariate logistic regression analyses showed that: (1) higher scores on IES-R Intrusion subscale were associated with higher age, female sex, and higher scores on HADS-Anxiety subscale; (2) higher scores on IES-R Hyperarousal subscales were related to higher scores on HADS-Anxiety subscale; and (3) higher scores on IES-R Avoidance scale were associated with higher age, and higher scores on HADS-Anxiety subscale (Table 3).

4. Discussion

In the present study, we demonstrated an increased frequency of epileptic seizures during lockdown (i.e. two months between March and April 2020) when compared to the pre-lockdown period (i.e. two months between January and February 2020). This pattern of increased frequency is particularly notable for those patients experiencing a greater psychological distress related to the COVID-19 outbreak as measured using IER-S. Compared with non-distressed, epileptic-distressed patients more prone to experience repeated thoughts about the ongoing pandemic (i.e., with high scores on IES-R Intrusion), or those more engaged in effortful attempts not to think about them (i.e., with high scores on IES-R Avoidance), showed an increased frequency of seizures. These results seem to support a probable interplay between these two clusters of stress-related symptoms [11]. Indeed, previous evidence suggested that avoidance may help the individual to regulate negative affect that is generated by intrusive reminders of the traumatic event.

Psychological stress is defined as a subjective experience of a threat of homeostasis [14], and adaptive responses to it consist of changes oriented to restore it. Nevertheless, events inducing a prolonged activation of the stress system, such as COVID-19 outbreak, might cause long-term maladaptive consequences (i.e., psychological distress) by provoking changes in brain structures and functioning as well as in neuroendocrine response. Particularly, abnormal corticotropin releasing hormone related to distress appears to be proconvulsant, increasing excitatory transmission causing epilepsy worsening [15].

Table 1
Descriptive statistics.

Variable	Median (IQR) or Count (Percentage)
Demographic:	
Age, years	33.5 (25.0)
Sex, male	8 (20%)
Clinical:	
Seizure, focal/generalized	18 (41%)/22 (59%)
Disease duration, years	7.0 (17.0)
HADS-Anxiety subscore	8.0 (8.7)
HADS-Depression subscore	4.0 (4.7)
Insomnia Severity Index	4.0 (7.0)
Hours/die of lockdown	24.0 (0.0)
Number of seizures pre-lockdown period (January–February 2020)	0.0 (8.0)
Number of seizures lockdown period (March–April 2020)	0.5 (11.0)
Impact Event Scale:	
IES-R Intrusion	10.0 (13.0)
IES-R Hyperarousal	7.5 (8.7)
IES-R Avoidance	10.0 (8.7)

Note. IQR, interquartile range or 75th minus 25th percentiles; SD, Standard Deviation; HADS, Hospital Anxiety and Depression Scale; IES-R, Impact Event Scale-Revised.

In this regard, previous studies demonstrated that the frequency of seizures increased in a part of adult patients with epilepsy exposed to objective major life events, such as war and evacuation [16]. Consistently, questionnaire studies showed that 8–83% of patients of all ages reported psychological distress as one of the main seizure precipitant factor [17]. Moreover, a similar pattern of results was also found in the first diary-based study, performed by Temkin and Davis [18], which showed that a large part of patients with epilepsy experienced significantly more seizures during "high-distress days" compared to "low-distress days".

Taken together, these results suggest that the same traumatic events may induce psychological distress, and consequently increase the frequency of seizures, in a large proportion but not in all patients with epilepsy. Therefore, it is crucial to identify a subgroup of patients at risk of experiencing more marked psychological distress when facing traumatic events, such as COVID-19 outbreak, to provide them with a more adequate support. Our logistic regression results revealed that higher levels of psychological distress related to COVID-19 outbreak were associated with anxiety symptoms in our population. In epileptic patients, the presence of anxiety disorders represents a well-known risk factor for clinical worsening [19], which need to be closely monitored. Indeed, the presence of interictal anxiety manifestations in terms of anticipatory seizure anxiety, seizure phobia, epileptic social phobia, and epileptic panic disorder may induce higher seizure frequency and poorer seizure control outcome with antiepileptic drugs [20]. Our results suggest that, during objective major life events such as COVID-19 outbreak, patients affected by more marked anxious symptoms should be strictly monitored because they are more prone to experience high levels of psychological distress and thus a potential increased frequency of seizures.

Moreover, we found that an older age was associated with high levels of psychological distress related to COVID-19, consisting of repeated intrusive thoughts or effortful attempts not to think about it. These findings are at odds with previous studies in general population, where the susceptibility to intrusive thoughts and the recourse to avoidance strategies [21] decreased in older people when compared to younger people. These inconsistent findings may be partially explained by the fact that older age has been associated with poor outcomes in patients affected by COVID-19 [4], inducing more marked intrusive thoughts and efforts of avoiding in elderly patients with epilepsy.

Table 3
Results of stepwise logistic regression analyses showing the variables associated with high levels of Impact Event Scale-Revised Intrusion and Avoidance.

	Beta (SE)	*p*-value	OR [95% CI]
IES-R Intrusion[a]			
Constant	−7.33 (2.70)	<0.01	0.00
Age, years	0.09 (0.04)	0.02	1.10 [1.01, 1.20]
Sex (male = 0, female = 1)	2.92 (1.41)	0.03	18.65 [1.16, 29.97]
HADS-Anxiety subscore	0.24 (0.10)	0.01	1.27 [1.04, 1.54]
Model: χ^2 = 20.53, *p*-value < 0.01, R^2 (Nagelkerke) = 0.54			
IES-R Hyperarousal[b]			
Constant	−15.62 (6.21)	<0.01	0.00
HADS-Anxiety subscore	0.66 (0.21)	<0.01	1.95 [1.28, 2.94]
Model: χ^2 = 32.46, *p*-value < 0.01, R^2 (Nagelkerke) = 0.75			
IES-R Avoidance[c]			
Constant	−6.95 (2.46)	<0.01	0.00
Age, years	0.16 (0.06)	0.01	1.17 [1.03, 1.33]
HADS-Anxiety subscore	0.35 (0.14)	0.01	1.43 [1.08, 1.89]
Model: χ^2 = 27.16, *p*-value < 0.01, R^2 (Nagelkerke) = 0.68			

Note. SE, Standard Error; IES-R, Impact Event Scale-Revised; HADS, Hospital Anxiety and Depression Scale. **a,** variables removed from the equation (*p*-value > 0.10): seizure (focal = 0, generalized = 1), disease duration, HADS depression subscore, Insomnia Severity Index, and hours/die of lockdown. **b,** variables removed from the equation (*p*-value > 0.10): age, sex, seizure (focal = 0, generalized = 1), disease duration, HADS depression subscore, Insomnia Severity Index, and hours/die of lockdown. **c**, variables removed from the equation (*p*-value > 0.10): sex (male = 0, female = 1), seizure (focal = 0, generalized = 1), disease duration, HADS, depression subscore, Insomnia Severity Index, and hours/die of lockdown.

Table 2
Results of Wilcoxon signed-rank tests (*Z*) showing the comparison of the number of epileptic attacks between pre- and lockdown periods; data are shown as median (interquartile range or 75th minus 25th percentiles).

	Number of seizures		*Z*	*p*-value	Adj-*p*
	pre-lockdown period	lockdown period			
IES-R Intrusion					
High (*n* = 22)	2.0 (6.5)	5.0 (15.0)	−2.8	<0.01	**0.03**
Lower (*n* = 18)	0.0 (10.0)	0.0 (1.5)	−0.1	0.91	1.00
IES-R Hyperarousal					
High (*n* = 17)	6.0 (10.0)	8.0 (14.0)	−1.5	0.11	0.68
Low (*n* = 23)	0.0 (1.0)	0.0 (1.0)	−1.0	0.30	1.00
IES-R Avoidance					
High (*n* = 25)	2.0 (8.0)	6.0 (15.0)	−2.9	<0.01	**0.01**
Low (*n* = 15)	0.0 (8.0)	0.0 (0.0)	−0.6	0.50	1.00

Note. IES-R, Impact of Event Scale-Revised; Adj-*p* represents *p*-value corrected for multiple comparisons using the Bonferroni correction and statistically significant differences are shown in **bold**.

Finally, we found that female patients were more prone to experience psychological distress related to COVID-19 outbreak, in the form of repeated intrusive thoughts. This result is consistent with previous evidence on general population, showing gender differences in intrusive memories following trauma [22]. It is possible that female patients with epilepsy had a greater consolidation of emotionally negative memories, which in turn may increase the psychological distress related to traumatic events (such as COVID-19 outbreak), and indirectly impact on frequency of seizures.

5. Conclusions

Our single center study revealed two important findings. First, we confirmed that a stressful event, like the COVID-19 outbreak, has the potential to negatively influence the course of a preexisting epilepsy [7–9]; second, the existence, in the context of a traumatic event, of a subgroup of patients (i.e. older female patients with higher intrusivity and avoidance and suffering from more marked anxious symptoms) at higher risk of experiencing psychological distress, and likely at higher risk of clinical worsening. The early identification of these patients more vulnerable to worsening is crucial to limit the risk of requiring hospital or clinical treatment during objective major life events as COVID-19 outbreak. Our study has some limitations worth noting such as a relatively small number of progressive epileptic patients, not matched for epilepsy type and for AE regimen. Future studies including larger populations and a more homogeneous patients sample are needed to verify these observations.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Fisher RS, Boas WVE, Blume W, Elger C, Genton P, Lee P, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia 2005;46(4):470–2. https://doi.org/10.1111/j.0013-9580.2005.66104.x.

[2] Frucht MM, Quigg M, Schwaner C, Fountain NB. Distribution of seizure precipitants among epilepsy syndromes. Epilepsia 2000;41(12):1534–9. https://doi.org/10.1111/j.1499-1654.2000.001534.x.

[3] Kuldeep D, Sharun K, Ruchi T, Shubhankar S, Sudipta B, Yashpal SM, et al. Coronavirus Disease 2019–COVID-19. Clin Microbiol Rev 2020;33(4). https://doi.org/10.1128/CMR.00028-20. e00028-20.

[4] Hozhabri H, Piceci F, Sohrabi H, Mousavifar L, Roy R, Scribano D, et al. The global emergency of novel coronavirus (SARS-CoV-2): An update of the current status and forecasting. Int J Environ Res Public Health 2020;17(16):5648. https://doi.org/10.3390/ijerph17165648.

[5] Moreno C, Wykes T, Galderisi S, Nordentoft M, Crossley N, Jones N, et al. How mental health care should change as a consequence of the COVID-19 pandemic. Lancet Psychiatry 2020;7(9):813–24. https://doi.org/10.1016/S2215-0366(20)30307-2.

[6] Bhaskar S, Bradley S, Israeli-Korn S, Menon B, Chattu VK, Thomas P, et al. Chronic neurology in COVID-19 era: clinical considerations and recommendations from the REPROGRAM Consortium. Front Neurol 2020;11:664. https://doi.org/10.3389/fneur.2020.00664.

[7] Huang S, Wu C, Jia Y, Li G, Zhu Z, Lu K, et al. COVID-19 outbreak: The impact of stress on seizures in patients with epilepsy. Epilepsia 2020;6:1884–93. https://doi.org/10.1111/epi.16635.

[8] 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;61(6):1166–73. https://doi.org/10.1111/epi.16544.

[9] Alkhotani A, Siddiqui MI, Almuntashri F, Baothman R. The effect of COVID-19 pandemic on seizure control and self-reported stress on patient with epilepsy. Epilepsy & Behavior 2020;112:107323. https://doi.org/10.1016/j.yebeh.2020.107323.

[10] Weiss DS, Marmar CR. The impact of events scale—revised. In: Wilson JP, Terence WM, editors. Assessing psychological trauma and PTSD. New York: Guilford Press; 1997. p. 399–411.

[11] Beck JG, Grant DM, Read JP, Clapp JD, Coffey SF, Miller LM, et al. The Impact of Event Scale-Revised: Psychometric properties in a sample of motor vehicle accident survivors. J Anxiety Disord 2008;22(2):187–98. https://doi.org/10.1016/j.janxdis.2007.02.007.

[12] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67(6):361–70. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x.

[13] Morin CM, Belleville G, Belanger L, Ivers H. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. Sleep 2011;34(5):601–8. https://doi.org/10.1093/sleep/34.5.601.

[14] Selye H. Stress and the general adaptation syndrome. Br Med J 1950;1(4667):1383–92. https://doi.org/10.1136/bmj.1.4667.1383.

[15] Baram TZ, Schultz L. Corticotropin-releasing hormone is a rapid and potent convulsant in the infant rat. Dev Brain Res 1991;61(1):97–101. https://doi.org/10.1016/0165-3806(91)90118-3.

[16] Moshe S, Shilo M, Chodick G, Yagev Y, Blatt I, Korczyn AD, et al. Occurrence of seizures in association with work-related stress in young male army recruits. Epilepsia 2008;49(8):1451–6. https://doi.org/10.1111/j.1528-1167.2008.01591.

[17] Pinikahana J, Dono J. The lived experience of initial symptoms of and factors triggering epileptic seizures. Epilepsy Behav 2009;15(4):513–20. https://doi.org/10.1016/j.yebeh.2009.06.004.

[18] Temkin NR, Davis GR. Stress as a risk factor for seizures among adults with epilepsy. Epilepsia 1984;25(4):450–6. https://doi.org/10.1111/j.1528-1157.1984.tb03442.x.

[19] Brooks-Kayal A, Bath K, Berg AT, Galanopoulou AS, Holmes GL, Jensen FE, et al. Issues related to symptomatic and disease-modifying treatments affecting cognitive and neuropsychiatric comorbidities of epilepsy. Epilepsia 2013;54:44–60. https://doi.org/10.1111/epi.12298.

[20] Beyenburg S, Mitchell AJ, Schmidt D, Elger CE, Reuber M. Anxiety in patients with epilepsy: systematic review and suggestions for clinical management. Epilepsy Behav 2005;7(2):161–71. https://doi.org/10.1016/j.yebeh.2005.05.014.

[21] Beadel JR, Green JS, Hosseinbor S, Teachman BA. Influence of age, thought content, and anxiety on suppression of intrusive thoughts. J Anxiety Disord 2013;27(6):598–607. https://doi.org/10.1016/j.janxdis.2012.12.002.

[22] Hsu CK, Kleim B, Nicholson EL, Zuj DV, Cushing PJ, Gray KE, et al. Sex differences in intrusive memories following trauma. PLoS One 2018;13(12):. https://doi.org/10.1371/journal.pone.0208575e0208575.