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**Title:** Adult-onset psychogenic nonepileptic seizures: a multicenter international study

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## **Abstract**

**Purpose:** The aim of this multi-center international cross-cultural study was to compare clinical variables in a large sample of people with adult-onset psychogenic nonepileptic seizures (PNES).

**Methods:** In this retrospective study, we evaluated persons with documented PNES, who were older than 16 years of age at the onset, from four countries (i.e., Iran, Brazil, Venezuela, and Argentina) regarding their age, gender, PNES semiology, and possible predisposing factors.

**Results:** We included 389 patients (244 from Iran, 66 from Brazil, 51 from Venezuela, and 28 from Argentina). Age at diagnosis was  $32 \pm 9$  years (range: 17-64 years) and age at the onset of seizures was  $27 \pm 8$  years (range: 17-49 years). There was a female predominance in all countries. The demographic characteristics and factors associated with PNES were similar among the countries. However, there were significant semiological differences among the countries.

**Conclusion:** This study corroborates the notion that PNES share more similarities than differences cross-culturally and across international borders. However, the background determined by cultural, ethnic and religious differences may influence the semiology of PNES. Further cross-cultural studies involving more than two continents may advance our understanding of PNES.

**Key words:** Adults; International; PNES; Psychogenic; Seizure; Semiology

## INTRODUCTION

Psychogenic nonepileptic seizures (PNES) are characterized by self-limited events that resemble epileptic seizures without ictal epileptiform discharges [1]. They are common occurrences; 20–25% of all patients referred to specialist epilepsy clinics have PNES [2–5]. Psychogenic nonepileptic seizures represent a universal human condition and are recognized as a worldwide phenomenon [6]; it is believed that despite cultural and socioeconomic differences, patients with PNES from middle- and high-income countries share several similarities [7]. The majority of patients who are diagnosed with this condition tend to be female and in the early years of adulthood [8–10].

However, patients with PNES are a heterogeneous patient population that may differ in their social adverse life experiences (e.g., sexual abuse or physical abuse) and psychiatric comorbidities [11]. Therefore, it is plausible to assume that there would be clinical differences between different cultures and among different ethnic populations. In a previous international cross-cultural study of PNES in adults, patients from the USA presented more subjective seizures and a higher diversity considering their seizure types compared to the Brazilian patients with PNES [12]. However, this study was limited by sample size and a comparison between only two countries. In this context, larger multi-center cross-cultural studies were deemed necessary to reveal any subtle, but significant cross-cultural differences of PNES.

In the current study, we compared a larger sample regarding various clinical characteristics of PNES between adult patients from multiple countries. This multi-center international cross-cultural comparative study is intended to advance our understanding of PNES in adults.

## **METHODS**

In this retrospective study, we investigated consecutively referred patients with PNES with an age at onset of above 16 years up to 49 years, who were admitted to the epilepsy monitoring units at centers in Iran (Shiraz Comprehensive Epilepsy Center, from 2008 until 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 until 2018), and Venezuela (Epilepsy Unit. La Trinidad Medical Center, from 2014 until 2018). Epileptologists experienced in making the diagnosis of seizures confirmed the diagnosis of PNES when the typical seizures were captured on video-EEG monitoring and no epileptiform activity before, during, or after the seizure was captured. The lack of ictal epileptiform activity, during video-EEG monitoring, was a mandatory criterion for all patients.

At the time of diagnosis, patients were evaluated either by epileptologists alone or together with psychologists/psychiatrists. Clinical data had been collected and entered into patient medical records according to the standard clinical care at each center (no standardized instruments were used across the centers). However, these data inquiries were routine in every single clinical evaluation in all of these settings and these questions were asked in the context of confirming diagnosis and attempting to document risk factors. Only variables that had been collected at all centers were chosen for inclusion in the current study. A data collection spreadsheet was developed (including structured semiological features and risk factors that the coders were given to look for and code presence or absence) and variables were defined in order to implement the maximum possible consistency in data collection and coding among centers. Accordingly, authors at each center reviewed the medical records of the patients (including their history and video-EEG monitoring report) and coded the

variables. All data regarding the patients' identity were kept confidential. Age, gender, 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. The Pearson Chi-Square and one-way Analysis of Variance (ANOVA) and Bonferroni correction tests were used for statistical analyses. P values less than 0.05 were considered significant. This study was conducted with the approval by Institutional Review Boards of all centers.

## **RESULTS**

Three hundred and eighty-nine patients were studied (244 from Iran, 66 from Brazil, 51 from Venezuela, and 28 from Argentina). Mean (standard deviation) age at diagnosis was  $32 \pm 9$  years (range: 17-64 years) and mean (standard deviation) age at onset of seizures was  $27 \pm 8$  years (range: 17-49 years). Duration of the illness in the whole population was  $4.1 \pm 5.3$  years (range: 0-30 years). The sex ratio of the patients was 2.36 (272 women and 117 men).

Table 1 shows the demographic characteristics of the patients. Demographic characteristics (i.e. age at onset, duration of illness, and sex ratio) of the patients were not statistically different among the nations. Table 2 describes the clinical characteristics of PNES. Clinical characteristics of psychogenic seizures in adult patients with PNES showed significant differences among the nations. Table 3 describes historical factors associated with PNES in the patients, which were found to be similar among the four nations.

Review of clinical characteristics compared in Table 2 showed that the most common (>50%) PNES semiological features in the Iranian sample to be aura before seizures, unresponsiveness, eyes closed during the attacks, intermittent movements, and generalized motor seizures. In Brazil, the majority of the patients had generalized motor seizures, but less frequently reported other semiological features. In Venezuela, the majority of the patients had a similar semiology as in Iran, with the addition of side to side head movements. Finally, in Argentina, the most common seizure semiology included auras and generalized motor seizures.

## **DISCUSSION**

This study investigated 389 adults with PNES across borders and among varying cultures. In this study, persons with adult onset PNES shared similarities regarding demographic variables and predisposing factors. However, it is of note that some aspects of PNES semiology differed between the nations significantly.

There was a remarkable diagnostic delay in all countries. Referral delay is worrisome since diagnosing PNES prevents unnecessary medical procedures, disadvantageous treatments and excessive costs [13]. As documented in this and previous studies, patients with PNES are at risk for iatrogenic harm, as they are more likely to receive unnecessary treatments [e.g., antiepileptic drugs (AEDs)] as the consequence of misdiagnosis of epilepsy [14-17]. In a previous study, the authors observed that the number of AEDs tried was associated with a longer delay until making the diagnosis [18]. In the current study, we noted that despite a similar delay for the diagnosis of PNES, more patients from Argentina and Venezuela received a diagnosis of comorbid epilepsy and all patients from those two countries received AEDs. Therefore, it is possible that the health-care system and health care



providers' attitude (e.g., degree of suspicion for PNES when seeing patients with paroxysmal events) are significant challenging factors in the management process of patients with PNES [6, 19].

The semiological differences between patients from different countries were probably the most significant findings of this study. The pathophysiology of PNES is complex and likely multifactorial. As reviewed by Szaflarski and LaFrance, functional neurological disorders in general (and PNES in particular) are probably network disorders and the symptoms are probably associated with the disruption of various neural networks [20]. According to Voon et al., cultural, ethnic, and religious differences may play an essential role in the modulation of semiology across different nations [21]. For example, altered responsiveness during PNES is hypothetically a marker of lower emotional resilience or ability to tolerate emotions among these patients [22]. Therefore, it is possible that the observed significant difference in the frequency of unresponsiveness among patients with PNES from different countries in our study reflects their cultural differences and their different abilities in recognizing, tolerating or expressing their emotions. A more severe clinical presentation represented by generalized motor seizures with ictal injury and urinary incontinence were frequently observed in the Iranian sample, which may be a consequence of their greater emotional repression for cultural and social reasons. Further studies addressing more than two continents may support these findings and reveal other significant, but subtle differences.

Interestingly, factors potentially predisposing to PNES had similar patterns among the countries in our study. However, the rates of abuse (both sexual and physical) were lower than that reported in previous studies from the USA [23]. The authors postulate that several factors related to the study design, physicians' and also patients' characteristics may account for this difference. Abuse is often underestimated, because most patients will not easily

disclose this history (“unspeakable dilemmas”), which is more likely to be reported during prolonged psychiatric/psychological follow-up, but not during an interview after the diagnosis [24]. This represents a limitation of our study and other studies with a similar methodology [10, 25]. Regarding patients and physicians-related factors, the cultural and religious background must be taken into account. By one side, patients from some countries may exhibit disinclination to share intimate details with health providers [25], and similarly, clinicians may inquire less about these historical details than in Western countries. On the other hand, the sample from Argentina (where psychoanalytic tradition, which underscores the significance of adverse childhood events, is firmly rooted in the culture [26]) revealed the highest rate of reported sexual abuse. Future international cross-cultural studies with a prospective design and a homogeneous data collection strategy may render distinct results.

This study has some limitations including its retrospective design. Data collection strategy was not consistent between the centers and as a consequence some data were missing. In addition, distinct physicians evaluated patients and our study lacks some critical data such as psychiatric comorbidities of the patients. However, it appears that patients with PNES across borders and between cultures share more similarities than differences. These findings might endorse the concept that PNES may result from neurobiological dysfunction and abnormal connectivity of specific neural networks [27]. Researchers may learn more about various aspects of PNES by designing multi-center international cross-cultural studies.

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**Conflict of interest**

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

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Others: no conflict of interest.

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**Table 1.** Demographic characteristics of adults with PNES in four nations

<b>Demographic Characteristic</b>	<b>Iran</b>	<b>Brazil</b>	<b>Venezuela</b>	<b>Argentina</b>	<b>P value</b>
Sex ratio (Female: Male)	161: 83	47: 19	44: 7	20: 8	0.03 *
Age at onset (mean $\pm$ standard deviation, years)	27 $\pm$ 8	29 $\pm$ 8	29 $\pm$ 9	28 $\pm$ 10	0.04 *
Duration of the illness (mean $\pm$ standard deviation, years)	3.7 $\pm$ 5.5	5 $\pm$ 5.4	4.6 $\pm$ 5.3	4.7 $\pm$ 3.5	0.2

**\*loses its significance after Bonferroni correction (significant predictive value of 0.016).**

**Table 2.** Clinical characteristics of seizures in adults with PNES in four nations

<b>Clinical Characteristic</b>	<b>Iran</b>	<b>Brazil</b>	<b>Venezuela</b>	<b>Argentina</b>	<b>P value</b>
Aura before seizures	154 (63%)	14 (21%)	44 (86%)	23 (82%)	0.0001
Unresponsiveness	208 (85%)	32 (48%)	42 (82%)	9 (32%)	0.0001
Intermittent (wax and wane) movements	131 (54%)	21 (32%)	40 (78%)	4 (14%)	0.0001
Side to side head turning	52 (21%)	13 (20%)	36 (71%)	9 (32%)	0.0001
Closed eyes during the attack	194 (80%)	20 (30%)	35 (69%)	3 (11%)	0.0001
Generalized motor seizures	210 (86%)	41 (62%)	43 (84%)	22 (79%)	0.0001
Akinetic seizures	26 (11%)	N/A	12 (24%)	5 (18%)	0.03 *
Urine incontinence	28 (11%)	1 (2%)	6 (12%)	1 (4%)	0.05
Ictal injury	75 (31%)	12 (18%)	8 (16%)	N/A	0.01 *
Comorbid epilepsy	33 (14%)	12 (18%)	23 (45%)	9 (32%)	0.0001
Taking antiepileptic drugs	143 (59%)	36 (55%)	51 (100%)	28 (100%)	0.0001

\*loses its significance after Bonferroni correction (significant predictive value of

**0.0045). N/A: not available.**



**Table 3.** Factors associated with PNES

<b>Associated Factor</b>	<b>Iran</b>	<b>Brazil</b>	<b>Venezuela</b>	<b>Argentina</b>	<b>P value</b>
Family history of seizures	69 (28%)	15 (23%)	10 (20%)	N/A	0.3
History of physical abuse	29 (12%)	14 (21%)	4 (8%)	N/A	0.07
History of sexual abuse	20 (8%)	6 (9%)	3 (6%)	6 (21%)	0.03 *
History of family dysfunction	85 (35%)	17 (26%)	15 (29%)	N/A	0.2

**\*loses its significance after Bonferroni correction (significant predictive value of 0.0125). N/A: not available.**