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The COVID-19 outbreak and PNES: The impact of a ubiquitously felt stressor

Kette D. Valente [a,*], Rudá Alessi [a], Gislaine Baroni [b], Rachel Marin [a], Bernardo dos Santos [a], André Palmini [b,c]

[a] Department of Psychiatry, Hospital das Clinicas, Faculdade de Medicina da Universidade de São Paulo (HCFMUSP), SP, Brazil
[b] Department of Clinical Neuroscience, School of Medicine, Pontificia University of Rio Grande do Sul (PUCRS), Porto Alegre, Brazil
[c] Service of Neurology, Hospital São Lucas, Pontificia University of Rio Grande do Sul (PUCRS), Porto Alegre, Brazil

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ABSTRACT

Objective: We aimed to assess frequency of functional seizures or psychogenic nonepileptic seizures (PNES) during the COVID-19 outbreak and to recognize possible factors associated with worsening in this population.
Methods: In this cross-sectional study conducted during the second phase of the pandemic, adult patients with PNES documented by video-EEG and followed up in two tertiary epilepsy centers responded to a structured telephone survey. Data were gathered on demographics, clinical features and frequency of PNES, history of psychiatric comorbidity, access to treatment, as well as on anxiety (GAD-7 items) and depressive symptoms (NDDI-E).
Results: Fifty-four patients (78% female; mean age of 31.36 years [SD = 10.6]) were contacted and 15 (28%) reported increased frequency of PNES during the pandemic. Higher scores of GAD-7 items ($p < 0.001$) and NDDI-E ($p < 0.001$) were associated with PNES worsening. There was strong evidence of a correlation between higher stress levels ($p < 0.001$) and poor sleep quality (p 0.005) with PNES aggravation. After regression, stress was the strongest predictor of PNES increased frequency.
Significance: Patients with functional neurological disorders are vulnerable during ubiquitously felt stressors. However, the atmosphere of uncertainty did not affect these patients equally. Patients with PNES showing symptoms of anxiety and depression are at higher risk of seizure worsening. Early identification of this subset of patients may prevent this detrimental outcome.

1. Introduction

Psychogenic nonepileptic seizures (PNES) or functional seizures are paroxysmal alterations in motor, sensory, autonomic, or cognitive functions not associated with ictal epileptiform activity of psychological etiology [1]. It is the most common subtype of functional neurological disorder (FND; conversion disorder), under the somatic symptom category and related disorders in DSM-5 [2]. It is known that functional disorders are frequently elicited by stressors, although the current diagnosis criteria (APA) do not require elicitable triggers [2].

There is strong evidence that universally felt stressors, such as acts of terrorism and natural disasters, can increase functional neurological symptoms and disorders in adults [3,4] and children [5] although the overall health effect is not restricted to those directly affected [6]. Extensive media coverage, imposed lockdown, and the sudden disruption of daily life activities are apparently equally detrimental [4–7].

The COVID-19 pandemic is an unprecedented stressful global event leading to an atmosphere of uncertainty. There is sparse information on the modes of transmission and the role of asymptomatic carriers in spreading SARS-CoV-2. The absence of a vaccine and specific treatment poses significant challenges for healthcare providers and the overall population. Consequently, emerging studies demonstrated the impact of the pandemic and the strict lockdown on mental health, especially to individuals with pre-existing psychiatric conditions [8–10].

Patients with functional disorders have higher comorbidity rates with other psychiatric disorders and are at higher risk of somatic complaints and worsening of their symptoms under stressful circumstances [11]. For instance, Lutgendorf et al. [12] showed that patients with "chronic fatigue syndrome" exposed

* Corresponding author at: Rua Dr. Ovidio Pires de Campos, 785, CEP 05403-903 São Paulo, SP Brazil.
E-mail address: kette.valente@hc.fm.usp.br (K.D. Valente).

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to hurricane Andrew were more likely to relapse and reported more symptoms and burden of illness corroborating the notion that this is a vulnerable population to environmental stressors.

There is a dearth of knowledge about the impact of COVID-19 in patients with PNES and thus we aimed to assess the possibility of increased frequency of PNES during the pandemic and possible factors associated with worsening in a sample of patients with documented diagnosis followed up in two tertiary care centers in Brazil.

2. Methods

This was a longitudinal study conducted from April 30th to June 30th, 2020. Patients with a previous documented PNES (by video-EEG) were followed up during the pandemic considering the period comprehended by the COVID-19 outbreak's restriction, and were invited to respond about their status considering the time period starting in mid-March, 2020, and extended to the time of telephone contact.

The Local Ethics committees approved this survey-based study, and participants gave informed consent. Before application, patients were informed about the nature of the questionnaire and the time necessary to respond.

2.1. Participants

All 69 patients with PNES from the databases of the HCFMUSP and the Service of Neurology at PUCRS who had PNES documented by video-EEG, 18 years of age or older, and at least five years of education, were contacted. We were able to contact 56 [81.2%] patients with PNES. Fifty-five [79.7%] patients agreed to respond to the questionnaire, but one [1.4%] was unable to inform or recall their seizure frequency before and during the pandemic, and therefore was excluded. Patients with coexistent epilepsy were not excluded. Hence, 54 patients comprised the final sample of the study.

2.2. Survey-based information

Participants who consented were interviewed by phone through a structured and pre-defined questionnaire designed for the current study. The elements that composed this survey are detailed below.

2.2.1. PNES worsening

We collected data on PNES frequency qualitatively, both before and during the pandemic (daily, weekly, monthly, one every 3 months, seizure-free in the past six months). Definition of worsening, improvement, or unchanged frequency of PNES was based upon change of frequency level.

2.2.2. Demographics, clinical data, felt (perceived) stress, and access to health care

This questionnaire gathered data about age, sex, education level, employment status (employed, unemployed, retired), occupation (job description, student, housewife, non-occupied with labor or educational activities), marital status (single, living with partner, divorced), financial circumstances (self-supported or provided by others), and number of family members currently living together.

In addition, we probed exposure to COVID-outbreak news (exposure to news/social media; search for reliable sources; no exposure by choice) and level of social isolation (total isolation, partial isolation, no isolation).

As perception of lack of treatment could be considered a source of stress, we collected information about access to healthcare (therapy for PNES and other forms of therapy for co-existing medical disorders) during the pandemic.

Additional data on medical history were investigated regarding the previous diagnosis of psychiatric disorder (e.g., anxiety disorder, depression, personality disorder) and active epilepsy.

Felt or perceived stress and sleep quality, after lockdown, was categorized into worsened, neutral (unaltered), or improved. Descriptive responses were not considered for the analysis.

2.2.3. Quantitative measures of depressive and anxiety symptoms

2.2.3.1. Depressive symptoms. The Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) screens adults for depressive symptoms, excluding symptoms that may overlap with epilepsy and AED side effects [13] and is validated for the Brazilian population [14]. Scores above 15 are considered positive for depression, with specificity of 90%, sensitivity of 81%, and positive predictive value of 0.62 for a diagnosis of major depression based on the mini international neuropsychiatric interview [15].

2.2.3.2. Symptoms of generalized anxiety disorder (GAD). The GAD-7 is a self-reported, seven-item scale that assesses general anxiety symptoms according to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) which also has a Portuguese version [16–18]. Participants are asked to rate their anxiety-related problems during the two weeks prior to administration of the questionnaire on a 4-point scale (0 = not at all, to 3 = nearly every day). Total scores range from 0 to 21 and higher scores are associated with generalized anxiety. For this study, we considered the following scores: none/normal (0–5 points), mild (5–9 points), moderate (10–14 points), and severe anxiety (15–21 points).

2.3. Statistical analysis

Statistical analysis was performed on R statistical package version 4.0.2.

Categorical variables were reported as absolute and relative frequencies, and numerical variables as mean and standard deviation. We categorized patients into two groups according to their seizure frequency (worsening and improvement/unchanged). They were compared on the interest factors using *t*-tests (Student and Welch versions) and Wilcoxon–Mann–Whitney tests for the numerical variables and chi-square and Fisher's exact test for categorical variables.

A multiple binary logistic regression was fit to predict the patients' perception based on the observed variables. Feature selection for the final model was conducted with the LASSO (least absolute shrinkage and selection operator) algorithm in a 10-fold cross-validation procedure observing the 1 standard error rule. This method aimed to select the explanatory variables that best predict the out-of-sample outcome and, therefore, better generalize the population's solution [19].

3. Results

3.1. Patients demographics and clinical data

Our sample was composed of 77.8% female with a mean age of 31.4 years [median 28 years; SD = 10.6]. The mean duration of PNES was 92.1 months (median 60 months, SD = 101.5). Most patients had high school (40.7%) or college (29.6%) education. Twenty-seven patients (50%) were employed, and 37 (69.8%) had a daily occupation. Twenty-three patients (42.6%) had a stable relationship, and only seven (13%) were considered as family financial providers. Only 16 patients (29.6%) reported total lockdown while

others reported still going out for basic needs (e.g., drugstore) or working.

Fifty patients (92.6%) had a previous diagnosis of psychiatric disorder and 23 (42.6%) had a coexisting diagnosis of active epilepsy. Out of these patients, 20 (66.7%) reported a worsening of the psychiatric disorders during the pandemic.

3.2. PNES worsening and risk factors

Fifteen patients (27.8%) reported worsening of their PNES during the pandemic. The remaining informed that their seizures were unaltered (35 patients [64.8%]) or had an improvement (four patients [7.4%]).

There was strong evidence of a correlation between higher stress levels and low sleep quality with PNES aggravation (Table 1) Higher scores of GAD-7 items ($p < 0.001$) and NDDI-E ($p < 0.001$) also showed association with PNES worsening (Table 2). After regression, stress was the strongest predictor of PNES aggravation.

4. Discussion

This study provided two main findings. First, in a series of patients with PNES, almost 30% had an aggravation of the seizure frequency. Second, higher levels of stress, anxiety, depressive symptoms, and poor sleep quality were a frequent complaint in this group that presented worsening of seizure frequency.

One-third of patients with PNES had seizure worsening during the first two phases of the pandemic. One may pose the question that for patients, the frequency of events remained unaltered or improved. It is well known that for some patients with specific psychiatric disorders (e.g., social anxiety), the social isolation leads to reduced stress levels [21]. Therefore, it is reasonable to postulate that for some patients with PNES, the restrictions imposed by the lockdown may decrease the burden of normality determined by working, academic life, and social interaction [22]. However, we consider that an approximated 30% rate of worsening in a severe and disabling disease that requests treatment during the pandemic

Table 1
Demographics and characteristics of patients with PNES.

Variable	Level	Improvement/ Unchanged		Aggravation		p
		N	%	N	%	
Sex	Female	28	66.67	14	33.33	0.091[a]
	Male	11	91.67	1	8.33	
Education	Infant School	2	66.67	1	33.33	0.328[b]
	Junior School	10	76.92	3	23.08	
	High School	18	81.82	4	18.18	
	College	9	56.25	7	43.75	
Employment	No	21	77.78	6	22.22	0.367[a]
	Yes	18	66.67	9	33.33	
Daily Activities[#]	No	12	75.00	4	25.00	0.728[a]
	Yes	26	70.27	11	29.73	
Marital Relationship	No	22	70.97	9	29.03	0.813[a]
	Yes	17	73.91	6	26.09	
Family Situation	Provider	3	42.86	4	57.14	0.065[a]
	Provided	36	76.60	11	23.40	
Epilepsy	No	22	70.97	9	29.03	0.813[a]
	Yes	17	73.91	6	26.09	
PNES Frequency (Before Pandemic)	No seizures	6	66.67	3	33.33	0.252[b]
	Quarterly	8	100.00	0	0.00	
	Monthly	10	62.50	6	37.50	
	Weekly/Daily	14	73.68	5	26.32	
Laboral Situation	Retired	17	77.27	5	22.73	0.529[a]
	Working	13	68.42	6	31.58	
Social Isolation	Partial	27	71.05	11	28.95	0.770[a]
	Total	12	75.00	4	25.00	
News Exposition	No exposition	16	80.00	4	20.00	0.589[a]
	Selected	20	66.67	10	33.33	
	Intense	3	75.00	1	25.00	
Access to treatment	No	28	80.00	7	20.00	0.086[a]
	Yes	11	57.89	8	42.11	
Psychiatric Disorders	None	4	100.00	0	0.00	0.380[b]
	Anxiety Disorder	12	80.00	3	20.00	
	Mood Disorders	10	58.82	7	41.18	
	Others	13	72.22	5	27.78	
Sleep worsening	No	27	87.10	4	12.90	**0.005**[a]
	Yes	12	52.17	11	47.83	
Felt (Perceived) Stress	No	37	100.00	0	0.00	**<0.001**[b]
	Yes	2	11.76	15	88.24	

PD: Psychiatric Disorders.
[#] Daily activities included work, school, and chores.
[a] Pearson's Chi-squared test.
[b] Fisher's Exact Test.

Table 2
Age, duration, depressive and anxiety symptoms.

Variable	PNES Frequency during the Pandemic	Mean	SD	Median	*P*
Age	Improvement/Unaltered	30.84	10.77	27	0.540[a]
	Aggravation	32.67	10.38	32	
GAD.7	Improvement/Unaltered	9.66	4.35	9	**<0.001**[b]
	Aggravation	14.93	3.67	15	
NDDI-E	Improvement/Unaltered	13.37	4.59	13,5	**<0.001**[c]
	Aggravation	19.07	2.34	20	

[a] Wilcoxon–Mann–Whitney test.
[b] Student's *t*-test.
[c] Welch's *t*-test.

is a matter of concern since it demands care from an overloaded healthcare system.

To identify individuals prone to present this worsening, we evaluated possible factors associated with it. We observed that patients with PNES that showed frequency aggravation had higher scores of anxiety and depression. It is well known that psychiatric comorbidity is quite common in patients with PNES [23,24]. The most frequently co-occurring disorders are PTSD, anxiety disorder, personality disorder, and depression [25]. As previously stated by others, patients with PNES and comorbid psychiatric disorders have more severe dysfunction and higher levels of stress [23].

North et al. [26], assessing the rates of functional impairment after the Oklahoma bombing, detected high psychopathology rates. The predictors were female-sex, secondary exposure (injury or death of loved ones), and premorbid psychopathological condition. Pre-existing mental health symptomatology, namely anxiety, is a risk factor for adverse outcomes of natural and human-made disasters [27]. Therefore, based on previous knowledge on PNES and other functional disorders, it is not surprising that patients with higher levels of anxiety and depression, consequently stress, represent a more vulnerable group to a severe stress factor. It would be expected that the patients with PNES and a co-existing psychiatric disorder would be more affected than others; however, psychiatric comorbidity is quite frequent and equally represented in all groups.

In a recent paper, Nisticò et al. [20] assessed the prevalence of stress, anxiety, depression, and symptoms related to post-traumatic stress disorder (PTSD) in a sample of 18 patients with functional neurological disorders (eight with PNES and 10 with functional motor disorders). Interestingly, the authors found that patients with PNES tended to behave similarly to controls rather than those with functional motor disorders. However, the authors regard their findings as preliminary due to their limited sample. Indeed, the analysis of eight patients with PNES may render false results.

In agreement with our findings, Guerriero et al. [5] showed that children's functional symptoms had a temporal relationship with the city-wide lockdown and excessive media coverage, after the Boston Marathon bombings. These factors probably caused a shared intense stressor that affected the whole community. According to Hasset et al. [28], this distress stems from living with a heightened state of alertness and harboring a fear of the unknown, given that there is an unpredictable threat that could strike indiscriminately. The fear of the unknown may lead to a high level of stress associated with somatic symptoms, especially in vulnerable patients.

This study had several limitations related to the lack of controls and its cross-sectional design that must be acknowledged. Healthy controls and patients with epilepsy were not considered for comparison since it was not the study's objective. This study analyzed the impact of acute stress in a group of patients with PNES. The long-term effect of these high levels of stress with a longitudinal study remains to be determined.

In conclusion, our study corroborates the concept that patients with functional neurological disorders, namely those with PNES, are a vulnerable group of people during these ubiquitously felt stressors. It is of note that the fear of uncertainty determined by these events does not affect these patients equally. During the pandemic, it is relevant to detect patients that are at higher risk of worsening of this disabling condition that may demand care from an overloaded healthcare system.

5. Ethical publication

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.'

6. Disclosure

None of the authors has any conflict of interest to disclose.

Authors contribution

Substantial contributions to the conception or design of the work: KDV.

Acquisition of data: GB, RA, RM.

Analysis, or interpretation of data for the work: KDV, BS.

Drafting the work or revising it critically for important intellectual content: KDV, BM, RA, AP.

Final approval of the version to be published: All authors.

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: All authors.

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.

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