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Effects of the COVID-19 pandemic on characteristics of functional (psychogenic) seizures

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\textbf{ABSTRACT}

Objective: We investigated whether the COVID-19 pandemic has affected the clinical characteristics of patients with functional seizure (FS) (at the time of diagnosis).

Methods: In a retrospective study of a prospectively developed and maintained database, all patients diagnosed with FS before and during the COVID-19 pandemic were studied at the outpatient epilepsy clinic at Shiraz University of Medical Sciences, Shiraz, Iran, from December 2008 until February 2021.

Results: Three hundred and eighty-eight patients were studied. Three hundred and sixty-four patients (94\%) were diagnosed before and 24 persons (6\%) during the pandemic. Patients diagnosed during the COVID-19 pandemic less frequently had generalized motor seizures [odds ratio (OR): 0.30, 95\% confidence interval (CI): 0.12–0.77; \(p = 0.012\)] and had higher seizure frequencies (OR: 1.00, 95\% CI: 1.00–1.01; \(p = 0.044\)). Functional seizures were inversely associated with the education level as a trend during the COVID-19 pandemic (OR: 0.36, 95\% CI: 0.13–1.01; \(p = 0.052\)).

Conclusion: The COVID-19 pandemic has affected the characteristics of patients with FS (at the time of diagnosis). Larger and multi-center studies are needed to investigate the links and associations between the COVID-19 pandemic and characteristics of FS.

\section{1. Introduction}

Functional seizures (FS), also known as psychogenic nonepileptic seizures (PNES) or dissociative seizures, are characterized by paroxysmal and self-limited changes in behavior, feelings, movements, and responsiveness. These seizures share semiological similarities with epileptic seizures, but without ictal epileptiform discharges in electroencephalography (EEG); they are often associated with psychological problems \cite{1}. While the etiological underpinnings of FS are not well-recognized yet, some precipitating factors (e.g., injury, death of or separation from family members or friends, job loss, natural disasters, relationship difficulties, etc.) may occur over days to months before the onset of seizures \cite{2}. Furthermore, semiology of FS may be associated with co-existing neuropsychiatric problems in these patients (e.g., patients with akinetic functional seizures may have fewer co-existing neuropsychiatric problems compared with those who have motor seizures) \cite{3–6}.

Since late 2019, the world has been experiencing a catastrophic phenomenon, a deadly pandemic of a coronavirus disease (COVID-19) \cite{7}. Iran reported its first confirmed patients of COVID-19 on 19 February 2020. As of 19 April 2021, there has been 66,732 COVID-19 deaths with 2,237,089 confirmed cases in Iran \cite{8}. This virus has a high potential for person to person transmission. Implementation of social distancing measures has been advocated to control the outbreak around the world; as a result, this deadly outbreak has disrupted businesses and routine social activities. It has also caused hundreds of thousands of deaths, massive job losses, and increasing numbers of relationship difficulties (all of which are considered as the potential precipitating factors for FS) \cite{2,9}. Therefore, it is plausible to consider this pandemic as a potentially significant factor that may affect the characteristics of FS.

In the current study, we investigated whether the COVID-19 pandemic has affected the clinical characteristics of patients with FS. We hypothesized that there exist significant differences in the characteristics of FS (diagnosed) during the COVID-19 pandemic compared to that in the pre-COVID-19 era. It was a hypothesis drawn from personal observations in everyday clinical practice (with the impression that patients were more distressed and had more severe manifestations).
2. Methods

2.1. Participants

This was a retrospective study of a prospectively developed and maintained database. We investigated all patients with FS, who were admitted at the epilepsy monitoring unit at Shiraz Comprehensive Epilepsy Center from December 2008 through February 2021. Patients had a confirmed diagnosis of FS, determined by clinical assessment and video-EEG monitoring with ictal recording of their seizures. There were no exclusion criteria. Written informed consent was obtained at the time of admission at the epilepsy monitoring unit from all patients.

2.2. Data collection

We dichotomized the patients into two groups: 1. Those who were diagnosed before the COVID-19 pandemic started (From 1 December 2008 until 19 February 2020); and 2. Those who were diagnosed during the pandemic (From 1 March 2020 until 28 February 2021). We extracted all the relevant clinical and demographic data from our database. We studied and compared the characteristics of the two groups at the time of diagnosis: (i) the demographic characteristics: sex, age, age at onset, duration of illness, and education level (low: below 5 grades vs. others: 5 grades or higher); (ii) the seizure characteristics: FS frequency, loss of responsiveness (LOR) with FS, urinary incontinence with FS, generalized motor seizures, and ictal injury; and (iii) the associated risk factors: a family history of seizures, a history of physical abuse (i.e., corporal punishment or any physical injury resulted from aggressive behavior towards the patient), a history of sexual abuse (i.e., rape), and family dysfunction (i.e., divorce, significant family disputes, etc.).

2.3. Statistical analyses

Values were presented as mean ± standard deviation (SD) for continuous variables and as number (percent) of subjects for categorical variables. Fisher’s exact test, Kolmogorov-Smirnov normality test, Mann Whitney-U test, and binary logistic regression analysis model were used for statistical analyses. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. A p value (2-sided) less than 0.05 was considered as significant. We investigated the factors in association with the COVID-19 pandemic era in univariate analyses. Variables that had significant/near significant associations (p < 0.1) were analyzed in a binary logistic regression analysis model.

2.4. Standard protocol approvals, registrations, and patient consents

The Shiraz University of Medical Sciences Institutional Review Board approved this study.

2.5. Data availability statement

The data are confidential and will not be shared as per the regulations of Shiraz University of Medical Sciences.

3. Results

3.1. General characteristics of the patients

Three hundred and eighty-eight patients with FS were studied. Three hundred and sixty-four patients (94%) were diagnosed before and 24 persons (6%) during the COVID-19 pandemic. The mean age of the patients was 29 years (SD: 10 years, range: 10 to 71 years, median 28 years, and interquartile range 15 years). They included 258 women (66%) and 130 men (34%).

Table 1 shows the clinical characteristics of patients diagnosed with FS before and during the COVID-19 pandemic in univariate analyses. Frequency of functional seizure per months and generalized motor semiology were significantly different between the two groups. During the pandemic 14 out of 24 patients (58%) had daily FS, but before the pandemic 127 out of 364 patients (35%) reported experiencing daily FS. Receiving psychiatric drugs and the education level showed a trend to be different between the two groups (more of the participants diagnosed before the pandemic received psychiatric drugs than the participants diagnosed during the pandemic (p = 0.096), and more of that participants diagnosed during the pandemic had a lower education level (p = 0.051).

We then included the variables with a p ≤ 0.1 (i.e., functional seizure frequency, generalized motor seizure semiology, taking psychiatric medications, and the level of education, as covariates) in a regression analysis model to clarify the role of each variable in association with the time of FS diagnosis (i.e., before or during the COVID-19 pandemic; the dependent variable). The results of the binary logistic regression analysis showed a significant model (p = 0.001). Patients diagnosed during the COVID-19 pandemic less frequently had generalized motor seizures (OR: 0.30, 95% CI: 0.12–0.77; p = 0.012) and had higher seizure frequencies (OR: 1.00, 95% CI: 1.00–1.10; p = 0.044). Functional seizures were inversely associated with the education level as a trend during the COVID-19 pandemic (OR: 0.36, 95% CI: 0.13–1.10; p = 0.052). Taking psychiatric medications lost its significance within the model (p = 0.103).

4. Discussion

In the current study, we observed that functional seizure characteristics (at the time of diagnosis) were significantly different during the COVID-19 pandemic compared with that before the pandemic started. Those who were diagnosed during the pandemic less frequently had generalized motor seizures, but had higher seizure frequencies. In addition, the ratio of patients with lower education levels of below 5 grades increased from one in ten (before the pandemic started) to one in four people (during the pandemic). There is no comparable study in the

Table 1

| Variables                               | COVID-era, N = 364 | Before COVID, N = 24 | P value, df |
|-----------------------------------------|--------------------|----------------------|-------------|
| Age at onset, years (mean ± SD)         | 24.5 ± 13.1        | 23.9 ± 10.5          | 0.429, 1    |
| Age at diagnosis, years (mean ± SD)     | 29.6 ± 11.3        | 29.1 ± 10.5          | 0.545, 1    |
| Duration of disease, years (mean ± SD)  | 5.1 ± 7.4          | 5.1 ± 7.2            | 0.883, 1    |
| Sex (Female)                            | 18 (75%)           | 240 (66%)            | 0.504, 1    |
| Frequency of seizure per months (mean ± SD) | 106.4 ± 300.7      | 34.4 ± 67.7          | 0.017, 1    |
| Loss of responsiveness with seizures   | 20 (83%)           | 308 (85%)            | 0.775, 1    |
| Incontinence with seizures              | 4 (17%)            | 44 (12%)             | 0.523, 1    |
| Generalized motor seizures              | 16 (67%)           | 315 (87%)            | 0.015, 1    |
| Ictal injury                            | 6 (25%)            | 113 (31%)            | 0.651, 1    |
| A history of family seizure            | 10 (42%)           | 109 (30%)            | 0.255, 1    |
| A history of physical abuse             | 4 (17%)            | 44 (12%)             | 0.515, 1    |
| A history of sexual abuse               | 4 (17%)            | 31 (9%)              | 0.254, 1    |
| A history of family dysfunction         | 7 (29%)            | 124 (34%)            | 0.822, 1    |
| Receiving antiseizure medications       | 15 (63%)           | 231 (64%)            | >0.99, 1    |
| Receiving psychiatric drugs             | 1 (4%)             | 69 (19%)             | 0.096, 1    |
| Low education (below 5 grades)          | 6 (25%)            | 39 (11%)             | 0.051, 1    |

def: degree of freedom. Data were not available in 5 patients for incontinence, in 10 for physical abuse, in 12 for sexual abuse, in 10 for family dysfunction, and in 8 people for education in pre-COVID-19 era.
literate, but below we try to provide some speculative explanations for these intriguing observations.

Frequent attacks are important factors in patients with FS; they are disabling and may disrupt the normal life activities. Seizure frequency was often the primary outcome measure in clinical trials involving patients with FS; psychosocial and functioning measures were often secondary outcomes [10]. Hypothetically, frequent FS may be a marker of higher stress levels or more psychiatric issues. Mental health issues such as stress, anxiety, depression, frustration, and uncertainty have emerged progressively during the COVID-19 outbreak [11,12]. These mental health problems may have caused more frequent attacks in patients with FS. Interestingly, in one recent study of 54 patients with FS, 28% of the participants reported increased frequency of FS during the pandemic [13]. Patients with FS showing symptoms of anxiety and depression were at higher risk of seizure worsening [13].

Similarly, the seizure semiology in FS may have associations with the co-existing neuropsychiatric problems [3–6]. The emerged mental health problems during the COVID-19 pandemic may have affected the semiology of FS, causing more patients to manifest non-motor seizures. We have to emphasize that any reliable semiological classification of FS should be done after ictal recording during video-EEG monitoring of the patient; seizure witnesses often provide unreliable accounts of the seizure semiology [14]. If access to video-EEG monitoring is limited, acquisition of home-video recordings of seizures may be helpful [14,15].

Finally, we observed that more patients had lower education levels during the pandemic compared with that before the pandemic started. Previous studies suggest that learning disability is a risk factor for the development of FS in children and adults [16,17]. People with learning disabilities and those with low educational backgrounds may have limitations in problem-solving and communication skills, or in their ability to verbalizing emotional distress and therefore, have increased risk of developing FS [16].

Speculatively, our observations could also be discussed in the light of high levels of alexithymia among patients with FS [18]. Functional seizures are part of a larger pattern of somatic symptoms responses to a wide range of negative events and emotions, including stress in adulthood (e.g., a pandemic) [19–21]. A study of 156 adult patients with FS showed elevated alexithymia and use of potentially more maladaptive emotion-focused coping strategies among patients with FS and comorbid post-traumatic stress disorder (PTSD) [22]. This line of discussion is worthy of further studies.

5. Limitations

This was a clinic-based series and may not represent the full spectrum of patients with FS; the mildest disease forms may not be referred to a busy university clinic and therefore, the possibility of selection bias exists. Furthermore, in functional neurological disorders, including FS, often some time passes between the onset and the diagnosis; in this study, we observed that for both groups averagely about 5 years had passed between these two time points. While we can talk about the differences of the characteristic of FS at the time of the diagnosis / at the time that patients sought medical attention for their condition, we cannot ascertain any differences at the onset of the disease and, most importantly, in general. In fact, we still do not know whether these characteristics will persist after the pandemic is over.

6. Conclusion

The COVID-19 pandemic has affected the characteristics of patients with FS (at the time of diagnosis). Larger and multi-center studies are needed to investigate the nature and the causes of the links and associations between the COVID-19 pandemic and characteristics of FS (considering the above observations and speculations).

Authors’ contributions

Ali A. Asadi-Pooya, M.D.: study design, data collection, statistical analyses, and manuscript preparation. Mohsen Farazdaghi: data collection and manuscript preparation.

None of the authors listed on the manuscript are employed by a government agency. All are academics. None of the authors are submitting this manuscript as an official representative or on behalf of the government.

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