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Pediatric-onset psychogenic nonepileptic seizures: A retrospective international multicenter study

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ABSTRACT

Purpose: We compared various clinical characteristics of pediatric-onset psychogenic nonepileptic seizures (PNES) between patients from five countries. The purpose of this study was to advance our understanding of pediatric-onset PNES cross-culturally.

Methods: In this retrospective study, we compared consecutive patients with PNES with an age at onset of 16 years and younger from epilepsy monitoring units in Iran, Brazil, the USA, Canada, and Venezuela. Age, gender, age at seizure onset, seizure semiology, predisposing factors, and video-EEG recordings of all patients were extracted. Pearson Chi-Square, one-way ANOVA and Bonferroni correction tests were used for statistical analyses.

Results: Two hundred twenty-nine patients were studied (83 from Iran, 50 from Brazil, 39 from Canada, 30 from the USA, and 27 from Venezuela). Mean age at the onset of seizures was 12.1 ± 3.2 years (range: 4–16 years). The sex ratio of the patients was 1.83: 1 (148 females and 81 males). Clinical characteristics of pediatric-onset PNES showed some significant differences among the nations. However, factors associated with pediatric-onset PNES in these five nations were similar.

Conclusion: This study underscores how international cross-cultural studies can make important contributions to our understanding of PNES. Patients with pediatric-onset PNES from different countries were similar on many risk factors associated with PNES. This suggests universality in many features of PNES. However, intriguing differences were also noted with regard to seizure semiology, which might be the result of cultural factors.

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1. Introduction

Psychogenic nonepileptic seizures (PNES) have a propensity to start at young ages (i.e., adolescence and young adulthood), although the seizures can begin at any age [1–5]. Clinical characteristics and predisposing risk factors of patients with PNES differ from those with epilepsy and also from healthy individuals [6,7]. More intriguingly, some clinical characteristics and risk factors of PNES (e.g., a history of abuse) may differ in those with early-onset PNES compared with that in patients with adult-onset disorder [2,8]. Therefore, studying clinical characteristics and risk factors of pediatric-onset PNES could be revealing and would advance our understanding of PNES.

In a previous, relatively small scale cross-cultural international study of PNES in children and adolescents [5], we observed that young patients with PNES between cultures shared more similarities than differences with regard to their demographic and clinical characteristics. However, a relatively small sample size (i.e., 51 patients) was the major limitation of that previous study [5]. In the current study, we compared much larger samples with regard to various clinical characteristics and risk factors of patients with pediatric-onset PNES from multiple countries across continents. This multi-center, international cross-cultural comparative study design is intended to achieve the goal of advancing our understanding of pediatric-onset PNES. Such a large scale international cross-cultural study of pediatric-onset PNES has never been done before.

2. Patients and methods

In this retrospective study, we investigated consecutive patients with PNES with an age at onset of 16 years and younger, who were admitted to the epilepsy monitoring units at one center in Iran (Shiraz Comprehensive Epilepsy Center, from 2008 until 2019), one center in Brazil (Institute of Psychiatry, Hospital das Clinicas, University of Sao Paulo from 2010 until 2016), one center in the USA (Northeast Regional Epilepsy Group, from 2013 until 2018), one center in Canada (Comprehensive Children's Epilepsy Center at Alberta Children's hospital, from 2008 until 2019), and one center in Venezuela (Epilepsy Unit. La Trinidad Medical Center from 2014 until 2018). All patients included in the study had undergone inpatient video-EEG monitoring at each center. Epileptologists experienced in making the diagnosis of seizures confirmed the diagnosis when the typical seizures were captured on video-EEG monitoring and no epileptiform activity before, during, or after the seizure was captured. There were no exclusions.

At the time of diagnosis, patients had been evaluated by an epileptologist alone or in combination with a psychologist. 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). Only variables that had been coded at all centers were chosen for inclusion in the current study. All the data were kept confidential.

Age, gender, age at seizure onset, seizure semiology (based on self, eyewitness-report and clinician-observed during video-EEG monitoring), pre-morbid factors potentially predisposing to PNES [a 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.), academic failure (school dropout or repeated grades), and family history of seizures], and video-EEG recording of all patients were registered routinely.

Demographic variables and relevant clinical variables were summarized descriptively to characterize the study populations. The Pearson Chi-Square for analysis of binary variable (e.g., sex) differences among all five nations (in one equation), one-way Analysis of Variance (ANOVA) for analysis of differences in means of numerical variables (e.g., age) among all five nations, and Bonferroni correction tests were used for statistical analyses. P values less than 0.05 were considered significant. All analyses were conducted using the statistical software package SPSS (SPSS Inc., Chicago, IL, USA). This retrospective study was conducted with the approval of an Institutional Ethics Review Board at each center.

3. Results

Two hundred twenty-nine patients were studied (83 from Iran, 50 from Brazil, 39 from Canada, 30 from the USA, and 27 from Venezuela). Mean age at the diagnosis was 16.7 ± 7.5 years (range: 6–41 years) and age at the onset of seizures was 12.1 ± 3.2 years (range: 4–16 years). It should be noted that since this was a retrospective study, we cannot ascertain the age at onset of psychogenic seizures *vs.* epileptic seizures in the patients with PNES and comorbid epilepsy. The sex ratio of the patients was 1.83: 1 (148 females and 81 males). Table 1 shows the demographic characteristics of the patients. The sex ratio of the patients was not statistically different among the nations, but their mean age at onset was statistically different ($p = 0.01$). In a secondary analysis, we excluded patients with comorbid epilepsy (81 patients); the mean age at onset of patients with PNES-only remained statistically different between the nations ($p = 0.007$).

Table 2 describes the clinical characteristics of psychogenic seizures

Table 1
Demographic characteristics of pediatric-onset PNES in five nations.

Demographic Characteristic	Iran	Brazil	USA	Canada	Venezuela	P value
Sex ratio (Female: Male)	1.68: 1	1.63: 1	1.73: 1	2: 1	2.86: 1	0.8
Age at onset (mean ± standard deviation, years)	12.82 ± 3.05	11.17 ± 3.40	11.86 ± 2.52	12.56 ± 2.75	11.01 ± 3.80	0.01

Table 2
Clinical characteristics of seizures in pediatric-onset PNES in five nations.

Clinical Characteristic	Iran	Brazil	USA	Canada	Venezuela	P value
Aura before seizures	56 (67%)	27 (54%)	17 (57%)	35 (90%)	16 (59%)	0.005
Unresponsiveness	67 (81%)	40 (80%)	22 (73%)	22 (56%)	16 (59%)	0.01*
Side to side head turning	14 (17%)	7 (14%)	4 (13%)	7 (18%)	7 (26%)	0.7
Closed eyes during the seizures	70 (84%)	19 (38%)	9 (30%)	25 (64%)	17 (63%)	0.0001
Generalized motor seizures	70 (84%)	31 (62%)	19 (63%)	21 (54%)	8 (30%)	0.0001
Ictal crying	4 (5%)	8 (16%)	7 (23%)	6 (15%)	6 (22%)	0.6
Urine incontinence	7 (8%)	2 (4%)	1 (3%)	2 (5%)	3 (11%)	0.6
Ictal injury	22 (27%)	4 (8%)	2 (7%)	4 (10%)	3 (11%)	0.009*

* Loses its significance after Bonferroni correction (significant predictive value of 0.006).

Table 3
Factors associated with pediatric-onset PNES in five nations.

Associated Factor	Iran	Brazil	USA	Canada	Venezuela	P value
Family history of seizures	28 (34%)	17 (34%)	10 (33%)	7 (18%)	10 (37%)	0.3
History of physical abuse	10 (12%)	8 (16%)	5 (17%)	1 (3%)	0 (0)	0.06
History of sexual abuse	8 (10%)	7 (14%)	6 (20%)	6 (15%)	1 (4%)	0.3
History of head injury	3 (4%)	Not reported	2 (7%)	4 (10%)	4	0.2
Family dysfunction	31 (37%)	21 (42%)	14 (47%)	14 (36%)	12 (44%)	0.7
Academic failure	16 (19%)	9 (18%)	7 (23%)	9 (23%)	13 (48%)	0.03*
Comorbid epilepsy	27 (33%)	20 (40%)	10 (33%)	15 (38%)	9 (33%)	0.8

* Loses its significance after Bonferroni correction (significant predictive value of 0.007).

in the patients. Clinical characteristics of pediatric-onset PNES showed significant differences among the nations; in particular, the reported rates of auras, closed eyes, and generalized motor seizures were different. The most common (> 50%) PNES semiological features in the Iranian sample included aura before seizures, unresponsiveness, eyes closed during the seizures, and generalized motor seizures. In Brazil, the majority of the patients had a similar semiology as in Iran, with the exception of closed eyes during the seizures. In Venezuela, the majority of the patients had a similar semiology as in Iran, with the exception of generalized motor seizures. In the USA, the most common seizure semiology included all of the above with the exception of eyes closed during the seizures (similar to the Brazilian sample). Finally, in Canada, the most common semiological features of PNES included all those mentioned in the Iranian sample.

Table 3 shows potential risk factors associated with pediatric-onset PNES in these samples. Factors associated with pediatric-onset PNES in these five nations were similar. The most common factors associated with pediatric-onset PNES in all five nations included family dysfunction, comorbid epilepsy, family history of seizures, and academic problems. Factors such as a history of abuse (sexual or physical) and head injury were less often reported.

4. Discussion

The present study included 229 patients with pediatric-onset PNES from countries in the Middle East (Iran), North America (Canada and USA) and South America (Brazil and Venezuela). These international samples revealed a substantial amount of similarities, but also some unique clinical characteristics.

The sex ratio of the patients with pediatric-onset PNES was similar among these five countries; although, the lowest sex ratio differential was reported in the Brazilian sample (1.63: 1) and the greatest was reported in the Venezuelan sample (2.86: 1); both from South America. Although, average age at the onset was statistically different among these five geographical centers (Venezuela: youngest at 11 years and Iran: oldest at 13 years); the clinical significance appears minimal since the mean age at onset for all included nations was between 11 and 13 years of age. The finding that average onset occurred between 11–13 years of age is interesting as it corresponds with the onset of many anxiety disorders in epidemiological studies [9]. This may suggest a potential link between PNES and development of anxiety over the lifespan, especially for those types of anxiety disorders involving a prominent autonomic nervous system component (e.g. social phobia and panic disorder) [10]. This age at onset also coincides with puberty. There are studies suggesting that sex differences in PNES may become pronounced with puberty [11]. The relationship between puberty and PNES is a question worth exploring in the future. The demographic characteristics of the patients in the current study were not only comparable to other cross-cultural studies of youth diagnosed with PNES [5], but also to previous US-based studies [12], which underscores the universality of these characteristics in PNES.

There were, however, some notable differences in certain seizure characteristics between these national samples. In particular, more severe presentations (e.g., generalized motor seizures) were more frequently observed in the Iranian sample. It could be speculated that more intense seizure presentations in Iranian patients are the result of greater emotional repression and suppression associated with their social and cultural features. This coincides with another observation that ictal injuries had a trend to be more prevalent in the Iranian sample. Ictal injuries in association with PNES are not commonly reported in children and adolescents in the Western studies [13], which makes this finding even more intriguing. A previous study from Iran including adult patients had also reported high numbers of ictal injuries (29%) [14]. Of note, these elevated rates of physically intense seizures and reported ictal injuries did not correlate with reported experiences of sexual or other forms of childhood abuse in the Iranian patients [14]. Therefore, these semiological differences in Iranian patients may be due to the existence of cultural differences between this nation and others in the Americas.

Similarly, loss of responsiveness had a trend to be more prevalent in the Iranian sample (81% in the Iranian sample and 56% in the Canadian sample). Change in responsiveness during seizures is hypothetically a marker of lower emotional resilience or ability to tolerate emotions among patients with PNES [15]; therefore, it is possible that the observed trend in varying rates of unresponsiveness among patients with pediatric-onset PNES from different countries reflects their cultural differences in how emotions are expressed and managed. This hypothesis should be studied in future international cross-cultural studies. However, although seizure semiology is very important and may help distinguish psychogenic from epileptic seizures, there is no pathognomonic feature for either diagnosis. In addition, eyewitness reports of semiology are often unreliable [16–18]. Since this is a retrospective study and the data have been entered into the databases over a long period of time, we cannot discriminate between the sources of the data (witness *vs.* V-EEG monitoring) for seizure semiology of the patients. The correct diagnosis of PNES vs. epilepsy can be made based on various combinations of data including a detailed clinical history, eyewitness reports, clinician observations, interictal EEG and ictal video-EEG recordings [19,20].

Because this is a sample with pediatric-onset PNES, it is necessary to recognize that factors potentially predisposing to PNES may be different than those usually observed in adult-onset PNES [2]. In the present multi-national study, rates of sexual and physical abuse were comparable to previous relatively low reports in pediatric samples from the US [21]. Speculatively, rates of reported abuse could be lower in pediatric samples due to some children potentially being dependent upon, living with, or otherwise involved with their abusers. One might expect that disclosure of abuse could be more difficult for these patients. In contrast, other relevant risk factors, including academic challenges and family dysfunction were among the highest reported factors in all five countries. This is consistent with previous reports [21], in which family dysfunction, loss (e.g. death of caregiver, divorce, etc.) and academic/school difficulties were found to predominate in younger patients with PNES. The numbers of patients who reported a family history of seizures or comorbid epilepsy were high and similar among the nations and were also similar to what have been reported in other studies [13];

these may represent a risk factor for PNES-either due to biological mechanisms or through behavioral modeling [22].

This study has some limitations, including its retrospective design that at times resulted in missing important data (e.g., comorbidities, medications, parental education and financial status, etc.). In addition, a standardized proforma was not used across the centers (e.g., no standard instruments were used to measure a history of abuse or family dysfunction). Hence, recording some data is likely to have been uneven and influenced by the clinical practices of those involved. Future prospective studies could benefit from inclusion of additional risk factors (e.g. psychiatric comorbidity, adverse life events, etc.) as well as treatments received.

In conclusion, this study underscores how international cross-cultural studies can make important contributions to our understanding of PNES across cultures and borders. We observed that patients with pediatric-onset PNES from different countries were similar on many demographic characteristics and risk factors associated with PNES. This suggests universality in many of the features of PNES. We also observed that, sexual and physical abuse were not the most common risk factors associated with pediatric-onset PNES. This is different than what has been observed in adults and suggests that younger or older ages at onset may be associated with different etiologies regardless of the nationality. Finally, intriguing differences were noted with regard to seizure semiology; these differences in seizure semiology between the nations might be the result of cultural factors.

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