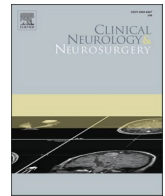




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# New-onset functional seizures during the COVID-19 pandemic

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## ABSTRACT

**Objective:** We investigated whether the COVID-19 pandemic has influenced the characteristics of functional seizures (FS) at the onset of seizures.

**Methods:** This was a retrospective study of all patients with new-onset FS, who were admitted at the epilepsy monitoring unit at Shiraz University of Medical Sciences, Shiraz, Iran, during two time periods: the onset of FS and also the diagnosis of FS in 2017–2019 (pre-COVID era) and the onset of FS and also the diagnosis of FS in 2020–2021 (COVID era).

**Results:** Forty-five patients were studied (32 patients from the pre-COVID era and 13 patients from the COVID era). Patients who developed FS during the pandemic more likely had comorbid epilepsy compared with the patients who presented with FS before the pandemic [30.1% vs. 9.4%; Odds ratio (OR): 81.2]. Furthermore, those who developed FS during the pandemic more likely were employed compared with the patients who presented with FS before the pandemic (46.2% vs. 12.5%; OR: 16.2). A family history of seizures was associated with the FS timing as a trend (OR: 8.4); those who developed FS during the pandemic more likely had a family history of seizures compared with the patients who presented with FS before the pandemic (53.8% vs. 18.8%).

**Conclusion:** This study showed that patients who developed FS during the COVID-19 pandemic had significant underlying differences (i.e., employment status, comorbid epilepsy, and a family history of seizures) compared with those who presented with FS before the pandemic.

## 1. Introduction

Functional seizures (FS) are associated with psychological problems in many patients [1–3]. The neuropsychological pathophysiology of FS is not entirely explained yet and in many patients several interacting factors may play a role; there are often some precipitating factors (e.g., death of family members or close friends, natural disasters) that happen prior to the onset of FS and seem to cause FS to begin [1].

The COVID-19 pandemic has caused more than 5.9 million deaths, huge numbers of job losses, various psychiatric issues, and millions of relationship difficulties in the world; these could be considered as precipitating factors for FS [1,4,5]. Hence, it is plausible to hypothesize that this pandemic has acted as a significant precipitating factor for FS (directly or indirectly).

In three previous studies, it was observed that the COVID-19 pandemic may have associations with some of the characteristics of FS at diagnosis [6–8]. However, in FS, often there is a significant delay

between the onset of functional seizures and the diagnosis of the condition. Therefore, those previous studies could not ascertain any effects of the pandemic at the onset of the disease and could not determine whether the pandemic has acted as a precipitating factor for FS. Here, we investigated whether the COVID-19 pandemic has influenced the characteristics of functional seizures at the onset of seizures.

## 2. Methods

### 2.1. Participants

This was a retrospective study of all patients with new-onset FS (i.e., duration of the illness before the diagnosis at our center: less than 6 months), who were admitted at the epilepsy monitoring unit at Shiraz University of Medical Sciences, Shiraz, Iran. Patients were investigated during two epochs: the onset of FS and also the diagnosis of FS in 2017–2019 (pre-COVID era) and the onset of FS and also the diagnosis of

*Abbreviations:* FS, Functional seizures.

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FS in 2020–2021 (COVID era). Patients had a documented diagnosis of FS (video-EEG monitoring with recording of the typical clinical events). A written informed consent was obtained at the time of the admission.

## 2.2. Data collection

We obtained the data from our database [(i) the demographics: sex, age at functional seizure onset, age at diagnosis, marital, employment, and education statuses; (ii) clinical features of FS: frequency of FS, semiology of FS [i.e., aura, loss of responsiveness, wax and wane semiology, motor seizures, prolonged seizures (>10 min.), and ictal injury]; and (iii) the associated risk factors: a history of sexual abuse, a history of physical abuse, a history of family dysfunction (i.e., divorce, single parent, significant family disputes), a family history of seizures, a history of medical comorbidities, a history of known psychiatric comorbidities (taking psychiatric drugs), and epilepsy comorbidity (based on the clinical history and the results of the video-EEG monitoring). All the data were collected by the senior epileptologist (AAP) in an interview with the patients and their care-givers.

## 2.3. Statistical analyses

Kolmogorov-Smirnov normality test was applied. Values were presented as mean  $\pm$  standard deviation (SD) or median/ interquartile range (IQR) (based on their normality) for continuous variables and as number (percent) of subjects for categorical variables. We first analyzed the factors in association with the COVID-19 pandemic era in univariate analyses: Fisher's exact test, Pearson Chi-square test, and Mann Whitney-U test (or t-test) were used (as appropriate) for the statistical analyses. Variables that had a  $p < 0.2$  in the first step (univariate analyses) were then analyzed in a binary logistic regression analysis model. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated and a  $p$  value (2-sided) less than 0.05 was considered as significant.

## 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.

## 3. Results

Forty-five patients were studied (32 patients from the pre-COVID era and 13 patients from the COVID era). They included 29 (64.4%) women and 16 (35.6%) men (sex ratio: 1.81). **Table 1** summarizes the demographic and the clinical characteristics of the patients and their comparisons in univariate analyses.

Age of the patients, a family history of seizures, employment status, and existence of comorbid epilepsy had  $p$  values  $< 0.2$  (the COVID-19 pandemic era vs. before the pandemic) in univariate analyses. Then, these variables were included in a regression analysis model to clarify the role of each variable in association with the time period of the FS onset (i.e., during or before the COVID-19 pandemic; the dependent variable). The model that was generated by this test was significant ( $p = 0.0001$ ). Comorbid epilepsy had the highest OR (81.2) (**Table 2**); those who developed FS during the pandemic more likely had comorbid epilepsy compared with the patients who presented with FS before the pandemic (30.8% vs. 9.4%). The employment status was also significantly associated with the timing of FS development (OR: 16.2) (**Table 2**); those who developed FS during the pandemic more likely were employed compared with the patients who presented with FS before the pandemic (46.2% vs. 12.5%). A family history of seizures was associated with the FS timing as a trend (OR: 8.4) (**Table 2**); those who

**Table 1**

Variables in association with the COVID-19 pandemic (univariate analyses).

Functional seizure related variables	Before COVID, N = 32	COVID-era, N = 13	P value
Age at onset, years (median, IQR)	23, 14	34, 7	0.018 <sup>u</sup>
Age at diagnosis, years (median, IQR)	23, 14	34, 7	0.017 <sup>u</sup>
Sex (Female)	20 (62.5%)	9 (69.2%)	0.743 <sup>f</sup>
Frequency of seizures per months (mean, SD)	49, 86	32, 43	0.487 <sup>t</sup>
Aura with seizures	23 (71.9%)	10 (76.9%)	0.999 <sup>f</sup>
Loss of responsiveness with seizures	23 (71.9%)	12 (92.3%)	0.238 <sup>f</sup>
Wax and wane semiology	19 (59.4%)	6 (46.2%)	0.515 <sup>f</sup>
Crying during the seizures	8 (25%)	4 (30.8%)	0.721 <sup>f</sup>
Motor seizures	24 (75%)	7 (53.8%)	0.286 <sup>f</sup>
Ictal injury	4 (12.5%)	3 (23.1%)	0.394 <sup>f</sup>
Prolonged seizures (status)	16 (50%)	6 (46.2%)	0.999 <sup>f</sup>
A family history of seizures	6 (18.8%)	7 (53.8%)	0.030 <sup>f</sup>
A history of physical abuse	3 (9.4%)	3 (23.1%)	0.334 <sup>f</sup>
A history of sexual abuse	3 (9.4%)	1 (7.7%)	0.999 <sup>f</sup>
A history of family dysfunction	6 (18.8%)	2 (15.4%)	0.999 <sup>f</sup>
Medical comorbidity	6 (18.8%)	2 (15.4%)	0.999 <sup>f</sup>
Comorbid epilepsy	3 (9.4%)	4 (30.8%)	0.168 <sup>f</sup>
Receiving psychiatry drugs at diagnosis	1 (3.1%)	1 (7.7%)	0.499 <sup>f</sup>
Employment	4 (12.5%)	6 (46.2%)	0.022 <sup>f</sup>
Education:	4 (12.5%)	1 (7.7%)	0.895 <sup>p</sup>
Below 5 grades	19 (59.4%)	8 (61.5%)	(df:2)
High school	9 (28.1%)	4 (30.8%)	
College			
Marital status:	19 (59.4%)	5 (38.5%)	0.323 <sup>f</sup>
Single	13 (40.6%)	8 (61.5%)	
Married	0	0	
Divorced			

Interquartile range (IQR); standard deviation (SD); f: Fisher's Exact test; p: Pearson Chi-square test; u: Mann-Whitney U test; t: t-test; df: degree of freedom.

**Table 2**

Variables in association with the COVID-19 pandemic (regression analysis).

Functional seizure related variables	Odds Ratio	95% confidence interval	P value
Age	0.296	0.004–22.587	0.582
Age at onset	3.909	0.050–304.331	0.540
A family history of seizures	8.393	0.969–72.666	0.053
Employment status (employed)	16.214	1.569–167.548	0.019
Comorbid epilepsy	81.168	2.962–2224.293	0.009

developed FS during the pandemic more likely had a family history of seizures compared with the patients who presented with FS before the pandemic (53.8% vs. 18.8%).

## 4. Discussion

The current study showed that patients who developed FS during the COVID-19 pandemic had significant background differences compared with those who presented with FS before the pandemic. Functional seizures occur in a heterogeneous patient population [1]. In most patients, several interacting variables may be identified as the underlying factors of FS. Predisposing factors (e.g., abuse and neglect) increase vulnerability to the development of FS. Precipitating factors (e.g., pandemic, death of or separation from family members or friends, job loss) may occur over days to months before the onset of the condition and seem to cause FS to start. Finally, perpetuating factors (e.g., isolation, anger, anxiety, depression) make it harder for patients to regain control of their FS or can aggravate the problem once FS have started [1].

The COVID-19 pandemic has had disastrous medical and social consequences for all human beings globally. This deadly outbreak has

disrupted businesses and routine social activities worldwide and has had a significant negative effect on the labor markets around the globe (loss of job or decreased income) [9]. Obviously, this may apply to the people who were employed at the time of this disastrous situation more than that in those who were already unemployed. One study showed that those who lost their job because of the COVID-19 pandemic (compared to others) reported worse mental health issues and depression [9]. Loss of job or income and the economic consequences of this unfortunate experience could be considered as a major stressor for many employed people; consequently, this stressor may act as a precipitating factor for FS. This scenario may indirectly explain our observation that more of the patients with FS during the pandemic were employed compared with the patients who presented with FS before the pandemic; the pandemic has acted as a stressor for the employed people who have lost their job or income. We did not explicitly inquire the economic consequences of the pandemic for the patients and this should be explored in future studies.

Epilepsy may contribute to the risk for developing FS; the experience (comorbid epilepsy) or observation (family history) of epileptic seizures may provide an opportunity for model learning, in some individuals [1]. This may explain our observations that more of the patients with FS during the pandemic had comorbid epilepsy and family history of seizures compared with the patients who presented with FS before the pandemic, at least to some extent. Hypothetically, the pandemic has acted as an acute major stressor and in the setting of model learning (i.e., comorbid epilepsy or family history of seizures), vulnerable people have developed FS; people have spent more time at home due to lockdowns and this has provided an opportunity for them to witness more attacks (seizures) of their cohabitants with epilepsy.

## 5. Limitations

This was a retrospective study from a tertiary center with a limited sample size. Furthermore, we did not inquire whether the participants (or their family members) had COVID-19 and its consequences since the start of the pandemic.

## 6. Conclusion

This study showed that patients who developed FS during the COVID-19 pandemic had significant underlying and background differences (i.e., employment status, comorbid epilepsy, and a family history of seizures) compared with those who presented with FS before the pandemic. These observations may provide an opportunity for research into the associated factors of FS during difficult circumstances.

## Declarations

None.

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## CRediT authorship contribution statement

**Ali A. Asadi-Pooya:** Conceptualization, Methodology, Software, Data curation, Writing – original draft, Visualization, Investigation, Supervision. **Mohsen Farazdaghi:** Methodology, Software, Data curation, Writing – original draft, Visualization, Investigation.

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