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Why is psychogenic nonepileptic seizure diagnosis missed? A retrospective study☆

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ABSTRACT

Purpose: The aim of this retrospective study was to scrutinize factors that are associated with a delay in making the diagnosis of psychogenic nonepileptic seizures (PNES).
Methods: In this study, patients with PNES, who were investigated at Shiraz Comprehensive Epilepsy Center, Iran, from 2008 to 2019, were studied. We categorized the patients into the following: 1. those with a definite diagnosis of PNES in less than a year since the onset of their attacks; 2. those with a definite diagnosis of PNES later than 10 years since the onset of their attacks.
Results: During the study period, 330 patients were recorded. In 98 patients (30%), the diagnosis of PNES was made in less than a year since their seizure onset. In 67 patients (20%), the diagnosis of PNES was made later than 10 years since their seizure onset. Taking antiepileptic drugs (AEDs) (odds ratio (OR) = 6) and a history of ictal injury (OR = 3.6) had a positive association, and age at the onset (OR = 0.8) had an inverse association with a delay in receiving a definite diagnosis of PNES (p = 0.0001).
Conclusion: Some demographic variables (i.e., early age at the onset of seizures), patients' clinical variables (i.e., severe seizure manifestations such as ictal injury), and finally, some physician-related variables (i.e., prescribing AEDs) have significant associations with a delay in making a definite diagnosis of PNES.

1. Introduction

Psychogenic nonepileptic seizures (PNES) are relatively common occurrences in neurology clinics and epilepsy centers [1]. In spite of the fact that PNES are the most common and the most important differential diagnoses of epileptic seizures, diagnostic delay and misdiagnosis are common in daily practice; the average time to diagnosis of PNES is often about five to seven years [2,3]. Therefore, patients with PNES are often at risk of iatrogenic harm, as they are more likely to receive unnecessary treatments [e.g., antiepileptic drugs (AEDs)] and hospital admissions [4,5]. In addition, undiagnosed PNES put a significant burden on individuals and their families, as well as on healthcare system. It has been shown that most patients, who have PNES diagnosed with video-electroencephalography (EEG) monitoring, experience substantial subsequent reductions in healthcare utilization and costs [6,7].

A few studies have addressed the issue of diagnostic delay in patients with PNES before; these studies reported conflicting results [2,5,8,9]. On the other hand, early diagnosis of PNES has prognostic significance with respect to the outcome, as it can lead to an appropriate management strategy [1,10]. Therefore, identifying factors that delay the diagnosis of PNES may have significant clinical implications in formulating appropriate treatment plans for these patients. The purpose of this retrospective study was to scrutinize factors that are potentially associated with a delay in making the diagnosis of PNES in a large cohort of patients.

2. Patients and methods

In the current database retrospective study, all patients with PNES, who were investigated at Shiraz Comprehensive Epilepsy Center at Shiraz University of Medical Sciences, Iran, from 2008 to 2019, were studied. All patients had documented PNES by ictal recording during video-EEG monitoring. There were no exclusions. This is the only epilepsy care center in south Iran, and the only center equipped with video-EEG monitoring units; therefore, all suspected patients in the region are referred to this center for making a definite diagnosis of their paroxysmal events (i.e., epileptic vs. nonepileptic seizures) by their treating physicians. For this study, the diagnosis was made if a detailed clinical history was compatible with the diagnosis; attacks (seizures) were witnessed by the epileptologist, showing semiology typical of PNES while on video-EEG monitoring; and finally, no epileptiform

☆ The authors conducted the statistical analyses.
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activity was detected immediately before, during, or after the attack that had been captured on the ictal video-EEG recording. We obtained a detailed clinical history in order to investigate the coexistence of epileptic seizures (e.g., presence of other seizure types, different from what we had captured during their video-EEG monitoring, if their description was compatible with epileptic seizures). We reviewed the recorded interictal EEG carefully to search for any possible epileptiform discharges.

The epileptologist examined all patients, and if they consented to share their information in the database, it was used. We have kept all the data confidential. In the current study, we categorized the patients into two groups: 1. those with a definite diagnosis of PNES in less than a year since the onset of their attacks; 2. those with a definite diagnosis of PNES later than 10 years since the onset of their attacks.

Age, gender, age at seizure onset, seizure characteristics (semiology and frequency), factors potentially predisposing to PNES [e.g., a history of sexual abuse, a history of physical abuse (corporal punishment or any physical injury resulted from aggressive behavior towards the patient), academic failure (school dropout or repeated grades), family function (i.e., divorce, single parent, significant family disputes, etc.), past history of head injury, and a family history of seizures], and video-EEG recordings of all patients were recorded routinely. Demographic variables and pertinent clinical variables were summarized descriptively to characterize the study population. 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 value less than 0.05 was considered as significant. We conducted this study with the approval by the Shiraz University of Medical Sciences Review Board and the Ethics Committee.

3. Results

During the study period, 330 patients were recorded in our database. The sex ratio (female to male) of the patients was 1.89 (216:114). The mean age (± standard deviation) of the patients was 29 (± 10) years (range: 10 to 71). Duration of their PNES before reaching a definite diagnosis (± standard deviation) was 5.3 (± 7.4) years (range: 0 to 35 years). In 98 patients (30%), the diagnosis of PNES was made in less than a year since their seizure onset (early diagnosis). In 67 patients (20%), the diagnosis of PNES was made later than 10 years since their seizure onset (late diagnosis). The associations between a delay in making a diagnosis of PNES of more than 10 years and clinicodemographic characteristics of the patients in univariate analyses appear in Table 1. Age at the onset of seizures, seizure frequency, a history of ictal injury, having comorbid epilepsy, and taking AEDs were significantly associated with a late diagnosis of PNES in univariate analyses. We then executed a logistic regression analysis, evaluating these five variables. A history of ictal injury, taking AEDs, and age at the onset of seizures retained their significance within the model that was generated by regression analysis; 80.9% of the cases were correctly predicted by this model ($p = 0.0001$). Table 2 shows the results of the regression analysis.

Table 1
The associations between a delay in making a diagnosis of psychogenic nonepileptic seizures and clinicodemographic characteristics of the patients in univariate analyses.

Risk factor	Patients with an early diagnosis, # 98	Patients with a late diagnosis, # 67	p value
Sex ratio (F:M)	60:38	41:26	1.0
Age at onset (mean, years ± standard deviation)	26 ± 11	17 ± 9	0.0001
Seizure frequency (mean per month ± standard deviation)	57 ± 87	26 ± 50	0.01
Aura	65 (66%)	40 (60%)	0.4
Loss of responsiveness	76 (78%)	57 (85%)	0.3
Urine incontinence	8 (8%)	8 (12%)	0.5
Ictal injury	22 (22%)	30 (45%)	0.006
Generalized motor seizures	80 (82%)	63 (94%)	0.08
Akinetic seizures	15 (15%)	4 (6%)	0.08
History of significant head trauma	5 (5%)	4 (6%)	1.0
Family history of seizures	30 (31%)	22 (33%)	0.8
History of physical abuse	8 (8%)	7 (10%)	0.5
History of sexual abuse	7 (7%)	5 (7%)	1.0
History of family dysfunction	22 (22%)	23 (34%)	0.07
History of academic failure	7 (7%)	3 (4%)	0.7
Medical comorbidities	28 (29%)	26 (39%)	0.2
Comorbid epilepsy	10 (10%)	22 (33%)	0.001
Taking antiepileptic drugs	46 (47%)	56 (84%)	0.0001

4. Discussion

In the current study, considering the average time to diagnosis of PNES, which was more than five years, we categorized the patients into two groups: those with a definite diagnosis of PNES in less than a year since the onset of their attacks and those with a definite diagnosis of PNES later than 10 years since the onset of their attacks. We observed that one-fifth of the patients had a delay in receiving a definite diagnosis of PNES of more than 10 years. Previous studies, from both the developed and the developing countries, have also shown similar results [1,2,5,8,9]; hence, it is a universal phenomenon, and identifying factors that may be contributing to this is clinically important. In this large cohort of patients, we could identify three main factors that were associated with this unwanted practice of having a long delay in making a diagnosis of PNES. Taking AEDs (OR = 6) and a history of ictal injury (OR = 3.6) had a positive association, and age at the onset of seizures (OR = 0.8) had an inverse association with a delay in diagnosis. A previous study of 313 patients with PNES found that younger age, interictal epileptiform discharges in the EEG, and AED therapy were associated with longer delays; other patient factors were not associated with delays in diagnosis [9]. Their results are similar to our observations. Other smaller studies have reported some other significant variables, such as a history of head injury [2] or a history of psychological abuse [5]; these factors did not show any association with a delay in diagnosis of PNES in the current study. In one study, the number of AEDs tried was associated with a longer delay until diagnosis [11].

The main reason that patients with PNES are given unnecessary AEDs is that they are believed to have epilepsy [12]. In one previous study, we observed that some patients' historical factors (e.g., urine incontinence associated with seizures) have strong association with unnecessary treatment with AEDs in patients with PNES [13]. Therefore, one may reasonably speculate that AED use is simply a marker for other factors that make misdiagnosis more likely, such as ictal injury. However, in the current study, AED use and ictal injury were both significantly associated with delay in diagnosis of PNES in the regression analysis model that we generated, which makes this speculation less likely as the only link between AED use and delay in diagnosis. Physicians should be aware of the risks of prescribing an AED, and only make such a decision after making a definite diagnosis of epilepsy in a patient with a paroxysmal event. Interestingly, in one study, 46.8% of the patients reported complete or partial remission of their seizures after being treated with AEDs [14]. Hence, a favorable response to AEDs

Table 2
Factors associated with delay in diagnosis of psychogenic nonepileptic seizures in logistic regression analysis.

Variable	Odds ratio	95% confidence interval	p value
Taking antiepileptic drugs	6.109	2.304–16.197	0.0001
Age at the onset of seizures	0.859	0.805–0.918	0.0001
Ictal injury	3.672	1.336–10.090	0.01
Seizure frequency	0.994	0.986–1.002	0.1
Comorbid epilepsy	2.287	0.675–7.747	0.1

may be mistakenly interpreted as supporting a diagnosis of epilepsy, which could be associated with diagnostic delay.

A history of ictal injury, which also had a positive association with delay in diagnosis of PNES, may be mistakenly associated with epileptic seizures and may lead to misdiagnosis and mismanagement in clinical practice. In one study, we observed that more than one-third of patients with PNES reported having dramatic features (i.e., urinary incontinence and bodily injury) with their attacks [15]. Therefore, these semiological features should not be used as a marker of epilepsy in patients with paroxysmal events and seizures.

Age at the onset of seizures had an inverse association with a delay in diagnosis of PNES. We do not have a concrete explanation for this observation; but, physician factors may play a role here; it is possible that physicians dealing with the pediatric populations (e.g., pediatricians and pediatric neurologists) have less index of suspicion for the diagnosis PNES in patients with paroxysmal events than physicians who deal with adult populations.

Our study has some limitations. This was a retrospective study, and patient data came from a single institution. In addition, we did not investigate other important factors (e.g., psychiatric comorbidities). It is noteworthy to mention that we did not investigate some important physician-related factors (e.g., level of training and degree of suspicion for the diagnosis of PNES in patients with paroxysmal events) that may significantly contribute to the delay in making an appropriate diagnosis; but, other investigators had a similar perception on the importance of physician factors in contributing to delays in the diagnosis of PNES [9].

Unfortunately, delay in making a diagnosis of PNES is common and some factors may contribute to this delay. Based on our observations and also those from previous studies, we can conclude that some demographic variables (i.e., early age at the onset of paroxysmal events), patients' clinical variables (i.e., more severe seizure manifestations such as ictal injury), and finally, some physician-related variables (i.e., prescribing AEDs) have significant associations with a delay in making a definite diagnosis of PNES in patients with paroxysmal events. Considering the relatively high occurrence of PNES in neurology clinics, it is important that physicians involved in the diagnosis and management of patients with paroxysmal events receive enough training to be able to make an early and definitive diagnosis of the condition.

Declaration of Competing Interest

Ali A. Asadi-Pooya, M.D.: Honoraria from Cobel Daruo; Royalty: Oxford University Press (Book publication). Zahra Bahrami, M.D. and Maryam Homayoun, M.D.: none.

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