Epilepsy & Behavior 97 (2019) 154–157

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Sex differences in demographic and clinical characteristics of psychogenic nonepileptic seizures: A retrospective multicenter international study

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ARTICLE INFO

Article history:
Received 9 May 2019
Revised 30 May 2019
Accepted 31 May 2019
Available online 25 June 2019

Keywords:
International
PNES
Psychogenic
Seizure
Sex

ABSTRACT

Purpose: Sex-related differences have been reported in patients with neurological and psychiatric disorders. It is also plausible to assume that there might be differences between females and males with psychogenic nonepileptic seizures (PNES).
Methods: In this retrospective study, we investigated patients with PNES, who were admitted to the epilepsy monitoring units at centers in Iran, the USA, Canada, Brazil, Argentina, and Venezuela. Age, sex, age at seizure onset, seizure semiology, factors potentially predisposing to PNES, and video-electroencephalography recording of all patients were registered routinely.
Results: Four hundred and fifty-one patients had PNES-only and were eligible for inclusion; 305 patients (67.6%) were females. We executed a logistic regression analysis, evaluating significant variables in univariate analyses (i.e., age, age at onset, aura, presence of historical sexual or physical abuse, and family dysfunction). The only variables retaining significance were historical sexual abuse ($p = 0.005$) and presence of aura ($p = 0.01$); physical abuse was borderline significant ($p = 0.05$) (all three were more prevalent among females).
Conclusion: Similarities between females and males outweigh the differences with regard to the demographic and clinical characteristics of PNES. However, notable differences are that females more often report lifetime adverse experiences (sexual and probably physical abuse) and auras. While social, psychological, and genetic factors may interact with lifetime adverse experiences in the inception of PNES, the link is not yet clear. This is an interesting avenue for future studies.

1. Introduction

It has been well documented that there is a predominance of female sex among patients with psychogenic nonepileptic seizures (PNES). Studies from all continents generally note PNES to be far more common in females, with a ratio of female to male of about 3:1 [1]. Reasons for this preponderance of females are not entirely clear [2]. Intrinsic brain connectivity differences between males and females may be one reason for higher rates of PNES in females [2]. In addition, some early life experiences that are associated with PNES (e.g., sexual abuse) are more

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https://doi.org/10.1016/j.yebeh.2019.05.045
1525-5050/

prevalent among females than in males [3,4]. These lifetime experiences may affect and alter brain connectivity in females differently compared with that in males [2]. Lastly, sex-related differences in those with PNES have also been reported with regard to psychiatric diagnoses and psychological symptomatology [3]. These neurobiological, social, and psychological differences may explain why PNES are predominantly seen in females [2]. Therefore, it is also plausible to assume that there might be clinical differences (e.g., seizure semiology, risk factors, etc.) between females and males, who are suffering from PNES.

In the current study, we investigated potential differences in demographic and clinical characteristics of PNES between females and males in large multicenter international samples in order to evaluate the above hypothesis.

2. Material and methods

In this retrospective study, we investigated consecutive patients with PNES, who were admitted to the epilepsy monitoring units at centers in Iran (Shiraz Comprehensive Epilepsy Center, from 2008 to 2019), the USA (Northeast Regional Epilepsy Group, from 2013 to 2018), Canada (Comprehensive Children's Epilepsy Center at Alberta Children's Hospital, from 2008 to 2019), Brazil (Clinics Hospital, Faculty of Medicine of the University of São Paulo, from 2006 to 2016), Argentina (Buenos Aires University, Epilepsy Center, Ramos Mejía and EL Cruce Hospitals, from 2014 to 2018), and Venezuela (Epilepsy Unit, La Trinidad Medical Center, from 2014 to 2018). Epileptologists experienced in making the diagnosis of seizures confirmed the diagnosis of PNES when the typical seizures were captured on video-electroencephalography (video-EEG) monitoring and no epileptiform activity before, during, or after the seizure was captured. Exclusion criteria included comorbid epilepsy (according to their clinical history and EEG findings) or incomplete clinical data.

At the time of diagnosis, patients were evaluated either by epileptologists alone or together with psychologists/psychiatrists. All data regarding the patients' identity were kept confidential. Age, sex, age at seizure onset, seizure semiology, factors potentially predisposing to PNES [history of physical abuse (i.e., corporal punishment or any physical injury resulted from aggressive behavior towards the patient), sexual abuse, family dysfunction (i.e., divorce, single parent, significant family disputes, etc.), and family history of seizures], and video-EEG recording of all patients were registered routinely.

Demographic and relevant clinical variables were summarized descriptively to characterize the study populations. First, we performed univariate analyses using Pearson Chi-square, Mann–Whitney, Kolmogorov–Smirnov, and t-test, as appropriate. Then, variables that were significant ($p < 0.05$) were assessed in a logistic regression analysis. Odds ratio (OR) and 95% confidence interval (CI) were calculated. p values less than 0.05 were considered significant. This study was conducted with the approval of Institutional Review Boards at all centers.

3. Results

The whole database included 629 patients. Four hundred and fifty-one patients had PNES-only and were eligible for inclusion [263 patients from Iran (167 females and 96 males), 86 from Brazil (62 females and 24 males), 43 from Venezuela (35 females and 8 males), 21 from Canada (14 females and 7 males), 19 from the USA (14 females and 5 males), and 19 patients from Argentina (13 females and 6 males)]. The sex ratios were not different between the nations ($p = 0.2$). Three hundred and five patients (67.6%) were females, and 146 individuals were males (32.4%); the sex ratio was 2.09. The mean age (± standard deviation) of the patients was 27 (± 11) years, and their age at onset of seizures was 22 (±10) years.

Table 1 shows the demographic characteristics of the patients in relation to their sex. The current age and the age at onset of PNES were both lower in males compared with those in females in univariate analyses. Table 2 shows the clinical characteristics of the seizures in relation to the sex of patients. The only variable that was significantly different between females and males in univariate analyses was the presence of preictal aura. Table 3 shows the factors potentially associated with PNES in relation to the sex of patients. Reported history of sexual abuse, physical abuse, and family dysfunction were significantly different in females compared with those in males in univariate analyses.

We then executed a logistic regression analysis, evaluating these significant variables (i.e., age, age at onset, aura, history of sexual abuse, history of physical abuse, and history of family dysfunction); 67% of the cases were correctly predicted by this model ($p = 0.0001$). Table 4 shows the results of regression analysis. The only variables that retained their significance in the regression analysis model were history of sexual abuse and presence of aura; history of physical abuse was borderline significant and showed a trend (all three were more prevalent among females).

Table 1
Demographic characteristics of the patients in relation to their sex.

	Females (#305)	Males (#146)	p value
Age (mean ± standard deviation) years	27.4 ± 10.7	24.9 ± 10.9	0.02*
Age at onset (mean ± standard deviation) years	23.1 ± 9.7	20.8 ± 9.7	0.02

* Statistically significant difference.

4. Discussion

In this study, we observed that similarities between females and males outweigh the differences with regard to the demographic and clinical characteristics of PNES. This is consistent with previous studies [5]. However, certain significant differences between females and males were confirmed in the current large multicenter international study of patients with PNES. In particular, history of sexual abuse, history of physical abuse, and presence of aura were more prevalent among females compared with those in males.

Consistent with previous studies, we observed that history of abuse (both sexual and physical) was a relatively common occurrence among patients with PNES, and the rates of sexual abuse (odds ratio = 4) and physical abuse (odds ratio = 2) were higher in females compared with those in males [6–11]. There are some plausible explanations for this observed sex difference. Firstly, there is the issue of population prevalence — history of abuse is more common in females compared with that in males in the general population [4]. A meta-analysis of around 10 million individuals showed that childhood sexual abuse is a

Table 2
Clinical characteristics of the seizures in relation to the sex of the patients.

	Females (#305)	Males (#146)	p value
Seizure frequency per month (mean ± standard deviation)	30 ± 57	51 ± 258	0.1
Aura	200 (66%)	80 (55%)	0.03*
Loss of responsiveness	226 (74%)	114 (78%)	0.4
Wax and wane semiology	133 (44%)	71 (49%)	0.4
Side-to-side head turning	80 (26%)	31 (21%)	0.2
Closed eyes during the attacks	207 (68%)	96 (66%)	0.5
Ictal crying	28 (9%)	9 (6%)	0.4
Urinary incontinence	28 (9%)	14 (10%)	0.8
Generalized motor seizures	236 (77%)	109 (75%)	0.5
Akinetic seizures[a]	35 (11%)	15 (10%)	0.6
Subjective seizures[b]	22 (7%)	12 (8%)	0.7
Ictal injury	60 (20%)	39 (27%)	0.1

[a] Seizures mainly characterized by unresponsiveness and the absence of movement.
[b] Seizures mainly characterized by experiential phenomena reported by the patients without loss of responsiveness.
* Statistically significant difference.

Table 3
Factors potentially associated with PNES in relation to the sex of the patients.

	Females (#305)	Males (#146)	p value
History of head injury	19 (6%)	10 (7%)	0.8
History of sexual abuse	44 (14%)	5 (3%)	0.0001*
History of physical abuse	44 (14%)	10 (7%)	0.01*
History of family dysfunction	113 (37%)	41 (28%)	0.04*
Family history of seizures	76 (25%)	38 (26%)	0.8
Taking antiepileptic drugs	164 (54%)	83 (57%)	0.6

* Statistically significant difference.

global problem and is 2.4 times more common in females than in males [4]. On the other hand, these sex-related differences might be due to unwillingness of males to admit to abuse because of cultural factors [11]. In addition, there exists the possibility of under-ascertainment — it is not just patients that may be reluctant to disclose. Physicians may not specifically ask, leading to underreporting. The overall rates of abuse in this study were lower than those from population studies [4], suggesting that there might have been a problem with under-ascertainment. However, there might be specific neurobiological reasons for this observation, too. There is evidence that suggests that abnormal connectivity between brain areas involved in emotional processing, cognitive integration, and motor regions may explain ictal events in patients with PNES [12]. Moreover, lifetime adverse experiences such as sexual abuse may affect and alter brain connectivity in females differently compared with that in males and more often predispose females to psychopathology [2,13–15]. These speculations should be investigated in future studies.

We also observed that auras are more commonly reported by females (in 66%) compared with that in males with PNES (in 55%). We do not have a clear and concrete explanation for this observation. However, we know that sex plays an important role in the anatomy and function of the human brain [16]. There are sex-related differences in brain connectivity, and these differences may underlie sex-related cognitive, emotional, and behavioral differences [16]. Another possibility is that these differences might be related to various defense mechanisms in females compared with that in males [8,17,18]. Intrapsychic trauma (e.g., abuse) is more often associated with defense mechanisms such as somatization, dissociation, and conversion in females while different defense mechanisms (e.g., repression) are more common in males [8,17,18]. Therefore, "auras" may represent the start of a dissociative event (a defense mechanism associated with psychological trauma), which might explain why females more often have auras with their attacks. These hypotheses should be investigated in future studies. On the other hand, auras may be wrongly associated with epileptic seizures in clinical practice, and this may lead to misdiagnosis and mismanagement [19,20].

This study has some limitations, including its retrospective design and lack of some important data such as psychiatric comorbidities. In addition, as this was a project conducted in multiple centers in diverse countries, each center had its own protocol for interviewing patients. In other words, a standardized proforma was not used across centers (e.g., no standard instruments were used to measure abuse). So, recording of data is likely to have been uneven and influenced by the clinical practices of those involved. As we have included all ages from different cultures, rates of stressors may look different from those in western studies with adult patients [3,21,22]. Finally, our sample may not represent the general population of patients with PNES; studies from video-EEG monitoring units have the advantage of including a well-defined group of patients but also have the disadvantage of excluding some patients (e.g., patients with akinetic events resembling syncope; patients who have PNES but do not have an event in the video-EEG monitoring unit; and patients who cannot afford to come to the video-EEG monitoring unit).

Table 4
Regression analysis showing the significant differences between females and males with PNES.

	Odds ratio	95% confidence interval	p value
History of sexual abuse	4.06	1.54–10.73	0.005*
Aura	1.75	1.14–2.70	0.01*
History of physical abuse	2.09	0.98–4.42	0.05
History of family dysfunction	1.50	0.95–2.38	0.07
Age	1.01	0.97–1.04	0.5
Age at onset	1.02	0.98–1.06	0.2

* Statistically significant difference.

In conclusion, similarities between females and males outweigh the differences with regard to the demographic and clinical characteristics of PNES. However, notable differences are that females more often report lifetime adverse experiences (sexual and probably physical abuse) and auras. While social, psychological, and genetic factors may interact with lifetime adverse experiences in the inception of PNES, the link is not yet clear. This is an interesting avenue for future studies.

Declaration of Competing Interest

Ali A. Asadi-Pooya: Honoraria from Cobel Daruo; Royalty: Oxford University Press (Book publication); Grant from National Institute for Medical Research Development.

Kette Valente: Grant from National Council for Scientific and Technological Development (CNPq). Timothy Nicholson is funded by a UK National Institute of Health Research (NIHR) Clinician Scientist Award. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health. Others: no conflict of interest.

Acknowledgments

This study was supported by the Pharmaceutical Sciences Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.

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