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Brief Communication

Epilepsy course during COVID-19 pandemic in three Italian epilepsy centers

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ABSTRACT

During epidemic outbreaks, epilepsy course can be modified by different physical and psychological stressors and, most importantly, by irregular therapy intake.
The effect of COVID-19 and quarantine isolation on the course of epilepsy and on incidence of new-onset seizures is still unclear.
With the aim of managing epilepsy in quarantined patients, three Italian Epilepsy Centers set up telephone consultations using a semistructured interview, allowing a prospective collection of data on seizure course and other seizure-related problems during pandemic. The collected data on seizure course were compared with the analogous period of 2019.
The level of patients' concern relating to the COVID-19 pandemic was also assessed using a numeric rating scale.
To address the effect of COVID-19 pandemic on seizure incidence, data collection included the number of consultations for first seizures, relapse seizures, and status epilepticus (SE) in the emergency department of one of the participating centers.
Clinical telephone interviews suggest the absence of quarantine effect on epilepsy course in our cohort. No differences in incidence of emergency consultations for seizures over a two-month period were also observed compared with a control period.
As demonstrated in other infective outbreaks, good antiepileptic drug (AED) supplying, precise information, and reassurance are the most important factors in chronic conditions to minimize psychological and physical stress, and to avoid unplanned treatment interruptions.

1. Introduction

The coronavirus disease (COVID-19) outbreak started in December 2019 in the city of Wuhan, in the Chinese province of Hubei with a worrying surge of bilateral interstitial pneumonia cases, needing intensive care from 6.1% to 32% of the cases [1,2]. After spreading to other Asian countries (Japan, South Korea), Italy was rapidly invested by the fast spreading viral pandemic [3]. A strict quarantine period started in Italy on March 9, 2020, forcing a large part of the Italian population at home.

From that point on, all medical activities considered as "nonurgent", including most of the clinical and electroencephalogram (EEG) activities of Epilepsy Centers, stopped, waiting for the reduction of the viral spread.

The basic principle of avoiding contacts among an uncontrolled and potentially infective population introduces a radical change in medical practice, with an unknown effect on epilepsy course in the quarantined patients. Most Epilepsy Centers, in Italy as abroad, declare that some

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activities related to the epilepsy management were conducted using phone consultations or other telemedicine means to avoid unnecessary physical interactions.

Telephone consultations are ideally suited to patients with epilepsy follow-up, which is based on verbal updates, answer to patients' questions, advice on therapy adjustments, and only rarely physical examination [4].

As described during natural disasters [5,6] and other epidemic outbreaks, such as Severe Acute Respiratory Syndrome (SARS) in 2003 [7], epilepsy course may be modified by different physical and psychological stressors and, most importantly, by irregular therapy intake.

With the aim of managing epilepsy in quarantined patients during COVID-19 pandemic, three Italian Epilepsy Centers set up telephone consultations using a semistructured interview, allowing collection of data on seizure course during pandemic. Collected information regarded possible stressors, such as antiepileptic drugs (AEDs) availability, work situation, difficulties in performing diagnostic procedures, and subjective changes in seizure frequency or semiology.

2. Materials and methods

The study involved the Epilepsy Centers of three hospitals of two Northern Italian Regions (Liguria and Lombardia) struck by COVID-19 pandemic: IRCCS Ospedale Policlinico San Martino (Genova), Fondazione IRCCS Istituto Neurologico "Carlo Besta" (Milano), and E.O. Ospedali Galliera (Genova).

Outpatients with confirmed epilepsy diagnosis, expecting a follow-up visit in the outpatient clinic between March 9th and April 30th 2020, were telephone contacted by the neurologist in charge. A clinical interview was submitted to manage possible seizure variations and treatment-related problems. The interview was conducted in a semistructured way, with the help of a predefined form. The following information were collected for each interview: sex, age, place of residence, working position, age at epilepsy onset, seizure type, number of seizures during the last year, date of last seizure, seizure frequency and change during COVID-19 period, difficulty in obtaining AEDs, and difficulties in performing clinical and instrumental examinations. A numeric rating scale defining the level of concern related to the COVID-19 pandemic was also administered. The COVID period was considered as starting from March 1st.

Descriptive statistics described our patient population. Continuous data are expressed as median and interquartile range (IQR). Reported concern score was compared between working and nonworking people using an unpaired Mann–Whitney test. A similar analysis was performed grouping patients according to difficulties in obtaining AEDs. Differences were considered significant for $p < 0.05$.

To address the effect of the COVID-19 pandemic on seizure incidence in an emergency setting, data collection included the number of EEG exams performed during a quarantine period (from March 1st to April 30th) for first unprovoked seizures, relapse seizures, and status epilepticus (SE) in the Emergency Department and intensive care unit (ICU) of one of the participating centers (Ospedale San Martino, Genova). The diagnosis of first unprovoked seizure, relapse seizure, and SE at discharge from the Emergency Department was then confirmed examining the hospital records.

The study complied with the ethical guidelines of the involved institutions, and the publication was approved by the ethics committee of the study coordinator center (Ospedale San Martino).

3. Results

A total of 189 patients were enrolled; demographic characteristics are summarized in Table 1. All patients or their caregiver accepted to conduct their follow-up visit via telephone, and a "face to face" visit to make the patient or the caregiver understand the decisions or recommendations of the referring neurologist was not necessary.

Table 1
General characteristics of the cohort.

Male/female	86/103
Age [median, IQR]	45 (33–57)
Employed	100 (52.9%)
Working during COVID-19 pandemic	35 (18.5%)
Smart working	41 (21.7%)
Students	7 (3.7%)
Age at epilepsy onset [median, IQR]	19 (12–37)
Patients with uncontrolled seizures[a]	109 (57.7%)
Seizure type	
Focal	83 (44%)
Generalized	48 (25.4%)
Focal to bilateral tonic–clonic	55 (29.1)
Subjective seizure modification	18 (9.5%)
Frequency increase	8
Frequency decrease	8
Semiology modification	2[b]
Monotherapy	95 (50.2%)
Difficulty in AED supplying	51 (27%)[c]

[a] At least one seizure in the last year.
[b] One patient reported longer duration of each seizure, the other an increase of falls.
[c] No patients reported to have interrupted or reduced AEDs intake.

As reported in Table 1, 18 (9.5%) patients reported seizure changes during the COVID period. Sixteen patients reported a change in seizure frequency (an increase in 8 and a decrease in 8); 2 a change in seizure semiology.

The number of EEG evaluations for first unprovoked seizures, relapse seizures, and SE during the quarantine period was 38, against 32 in the comparable period of 2019. During quarantine period, 9 EEGs were performed for first unprovoked seizures, 4 for SE. During the same period of 2019, 12 EEGs were performed for first unprovoked seizure and 2 for SE, thus confirming the comparable results in the two considered periods.

Median score for COVID-19 concern was 6 (IQR: 3–8), with 65 patients scoring 0–4 and 117 scoring 5–10 (7 missing values). The score did not differ significantly in 8 patients reporting an increasing number of seizures (median concern score of 4, range: 0–10) and the 8 reporting a decreasing number (median concern score: 5, range: 2–9). Median concern score was identical between people experiencing seizures during the COVID-19 period (median: 6, IQR: 3–8) and those who did not (median: 6, IQR: 4–8).

The working status did not influence how much patients felt concerned since no difference emerged between working (median: 7, IQR: 3–8) and not working (median: 6, IQR: 3–7) patients ($p = 0.8$). Concern score in patients with difficulty in obtaining AEDs (median: 6, IQR: 4–8) is also not significantly different with respect to patients without such a problem (median: 5, IQR: 3–8) ($p = 0.4$).

4. Discussion

The relationship between seizures and infective events may be twofold: uncontrolled seizure and SE may be considered risk factors for developing infections [8], whereas infections may induce acute symptomatic seizures through encephalitis or metabolic imbalances [9]. The effect of COVID-19 and quarantine isolation on the course of epilepsy and on prevalence of new-onset seizures remains but still unclear [8].

Recent literature on COVID-19 reports the presence of various central and peripheral neurologic manifestations in more than 30% of the patients [10], probably related to ACE2 receptor presence on neurons and glial cells [11]. Neurological involvement includes acute cerebrovascular diseases, encephalitis [12], peripheral nerve [13], and skeletal muscle injury. Seizures [14] and unclassified disturbances of consciousness are also reported, but scanty clinical information and lack of EEG recordings do not allow better characterization of such clinical reports.

In a recent retrospective cohort of 304 patients, 27% presented "brain insults or metabolic imbalances", but none of them presented acute symptomatic seizures or SE. Two patients presented "seizure-like symptoms", related to a "stress reaction" and hypocalcemia. However, none of the cohort patients was submitted to an EEG exam for safety reasons [15].

Natural disasters may result in mental and physical health deterioration in healthy people. Patients with chronic disorders are at higher risk of developing health problems. Previous reports have documented an increase in the number of sudden cardiac deaths, and a difficult glycemic control in patients with diabetes mellitus after the Northridge and the Kobe earthquakes [16,17]. These reports concluded that life-threatening stress contributed to aggravation of certain pathological conditions. Seizure facilitation can be therefore expected during pandemic as reported during other natural disasters [5,6]. Shortage of AED supplying and psychological and physical distress, such as worry for life and sleep deprivation, were the hypothetical causes of such facilitation.

Our study, while confirming the possibility of effectively managing epilepsy by remote means during emergency periods, allowed us to gather information on the relation between COVID-19 infection, acute seizures, and epilepsy. Our approach was twofold: first, during the period of quarantine, telephone consultations were set up using a semistructured interview, with the purpose of managing seizures and AED treatment and, at the same time, for answering to questions related to COVID-19 infection for patients' reassurance. Second, data on incidence of emergency consultations for seizures (first unprovoked occurrence and relapse events, with diagnosis confirmed at discharge from the hospital) were gathered by one of the participating centers, which is, with its 85.000–95.000 emergency consultations per year, a hub for emergency for a vast northern Italian area.

With this aim, we retrospectively examined the EEG database, listing all the EEG recordings performed after admissions in the Emergency Area during quarantine period and the same period of the previous year. No differences in incidence of emergency consultations for seizure over a two-month period were observed compared with the control period. Interestingly, the consultations for a first seizure and SE were similar during the COVID-19 period and the control period.

On the other hand, only two patients with COVID-19 presented an EEG-documented SE during their stay in the ICU, one due to unduly suspension of AED chronic treatment few days before hospitalization and the other related to a documented severe hypoxia in a patient without epilepsy. In one adjunctive case, an EEG was performed for a suspected generalized motor seizure occurring in the phase of sedative drugs weaning, but no epileptic abnormalities were observed.

Our data suggest that COVID-19 infection, not increasing the rate of emergency consultations for seizures, is not a risk factor for new-onset and relapse seizures in a quite large population of patients, afferent to a center for emergency.

Clinical telephone interviews confirmed the absence of COVID-19 quarantine effect on epilepsy course in our cohort, since we did not find any significant change in seizure frequency during that period compared with a control period. On the other hand, those few patients reporting an increase or decrease of seizure frequency showed comparable levels of preoccupation, suggesting that such frequency variation had little or no psychologic impact on our patients' cohort. We also found that the level of preoccupation did not change depending on working status or AED availability.

In our cohort, 27% of the patients reported some difficulties in AED supplying during quarantine, but none of them had to reduce or to suspend AEDs intake. Providing information on COVID-19 infection and epilepsy prevented unduly AED interruption in our patients.

5. Conclusions

We conclude that epilepsy management during pandemic emergency can be effectively maintained via telephone contact, which must be considered an indispensable resource to improve surveillance of patients, contain the spread of the disease, and ensure continuity of care of patients with chronic conditions [18] such as epilepsy. Our data suggest that the COVID-19 infection neither facilitate seizures and SE nor increase the risk for patients with epilepsy of developing COVID-19 infection. As demonstrated by other natural disasters and infective outbreaks AED supplying is a key factor for avoiding seizure relapse. Providing precise information and reassurance are the most important factors in chronic conditions to minimize psychological and physical stress and to avoid unplanned treatment interruptions.

5.1. Limitations

The main limitation of the study is a possible selection bias, related to the cohort characteristic of only outpatients expecting a follow-up visit in the outpatient clinic during the selected time period, and the self-reported modification of seizures' trend. Another possible limitation could be the small size of the number of SE cases, mainly due to the selection method including only first unprovoked seizure, relapse seizure, and SE as the main diagnosis of discharge from the Emergency Department.

Data availability statement

Raw data are available upon appropriate request.

Ethical publication statement

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

Declaration of competing interest

None.

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References

[1] Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708–20. https://doi.org/10.1056/NEJMoa2002032.
[2] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. 2020;395:497–506. https://doi.org/10.1016/S0140-6736(20)30183-5.
[3] Colaneri M, Sacchi P, Zuccaro V, Biscarini S, Sachs M, Roda S, et al. Clinical characteristics of coronavirus disease (COVID-19) early findings from a teaching hospital in Pavia, North Italy, 21 to 28 February 2020. Eurosurveillance. 2020;25. https://doi.org/10.2807/1560-7917.ES.2020.25.16.2000460.
[4] Smith P. Telephone review for people with epilepsy. Pract Neurol. 2016;16:475–7. https://doi.org/10.1136/practneurol-2016-001504.
[5] Kobayashi S, Endo W, Inui T, Wakusawa K, Tanaka S, Onuma A, et al. The lack of antiepileptic drugs and worsening of seizures among physically handicapped patients with epilepsy during the Great East Japan Earthquake. Brain Dev. 2016;38:623–7. https://doi.org/10.1016/j.braindev.2016.01.005.
[6] Shibahara I, Osawa S-I, Kon H, Morita T, Nakasato N, Tominaga T, et al. Increase in the number of patients with seizures following the Great East-Japan Earthquake. Epilepsia. 2013;54:e49–52. https://doi.org/10.1111/epi.12070.
[7] Lai S-L, Hsu M-T, Chen S-S. The impact of SARS on epilepsy: the experience of drug withdrawal in epileptic patients. Seizure. 2005;14:557–61. https://doi.org/10.1016/j.seizure.2005.08.010.

[8] Kuroda N. Epilepsy and COVID-19: associations and important considerations. Epilepsy Behav. 2020;108:107122. https://doi.org/10.1016/j.yebeh.2020.107122.
[9] Misra UK, Kalita J. Seizures in encephalitis: predictors and outcome. Seizure. 2009; 18:583–7. https://doi.org/10.1016/j.seizure.2009.06.003.
[10] 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. https://doi.org/10.1001/jamaneurol.2020.1127.
[11] Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host–virus interaction, and proposed neurotropic mechanisms. ACS Chem Nerosci. 2020;11:995–8. https://doi.org/10.1021/acschemneuro.0c00122.
[12] 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; 94:55–8. https://doi.org/10.1016/j.ijid.2020.03.062.
[13] Zhao H, Shen D, Zhou H, Liu J, Chen S. Guillain-Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence? Lancet Neurol. 2020;19:383–4. https://doi.org/10.1016/S1474-4422(20)30109-5.
[14] Sohal S, Mansur M. COVID-19 presenting with seizures. ID Cases. 2020;20:e00782. https://doi.org/10.1016/j.idcr.2020.e00782.
[15] 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. https://doi.org/10.1111/epi.16524 epi.16524.
[16] Leor J, Poole WK, Kloner RA. Sudden cardiac death triggered by an earthquake. N Engl J Med. 1996;334:413–9. https://doi.org/10.1056/NEJM199602153340701.
[17] Inui A, Kitaoka H, Majima M, Takamiya S, Uemoto M, Yonenaga C, et al. Effect of the Kobe earthquake on stress and glycemic control in patients with diabetes mellitus. Arch Intern Med. 1998;158:274. https://doi.org/10.1001/archinte.158.3.274.
[18] Omboni S. Telemedicine during the COVID-19 in Italy: a missed opportunity? Telemed E-Health. 2020. https://doi.org/10.1089/tmj.2020.0106 tmj.2020.0106.