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An international study of the effects of the COVID-19 pandemic on characteristics of functional seizures

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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) in a large multicenter international study.
Methods: This was a retrospective study. We investigated all patients with FS, who were admitted at the epilepsy monitoring units at six centers in the world: 1. Shiraz, Iran; 2. Salzburg, Austria; 3. Nancy, France; 4. Atlanta, USA; 5. Kuwait City, Kuwait; and 6. Cairo, Egypt. Patients were studied during two time periods: admitted in 2018–2019 (pre-COVID era) and 2020–2021 (COVID era).
Results: Three hundred and twenty-six patients were studied. Two hundred and twenty-four (68.7%) patients were diagnosed before and 102 (31.3%) persons during the COVID-19 pandemic. Only, a history of family dysfunction was significantly associated with the COVID-19 pandemic era (Odds Ratio: 1.925, 95% Confidence Interval: 1.099–3.371; $p = 0.022$). A low level of education might also be associated with FS during the COVID-19 pandemic, at least in some cultures (e.g., the Middle-East).
Conclusion: The COVID-19 pandemic has not affected the clinical characteristics of patients with FS (at the time of diagnosis). However, a history of family dysfunction was significantly more frequently associated with FS during the COVID-19 pandemic. Multiagency integration of law enforcement responses, social services, and social awareness is recommended to address family dysfunction and domestic violence and support the victims during this pandemic.

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1. Introduction

Functional seizures (FS), also known as dissociative seizures (DS) or psychogenic non-epileptic seizures (PNES), are often associated with psychological problems [1–3]. Previous studies have shown a higher prevalence of psychopathologies in patients with

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FS compared to patients with epilepsy [4]. On the other hand, semiology of FS may be associated with the co-existing neuropsychiatric conditions in these patients. For example, patients with akinetic FS may have fewer co-existing neuropsychiatric problems compared with those who have motor FS [5–7].

While the underlying pathomechanisms of FS are not fully understood yet, some precipitating factors (e.g., relationship difficulties, natural disasters, job loss) may occur over days to months before the onset of FS [1]. Since late 2019, the world has been experiencing a catastrophic and deadly pandemic of severe acute respiratory syndrome coronavirus-2 [Coronavirus disease 2019 (COVID-19)] [8]. This virus is highly contagious and has a high potential for person-to-person transmission. This deadly outbreak has caused more than five million deaths, massive job losses, various psychiatric problems, and increasing numbers of relationship difficulties worldwide (all of which may be considered as potential precipitating factors for FS) [9–12]. Therefore, it is plausible to consider this pandemic as a potentially significant factor that may affect the characteristics of FS. In a previous study, at one of the centers involved in the current study, we observed that patients diagnosed during the COVID-19 pandemic less frequently had generalized motor FS and had higher seizure frequencies. In addition, FS were inversely associated with the education level as a trend during the COVID-19 pandemic [13]. However, this was a single center study with a limited number of patients during the COVID-19 pandemic (24 persons).

In the current study, we investigated whether the COVID-19 pandemic has affected the clinical characteristics of patients with FS in a large multicenter international study. Considering the magnitude of the global impacts of the COVID-19 pandemic and also the prevalence and importance of FS [14], it was important to reproduce the previous study in a larger international multicenter study. Changes in the characteristics of FS have never been studied during other widespread societal traumas/events, to the best of our knowledge. This unique occasion (of COVID-19 pandemic) may have provided an enlightening window for research into the associated factors of FS on a global scale.

2. Methods

2.1. Participants

This was a retrospective study. We investigated all patients with a new diagnosis of FS, who were admitted at the epilepsy monitoring units at six centers in the world: 1. Shiraz, Iran; 2. Salzburg, Austria; 3. Nancy, France; 4. Atlanta, USA; 5. Kuwait City, Kuwait; and 6. Cairo, Egypt. Patients were studied during two time periods: admitted in 2018–2019 (pre-COVID era) and 2020–2021 (COVID era). 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 units from all patients to register their data.

2.2. Data collection

We extracted all the relevant demographic and clinical data from our databases. These included: (i) the demographic characteristics: sex, age at onset, age, duration of illness, marital status, and education level; (ii) the functional seizures characteristics: FS frequency, semiology of FS including aura, loss of responsiveness (LOR), generalized motor seizures, urinary incontinence with FS, prolonged seizures (>10 min), 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 toward the patient), a history of sexual abuse (i.e., rape), a history of family dysfunction (i.e., divorce, significant family disputes, single parent), a history of medical comorbidities (self-declared), 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 an epileptologist in an interview with the patient and their care-givers.

2.3. Statistical analyses

Kolmogorov–Smirnov normality test was performed. Values were presented as mean ± standard deviation (SD) or median/interquartile range (IQR) (based on their normality) for continuous variables and as number (percent) of subjects for categorical variables. Fisher's exact test, Pearson Chi-square test, Mann–Whitney-U test (or t-test), and binary logistic regression analysis model were used (as appropriate) for statistical analyses. Since we have applied a regression analysis on the variables with a $p < 0.2$ in univariate analyses, application of Bonferroni correction test was not necessary. 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 a $p < 0.2$ in univariate analyses were analyzed in a binary logistic regression analysis model.

2.4. Standard protocol approvals, registrations, and patient consents

The Institutional Review Boards of each center approved this study.

2.5. Data availability statement

The data are confidential and will not be shared.

3. Results

Three hundred and twenty-six patients were studied. Patients were recruited from six centers: 90 (27.6%) from Iran, 55 (16.9%) from Egypt, 46 (14.1%) from Austria, 45 (13.8%) from Kuwait, 45 (13.8%) from the USA, and 45 (13.8%) from France. They included 222 (68.1%) women and 104 (31.9%) men (sex ratio: 2.13). Two hundred and twenty-four (68.7%) patients were diagnosed before and 102 (31.3%) persons during the COVID-19 pandemic.

Table 1 summarizes the clinical characteristics of the patients diagnosed with FS during and before the COVID-19 pandemic in univariate analysis. A history of family dysfunction (i.e., divorce, significant family disputes, etc.) were significantly more frequent among patients diagnosed during the COVID-19 pandemic (42.2%) compared with those who were diagnosed before the pandemic (31.7%) ($p = 0.036$). Then, the variables with a $p < 0.2$ in univariate analyses [i.e., duration of illness, a history of family dysfunction, a family history of seizures, receiving psychiatry drugs at diagnosis, and the level of education (below 5 grades *vs.* above); covariates] were included in a regression analysis model to clarify the role of each variable in association with the time period of FS diagnosis (i.e., during or before the COVID-19 pandemic; the dependent variable). The model that was generated by this test was significant ($p = 0.028$). Only, a history of family dysfunction was significantly associated with the COVID-19 pandemic era (OR: 1.955, 95% CI: 1.119–3.418; $p = 0.019$) (Table 2).

In a subanalysis, we categorized the nations into the Western countries (i.e., Austria, France, USA; $N = 136$) and the Middle-Eastern nations (i.e., Iran, Egypt, Kuwait; $N = 190$). We performed

Table 1
Variables in association with the COVID-19 pandemic in univariate analyses.

Functional seizure-related variables	Before COVID, *N* = 224	COVID-era, *N* = 102	*P* value
Age at onset, years (median, IQR)	22, 15	24, 17	0.718
Age at diagnosis, years (median, IQR)	28, 21	29, 17.5	0.619
Duration of disease, years (median, IQR)	2, 6	1, 4	0.080
Sex (Female)	158 (70.5%)	64 (62.7%)	0.200
Frequency of seizure per months (median, IQR)	4, 13	5, 28	0.298
Aura with seizures	131 (58.5%)	64 (62.7%)	0.543
Loss of responsiveness with seizures	153 (68.3%)	65 (63.7%)	0.374
Urinary incontinence with seizures	24 (10.7%)	11 (10.8%)	>0.999
Generalized motor seizures	174 (77.7%)	77 (75.5%)	0.885
Ictal injury	42 (18.7%)	14 (13.7%)	0.342
Prolonged seizures (status)	55 (24.5%)	19 (18.6%)	0.255
A family history of seizures	44 (19.6%)	30 (29.4%)	0.118
A history of physical abuse	44 (19.6%)	25 (24.5%)	0.773
A history of sexual abuse	28 (12.5%)	17 (16.7%)	0.493
A history of family dysfunction	71 (31.7%)	43 (42.2%)	**0.036**
Emotional trigger for seizures	139 (62.0%)	71 (69.6%)	0.209
Medical comorbidity	60 (26.9%)	23 (22.5%)	0.493
Comorbid epilepsy	60 (26.9%)	23 (22.5%)	0.493
Receiving antiseizure medications at diagnosis	148 (66.1%)	60 (58.8%)	0.216
Receiving psychiatry drugs at diagnosis	47 (21.0%)	29 (28.4%)	0.158
Education:			0.135
Below 5 grades	22 (9.8%)	19 (18.6%)	
High school	116 (51.8%)	51 (50.0%)	
College	50 (22.3%)	30 (29.4%)	
Marital status:			0.594
Single	110 (49.1%)	51 (50.0%)	
Married	85 (37.9%)	46 (45.1%)	
Divorced	18 (8.0%)	5 (4.9%)	

Significant *p* values are in bold. Interquartile range (IQR). Some data were missing.

Table 3
Variables in association with the COVID-19 pandemic in the Middle-East.

Functional seizure-related variables	Before COVID, *N* = 134	COVID-era, *N* = 56	*P* value
Age at onset, years (median, IQR)	22, 14	23, 17	0.507
Age at diagnosis, years (median, IQR)	27, 15	27.5, 17.5	0.222
Duration of disease, years (median, IQR)	2, 5	1.5, 4.5	0.306
Sex (Female)	91 (67.9%)	36 (64.3%)	0.736
Frequency of seizure per months (median, IQR)	4, 10	4.5, 28	0.298
Aura with seizures	76 (56.7%)	36 (64.3%)	0.419
Loss of responsiveness with seizures	98 (73.1%)	38 (67.9%)	0.484
Urinary incontinence with seizures	14 (10.4%)	5 (8.9%)	>0.999
Generalized motor seizures	110 (82.1%)	42 (75.0%)	0.535
Ictal injury	25 (18.7%)	7 (12.5%)	0.397
Prolonged seizures (status)	49 (36.6%)	17 (30.4%)	0.504
A family history of seizures	19 (14.2%)	14 (25.0%)	0.213
A history of physical abuse	10 (7.5%)	8 (14.3%)	0.431
A history of sexual abuse	12 (8.9%)	4 (7.1%)	0.779
A history of family dysfunction	29 (21.6%)	21 (37.5%)	0.072
Emotional trigger for seizures	82 (61.2%)	40 (71.4%)	0.180
Medical comorbidity	24 (17.9%)	9 (16.1%)	0.836
Comorbid epilepsy	37 (27.6%)	13 (23.2%)	0.592
Receiving antiseizure medications at diagnosis	87 (64.9%)	31 (55.4%)	0.252
Receiving psychiatry drugs at diagnosis	11 (8.2%)	7 (12.5%)	0.416
Education:			**0.001**
Below 5 grades	4 (2.9%)	10 (17.9%)	
High school	82 (61.2%)	29 (51.8%)	
College	18 (13.4%)	16 (28.6%)	
Marital status:			0.786
Single	62 (46.3%)	27 (48.2%)	
Married	59 (44.0%)	29 (51.8%)	
Divorced	2 (1.5%)	0 (0)	

Significant *p* values are in bold. Interquartile range (IQR). Some data were missing.

Table 2
Variables in association with the COVID-19 pandemic in regression analysis.

Functional seizure-related variables	Odds Ratio	95% confidence interval	*P* value
A history of family dysfunction	1.955	1.119–3.418	**0.019**
A family history of seizures	1.355	0.730–2.515	0.336
Duration of illness	0.967	0.930–1.006	0.092
Receiving psychiatry drugs at diagnosis	0.655	0.326–1.318	0.236
Level of education (below 5 grades *vs.* above)	0.680	0.327–1.414	0.302

Significant *p* values are in bold.

Table 4
Variables in association with the COVID-19 pandemic in the Middle-East.

Functional seizure-related variables	Odds Ratio	95% confidence interval	*P* value
Level of education (below 5 grades *vs.* above)	5.557	1.571–19.660	**0.008**
A history of family dysfunction	1.786	0.859–3.712	0.120
Emotional trigger for seizures	1.388	0.643–2.993	0.403

Significant *p* values are in bold.

a series of univariate tests, separately, and then applied the regression analysis on the variables with $p < 0.2$. Among the Middle-Eastern patients (Table 3), only a low education was associated with the COVID-19 pandemic era. The regression analysis model that included variables with $p < 0.2$ from the univariate analysis (i.e., a history of family dysfunction, emotional trigger for seizures, and education) was significant ($p = 0.015$). Only, a low education (below 5 grades *vs.* above) was associated with the COVID-19 pandemic era (OR: 5.557, 95% CI: 1.571–19.660; $p = 0.008$) (Table 4). Among the Western patients (Table 5), none of the variables was significantly associated with the COVID-19 pandemic era (many had small values for a reliable statistical analysis).

4. Discussion

In the current study, we observed that a history of family dysfunction was significantly more frequently associated with FS during the COVID-19 pandemic. Otherwise, the clinical and semiological characteristics of patients with FS were similar between patients who were diagnosed before the pandemic compared with those who received the diagnosis during the pandemic. Therefore, we can conclude that while this deadly outbreak has caused significant stress for everyone [9–12], it has not affected the characteristics of FS significantly.

While it was not clear whether family dysfunction circumstances happened during the COVID-19 outbreak or before the pandemic in the current study, the observation that the report of family dysfunction (i.e., divorce, significant family disputes, etc.) was significantly more frequently associated with FS during the COVID-19 pandemic may have important implications. A recent systematic review concluded that domestic violence has been a considerable worldwide issue imposed by the COVID-19 epidemic. The home confinements have led to constant contact between perpetrators and victims, resulting in increased violence and decreased reports [15]. The intimate partner violence could be in various forms: physical, sexual, and psychological [16]. Due to

Table 5
Variables in association with the COVID-19 pandemic in the West.

Functional seizure-related variables	Before COVID, *N* = 90	COVID-era, *N* = 46	*P* value
Age at onset, years (median, IQR)	21, 20	27, 16	0.701
Age at diagnosis, years (median, IQR)	34, 24	31, 19.5	0.632
Duration of disease, years (median, IQR)	3, 9	1, 3.5	0.364
Sex (Female)	67 (74.4%)	28 (60.9%)	0.177
Frequency of seizure per months (median, IQR)	5, 27	5, 28	0.561
Aura with seizures	55 (61.1%)	28 (60.9%)	>0.999
Loss of responsiveness with seizures	55 (61.1%)	27 (58.7%)	0.711
Urinary incontinence with seizures	10 (11.1%)	6 (13.0%)	0.783
Generalized motor seizures	64 (71.1%)	35 (76.1%)	0.684
Ictal injury	17 (18.9%)	7 (15.2%)	0.644
Prolonged seizures (status)	6 (6.7%)	2 (4.3%)	0.712
A family history of seizures	25 (27.8%)	16 (34.8%)	0.429
A history of physical abuse	34 (37.8%)	17 (36.9%)	>0.999
A history of sexual abuse	16 (17.8%)	13 (28.3%)	0.195
A history of family dysfunction	42 (46.7%)	22 (47.8%)	0.149
Emotional trigger for seizures	57 (63.3%)	31 (67.4%)	0.849
Medical comorbidity	36 (40.0%)	14 (30.4%)	0.348
Comorbid epilepsy	23 (25.6%)	10 (21.7%)	0.678
Receiving antiseizure medications at diagnosis	61 (67.8%)	29 (63.0%)	0.702
Receiving psychiatry drugs at diagnosis	36 (40.0%)	22 (47.8%)	0.464
Education:			0.635
Below 5 grades	18 (20.0%)	9 (19.6%)	
High school	34 (37.8%)	22 (47.8%)	
College	32 (35.6%)	14 (30.4%)	
Marital status:			0.455
Single	48 (53.3%)	24 (52.2%)	
Married	26 (28.9%)	17 (36.9%)	
Divorced	16 (17.8%)	5 (10.9%)	

Interquartile range (IQR). Some data were missing.

the social distancing measures and the mobility restrictions, a lack of support from family, friends, and coworkers, may contribute to the increased rates of family dysfunction and violence during the pandemic [17]. Therefore, social services (e.g., social work practitioners, therapists, etc.) for cases of family dysfunction and domestic violence must be resourced during the pandemic [17]. Multiagency integration of law enforcement responses (e.g., protection orders, arrest), social services (e.g., hotlines, shelters), and social awareness are recommended to address relationship problems and domestic violence, and support victims [18]. Having said that, we cannot ascertain a cause-and-effect relationship between the COVID-19 pandemic, family dysfunction, and FS in the current study. The nature of the link between the COVID-19 pandemic, family dysfunction, and FS deserves further studies and explorations.

A low level of education might also be associated with FS during the COVID-19 pandemic, at least in some cultures (e.g., the Middle-East in the current study). Previous studies suggest that learning problems are a risk factor for the development of FS in children and adults [19,20]. Generally speaking, individuals with low educational backgrounds may have limitations in problem-solving and communication skills, or in their ability to verbalize emotional distress and hence, may be at increased risk of developing FS in response to a significant stress, such as the COVID-19 pandemic [21]. Why might a low level of education be a factor in some cultures, but not others, should be clarified in future studies.

In a survey of 54 patients with FS, 15 people (28%) reported increased frequency of FS during the pandemic in Brazil [22]. In contrast, in a survey of 18 people with FS, 22.2% reported an improvement in seizure control during the peak of the COVID-19 pandemic in New York City [23]. The nature of these studies (survey) and the risk of recall bias associated with their methodology may explain their contradictory results. Importantly, patients with functional neurological disorders (FND) may show higher levels of anxiety, symptoms related to post-traumatic stress disorder (PTSD), and perceived stress compared with healthy controls during the COVID-19 pandemic [24]. Video-telemedicine is a feasible and effective way to provide care for patients with FS during such difficult times as this pandemic [25].

5. Limitations

This study may not represent the full spectrum of patients with FS; the mildest disease forms may not be referred to busy university clinics and therefore, the possibility of selection bias exists. Furthermore, in patients with FS, often some time passes between the onset and the diagnosis. While we can explore and discuss the differences of the characteristic of FS at the time of the diagnosis in the current study, we cannot ascertain any differences at the onset of the disease.

6. Conclusion

The COVID-19 pandemic has not affected the clinical characteristics of patients with FS (at the time of diagnosis). However, a history of family dysfunction was significantly more frequently associated with FS during the COVID-19 pandemic. Multiagency integration of law enforcement responses, social services, and social awareness is recommended to address family dysfunction and domestic violence and support the victims during this pandemic. A low level of education might also be associated with FS during the COVID-19 pandemic, at least in some cultures (e.g., the Middle-East).

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Authors' contributions

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

Others: data collection and manuscript preparation.

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