



Outcome of patients with psychogenic nonepileptic seizures with limited resources: A longitudinal study



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ABSTRACT

Purpose: The aim of the current study was to investigate the long-term outcome of patients with psychogenic nonepileptic seizures (PNES) and factors potentially associated with their outcome in Iran. **Methods:** We investigated all patients with PNES admitted to the epilepsy monitoring unit at the Shiraz Comprehensive Epilepsy Center from 2008 through 2013. Patients included in this study had a confirmed diagnosis of PNES. In a phone call interview to the patients in December 2017, we obtained the following information: seizure outcome (seizure-free during the past 12 months or not), history of receiving any psychotherapy after confirming their diagnosis in the past, and number of psychotherapy sessions the patient had received.

Results: Eighty-six patients (54 females and 32 males) met the inclusion criteria. Seventy-four (86%) patients did not receive appropriate psychotherapy. Forty-seven (54.7%) patients were seizure-free during the past 12 months. Age at onset ($P=0.02$), education ($P=0.01$), and taking psychiatric drugs ($P=0.007$) were associated with this outcome.

Conclusions: Resources to treat patients with PNES are limited in Iran; however, more than half of the patients became free of seizures. Lower education, comorbid psychiatric problems, and a later age at the onset of seizures may affect the seizure outcome in patients with PNES. Well-designed multi-center cross-cultural long-term studies should address factors associated with outcome in patients with PNES, considering that seizure frequency should not be the only outcome measure.

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1. Introduction

Psychogenic nonepileptic seizures (PNES) are common occurrences in epilepsy inpatient and outpatient centers [1]. Unfortunately, misdiagnosis and delay in diagnosis are common in patients with PNES [2]. In addition, long-term studies suggest that many patients with PNES will continue to experience seizures despite receiving neurological and psychotherapeutic care [3]. In a systematic review [4], the prognosis of PNES in adults was shown to be poor. From their reviewed data, fewer than 40% of newly diagnosed adults could be expected to become seizure-free within 5 years after making a diagnosis of PNES [4].

Data on PNES and their outcome is scarce from the developing countries, where the resources are limited. Predictors of outcome are not well-characterized, particularly in the developing world,

either. In one previous study from Iran [5], we observed that there were no significant differences between Iranian patients and Western patients with respect to the clinical and semiological characteristics of PNES. However, access to resources are limited in Iran and many other developing countries compared to that in the Western countries. Current best practice in the management of patients with PNES includes combined psychotherapy (e.g., cognitive behavioral therapy) and treatment of any psychiatric comorbidities [6]. In spite of that, access to appropriate psychotherapy is limited in many places in Iran (see the methods). The aim of the current study was to investigate the long-term seizure outcome of patients with PNES and factors potentially associated with their seizure outcome in Iran (a developing country with limited resources).

2. Patients and methods

The original data, on which the current study is elaborated, was published previously [5]. We investigated all patients with PNES admitted to the epilepsy monitoring unit at the Shiraz Comprehensive Epilepsy Center from 2008 through 2013. Patients

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included in the current study had a confirmed diagnosis of PNES, determined by clinical assessment and video-EEG monitoring with ictal recording of their seizures. We routinely refer all the patients with PNES to our psychologist, who is the only psychologist with expertise in delivering an appropriate care to these patients in the region, for further assessment and treatment plans [typically, cognitive behavioral psychotherapy (CBT)]. However, since there is not such a service in other cities (other than Shiraz) in the region and also because psychotherapy is not covered by insurance companies and patients have to pay 100% out of the pocket, many patients would not receive such therapy. We excluded patients with comorbid epilepsy, abnormal EEG, or insufficient data. We excluded the patients with abnormal EEG to make sure that none of the patients included in the study had epilepsy, despite the fact that some patients with PNES may have abnormal EEG (e.g., as a genetic trait) without having epilepsy.

We extracted all of the relevant clinical and demographic data from our database. We studied the following variables at the time of the diagnosis: gender, age at onset, age at referral, disease duration before making the definite diagnosis, education (less than college and college education), employment, marital status, seizure characteristics and semiology, risk factors for PNES [i.e., sex abuse, physical abuse, childhood abuse (neglect, forced child labor, etc.), head injury, dysfunctional family (problematic relationships, divorce, etc.), and family history of seizures; these factors are often being asked in a one-to-one interview of the patients by the treating epileptologist], receiving any psychiatric drugs (as an indication of suffering from psychiatric illnesses, since we did not perform a standard psychiatric evaluation in our patients), and receiving antiepileptic drugs (AEDs). From 2014 until 2017, our epilepsy center was not active, as the primary investigator of the current study, who is the only epileptologist at this center, was out of the country. We re-established our epilepsy center in 2017. We decided to perform this investigation by calling all the patients and inquiring about their seizure outcome, if they were available and agreed to participate. In a phone call interview to the patients in December 2017, we tried to obtain the following information: seizure outcome (seizure-free during the past 12 months or not), history of receiving any psychotherapy after confirming their diagnosis in the past, and number of psychotherapy sessions the patient had received.

We studied factors potentially associated with the seizure outcome using Pearson Chi-square, Fisher's exact, Mann-Whitney, and Kolmogorov-Smirnov tests. Variables that were significant in

univariate tests were assessed in a logistic regression model. Odds ratio and 95% confidence interval (CI) were calculated. Receiver operating characteristic curve (ROC curve) was run to identify the best cutoff point and the discriminatory ability of the age at onset to correctly pick up patients who were seizure-free in their follow-up. P values less than 0.05 were considered significant. The Shiraz University of Medical Sciences Institutional Review Board approved this study.

3. Results

Of the 249 patients with PNES in our database, 111 patients had available contact numbers and were contacted. One patient refused to participate. Eighty-six patients (54 females and 32 males) met the inclusion criteria and were studied. Age of the patients at the onset of seizures was 24 ± 10 years (minimum = 6 and maximum = 67 years). Seventy-four (86%) patients did not receive appropriate psychotherapy (53 patients did not receive any and 21 patients received five or less sessions of CBT). Therefore, we did not include receiving CBT in our statistical analyses (only 12 patients received six or more sessions of psychotherapy; an arbitrary grouping compared with 13 sessions in CODES trial [7]). Forty-seven (54.7%) patients were seizure-free during the past 12 months and 39 (45.3%) patients were still suffering from seizures. Demographic and clinical characteristics of these two groups of patients (seizure-free vs. not) are shown in Table 1. We put the variables with a $P < 0.05$ in the univariate analyses (marital status, education, age at onset, and taking psychiatric drugs) in a logistic regression model to investigate their independent significance. The model was significant ($P = 0.0001$) and could correctly classify 73.3% of the patients. Later age at onset ($P = 0.02$; Odds ratio: 1.067; 95% confidence interval: 1.010–1.128), lower educational level ($P = 0.01$; Odds ratio: 0.152; 95% confidence interval: 0.034–0.681), and taking psychiatric drugs ($P = 0.007$; Odds ratio: 6.257; 95% confidence interval: 1.640–23.866) remained significant in the model. In ROC curve, area under the curve was 0.652 ($P = 0.01$) and the best cutoff point and the discriminatory ability of the age at onset was at 22 years to correctly pick up patients who were seizure-free in their follow-up (classifying ability was poor: sensitivity = 59% and specificity = 60%).

In an additional analysis, we selected the patients who did not receive any CBTs (53 patients); 39 patients (74%) were seizure-free. However, no factor was significantly associated with seizure outcome in this group of patients when we compared patients who

Table 1
Demographic and clinical characteristics of patients with psychogenic nonepileptic seizures (seizure-free vs. not).

	Seizure-free patients 47 (54.7%)	Patients with seizures 39 (45.3%)	P value
Sex (Female: Male)	29: 18	25: 14	1
Age at onset (years)	21 ± 8	27 ± 10	0.01
Duration of the condition before making the diagnosis (years)	4.7 ± 8	2.7 ± 4.2	0.4
Employed	24 (51%)	17 (44%)	0.5
Married	18 (38%)	24 (62%)	0.03
College education	13 (28%)	3 (8%)	0.02
History of abuse (sexual, physical, or childhood)	11 (23%)	10 (26%)	1
Dysfunctional family	14 (30%)	13 (33%)	0.8
Family history of seizures	17 (36%)	9 (23%)	0.2
History of head injury	4 (9%)	3 (8%)	1
Seizure frequency per month	28 ± 41	58 ± 104	0.2
Bizarre movement during seizures	21 (45%)	16 (41%)	0.8
Incontinence with seizures	7 (15%)	3 (8%)	0.3
Nocturnal seizures	12 (26%)	15 (38%)	0.2
Prolonged seizures (>30 min)	12 (26%)	12 (31%)	0.6
Hospital admission due to seizures	22 (47%)	21 (54%)	0.6
Ictal injury	8 (17%)	12 (31%)	0.2
Taking psychiatric drugs	31 (66%)	35 (90%)	0.01
Taking antiepileptic drugs	21 (45%)	22 (56%)	0.3

were seizure-free (39 patients) with those who were still suffering from seizures (14 patients) (probably, because of the small numbers in most cells). Finally, just six patients received enough (13 sessions [7]) CBT; three (50%) were seizure-free (the numbers were too small for any statistical analyses).

4. Discussion

In this study, we observed that many patients with PNES did not receive an appropriate treatment, probably because of the lack of resources or the resources were not easily accessible to them. This is an important shortcoming that may affect many patients with PNES and other conditions as well. In Iran, the available resources are usually concentrated in a few large cities, while most places in the nation are deprived and have limited access to the resources. In addition, even in large cities, most patients have to pay some of the expenses (e.g., psychotherapy sessions) out of their pocket (the authors' observations). In a recent international survey by the ILAE PNES Task Force, PNES were recognized as a diagnostic and therapeutic problem in all countries. There was a clear relationship between income and access to diagnostic tests and expertise; this was most commonly reported from the developing countries [8].

In our study, in long-term, more than half of the patients became free of seizures. In one recent study of 27 patients from Italy, majority of the patients (63%) became seizure-free (after 14–38 months) with communication of the diagnosis as the only intervention [9]. However, this is somehow in contrary to what we have seen in most Western studies [10–12]; in one example, 71% of the patients were still having seizures 1–10 years after making the diagnosis [10]. While cultural and social differences between a Western society and a Middle Eastern country might explain this difference to some extent (for example, family support may be different between the two: the author's opinion), the reasons behind this observation should be investigated in future multi-center cross-cultural studies. In designing such studies, one should consider that using seizure frequency as the sole measure outcome in patients with PNES is not sufficient and should be interpreted with caution [13]. For example, in one previous study, 43% of patients with seizure remission were still unproductive due to other psychiatric problems [14]. Determining the long-term outcome of PNES across borders and cultures has important clinical implications. For example, a recent well-designed clinical trial on 38 patients [6], with relatively a short follow up period (16 weeks), showed that the best current practice (combined CBT with sertraline) resulted in 59.3% seizure reduction which was significantly better compared with that in the treatment as usual group. A recent meta-analysis synthesized data from 13 studies with a total of 228 patients with PNES [15]; results showed that 47% of the patients with PNES were seizure-free upon completion of a psychological intervention. However, these figures are not much different from what we observed in our largely untreated patients in the long-term. This brings the question of the true effectiveness of psychological interventions in the long-term. Therefore, maybe it's useful to design cross-cultural clinical trials with longer follow up periods, in order to evaluate different treatment strategies in patients with PNES.

Factors that affected the seizure outcome in patients with PNES in our study included lower education, comorbid psychiatric problems, and a later age at the onset of seizures. These findings are consistent with those from previous studies [12]. Poor education was a predictor of negative outcome in previous studies [12]. Poor education may have some consequences and associations including lower income (that would restrict access to the resources) or different coping mechanisms in the patients. These should be investigated in future studies. Depression and anxiety had also negative effects on the prognosis in previous studies [12]; and age at onset affected the outcome either (pediatric populations showed a higher rate of seizure remission than that in adults) [12].

This implies that when a patient with PNES has a low education or their seizures start in adulthood we may want to consider special treatment strategies to improve their outcome; something that should be investigated and clarified in future studies. In addition, treatment of comorbid psychiatric problems may positively affect the outcome in these patients. However, some other factors with statistical significance in affecting the seizure outcome in previous studies [12], did not have associations with the seizure outcome in patients with PNES in our study. In the current study, gender, a dramatic seizure semiology (e.g., bizarre movements, incontinence, prolonged seizures, nocturnal seizures, and ictal injuries) or other dramatic features (e.g., history of abuse, history of head injury, seizure frequency, and hospital admissions) were not associated with the seizure outcome. These differences should also be investigated in future multi-center cross-cultural studies.

In conclusion, resources to treat patients with PNES are limited in Iran; however, more than half of the patients became free of seizures. Lower education, comorbid psychiatric problems, and a later age at the onset of seizures may affect the seizure outcome in patients with PNES. How the currently available and advised treatment strategies might affect the long-term outcome of patients with PNES should be investigated and clarified in future studies; for example, the way the treating physician presents the diagnosis to the patients and their care-givers may have some roles in the long-term outcome that should be clarified and the best (the most effective and practical) method of psychotherapy should also be clarified. Well-designed multi-center cross-cultural long-term studies should address factors associated with outcome in patients with PNES, considering that seizure frequency should not be the only outcome measure.

5. Limitations of the study

This was a retrospective study and recall bias is a probable limitation. Seizure frequency was the sole measure outcome in our study. Seizure outcome was investigated by a phone call interview with all the limitations associated with such a method (e.g., time constraints and willingness issues). Finally, this was a single center study.

Disclosures

Dr. Ali A. Asadi-Pooya, M.D., consultant: Cerebral Therapeutics, LLC and UCB Pharma; Honorarium: Hospital Physician Board Review Manual and Cobel Daru; Royalty: Oxford University Press (Book publication).

Fateme Ziyadee, M.D., reports no disclosures.

Contributions

Ali A. Asadi-Pooya, M.D.: Database development, study design, data collection, statistical analysis, manuscript preparation.

Fateme Ziyadee, M.D.: Data collection, statistical analysis, manuscript preparation.

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