Epilepsy & Behavior 90 (2019) 119–121

Contents lists available at ScienceDirect

Epilepsy & Behavior

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

Risk factors for the use of antiepileptic drugs in patients with psychogenic nonepileptic seizures

Ali A. Asadi-Pooya [a,b,*], Zahra Bahrami [a]

[a] Neuroscience Research Center, Shiraz Medical School, Shiraz University of Medical Sciences, Shiraz, Iran
[b] Jefferson Comprehensive Epilepsy Center, Thomas Jefferson University, Philadelphia, PA, USA

ARTICLE INFO

Article history:
Received 16 October 2018
Revised 12 November 2018
Accepted 13 November 2018
Available online 22 January 2019

Keywords:
Antiepileptic drug
Psychogenic
PNES
Seizure

ABSTRACT

Purpose: The aim of this study was to investigate the frequency of antiepileptic drug (AED) use in patients with psychogenic nonepileptic seizures (PNES) and to characterize the patients' historical risk factors that may be associated with such a practice.
Methods: In this retrospective database study, all patients with PNES, who were investigated at Shiraz Comprehensive Epilepsy Center at Shiraz University of Medical Sciences, from 2008 to 2018, were studied. Patients with concomitant epilepsy or abnormal Electroencephalogram (EEG) were not included.
Results: Two hundred and seventy patients had the inclusion criteria; 162 patients (60%) were taking AEDs, and 108 (40%) were not taking any AEDs at the time of the diagnosis. Reporting auras (odds ratio: 0.5; 95% confidence interval (CI): 0.301–0.952; $p = 0.03$), having ictal or postictal urinary incontinence (odds ratio: 3.86; 95% CI: 1.36–10.94; $p = 0.01$), reporting a dysfunctional family (odds ratio: 1.75; 95% CI: 1.002–3.072; $p = 0.04$), and a longer duration of the condition before the diagnosis (odds ratio: 1.057; 95% CI: 1.005–1.112; $p = 0.03$) were significantly associated with AED use; 63.7% of the cases were correctly predicted by the model that was generated by regression analysis ($p = 0.0001$).
Conclusions: Patients with PNES are at great risk of receiving unnecessary AEDs, and some patients' historical factors (e.g., urine incontinence) have a strong association with this practice.

1. Introduction

Psychogenic nonepileptic seizures (PNES) are relatively common occurrences in epilepsy centers [1]. They consist of paroxysmal changes in responsiveness, movements, or behavior that superficially resemble epileptic seizures but lack a neurobiological origin similar to epileptic seizures and are not associated with electrophysiological epileptic changes [1]. Although PNES are the most common and the most important differential diagnoses of epilepsy, they are not well characterized and are therefore often not well-managed [2]. Epilepsy and PNES have a variety of differing symptoms and signs; however, none of them is pathognomonic to PNES [3]. Thus, sometimes, clinical differentiation of epilepsy from PNES proves to be difficult, and therefore, misdiagnosis is common. In one previous study of 350 adult patients with uncontrolled seizures, who were taking antiepileptic drugs (AEDs), 9% were proved to have PNES [4]. In another similar study in 198 children, this figure was 1.5% [5]. As a result, patients with PNES are at risk of iatrogenic harm, as they are more likely to receive unnecessary treatments (e.g., AEDs) [6]. This observation of the patients with PNES receiving unnecessary AEDs has been documented in many previous studies in different parts of the world [3,6,7].

Many factors may put the patients with PNES at risk of receiving unnecessary treatment with AEDs; misdiagnosis by the treating physician is probably the most important etiology. But, no study has ever investigated the patients' historical risk factors that may influence such a practice. The aim of this study was to investigate the frequency of AED use in patients with PNES and to characterize some of the patients' historical risk factors that may be associated with such a phenomenon.

2. Methods and materials

In this retrospective database study, all patients with PNES, who were investigated at Shiraz Comprehensive Epilepsy Center at Shiraz University of Medical Sciences, from 2008 to 2018, were studied. The diagnosis was made by a careful clinical assessment and documented by ictal recording during video-EEG monitoring. Patients with concomitant epilepsy or abnormal EEG (e.g., ictal or interictal epileptiform discharges) were not included.

The epileptologist interviewed all the patients, and if they agreed to share their information in the study, it was used. All the data were kept confidential. Age, gender, age at seizure onset, seizure semiology, seizure frequency, factors potentially predisposing to PNES [history of

* Corresponding author at: Neuroscience Research Center, Shiraz Medical School, Shiraz University of Medical Sciences, Shiraz, Iran.
E-mail address: aliasadipooya@yahoo.com (A.A. Asadi-Pooya).

https://doi.org/10.1016/j.yebeh.2018.11.009
1525-5050/

physical abuse (corporal punishment or any physical injury resulted from aggressive behavior towards the patient), sexual abuse (rape), child abuse (neglect or physical abuse), academic failure, head injury, 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 population. Initially, we performed univariate analyses using Pearson Chi-square, Mann–Whitney, Kolmogorov–Smirnov, and t-test. Variables that were significant ($p < 0.05$) were assessed in a logistic regression. Odds ratio and 95% confidence interval (CI) were calculated. p value less than 0.05 was considered as significant. This study was conducted with the approval by Shiraz University of Medical Sciences Review Board.

3. Results

During the study period, 325 patients were registered in our database. Two hundred and seventy patients had the inclusion criteria and were studied; 162 patients (60%) were taking AEDs in mono- (108 patients) or polytherapy (54 patients) regimens, and 108 (40%) were not taking any AEDs at the time of the diagnosis. The delay to diagnosis was three years or more in 118 patients (44%) (mean ± standard deviation: 4.7 ± 6.9 years); it was 10–35 years in 47 patients (17%). One hundred and seventy-eight patients (66%) reported having auras before their seizures; the most common auras were headache (40 patients; 15%), dizziness (13 patients; 5%), and palpitation (10 patients; 4%). The associations between the patients historical risk factors and AED use in univariate analyses appear in Table 1. Age at onset, reporting an aura before the seizures (inverse association), having urinary incontinence associated with the seizures, reporting a dysfunctional family, and a longer duration of the condition before the diagnosis were significantly associated with AED use in univariate analyses (Table 1). We then performed a logistic regression analysis, assessing these five variables. Reporting auras (odds ratio: 0.5; 95% CI: 0.301–0.952; $p = 0.03$), having ictal or postictal urinary incontinence (odds ratio: 3.86; 95% CI: 1.36–10.94; $p = 0.01$), reporting a dysfunctional family (odds ratio: 1.75; 95% CI: 1.002–3.072; $p = 0.04$), and a longer duration of the condition before the diagnosis (odds ratio: 1.057; 95% CI: 1.005–1.112; $p = 0.03$) remained significant; 63.7% of the cases were correctly predicted by the model that was generated by regression analysis ($p = 0.0001$). Age at onset ($p = 0.1$) was not a significant risk factor in the model.

Table 1
Association between patients historical risk factors and AED use in univariate analyses.

Risk factor	Patients taking AED(s), 162	Patients not taking AED, 108	p value
Gender (F:M)	100:62	72:36	0.4
Age at onset (years)	22.9 ± 9.8	25.8 ± 10.4	0.02
Age at diagnosis (years)	28.7 ± 9.9	28.8 ± 10.6	0.9
Duration of PNES	5.8 ± 7.7	3 ± 5.1	0.0001
Seizure frequency (per month)	33 ± 69	34 ± 61	0.9
Aura	98	80	0.01
Loss of responsiveness	142	91	0.2
Prolonged seizures (>30 min)	18	7	0.5
Urine incontinence	26	5	0.003
Ictal injury	56	26	0.059
Generalized motor seizures	140	94	0.3
History of significant head trauma	9	4	0.5
Family history of seizures	47	34	0.6
History of physical abuse	21	10	0.4
History of sexual abuse	16	8	0.5
History of child abuse	18	9	0.5
History of dysfunctional family	65	30	0.03
History of academic failure	12	6	0.6

4. Discussion

In this study, we observed that many of the patients with PNES had a long delay before reaching to the correct diagnosis, and the majority of them were receiving unnecessary treatment with AEDs. The main reason that patients with PNES are given unnecessary AEDs is that they are believed to have epilepsy [8]. In one study [9], it was observed that the number of AEDs tried was associated with a longer delay until diagnosis. Therefore, physicians involved in the management of patients with paroxysmal event (e.g., epilepsy, PNES, syncope, etc.) should have enough training, knowledge, and experience in making a diagnosis of PNES versus other possible differential diagnoses.

We also observed that reporting auras decreased the chance of being treated with AEDs (odds ratio: 0.5) while having ictal or postictal urinary incontinence was strongly associated with receiving AEDs (odds ratio: 3.86). Auras are often reported by patients with PNES (66% in this study) and also, by patients with epilepsy [3]. However, auras are more often nonspecific in patients with PNES compared with that in patients with epilepsy (authors' opinion). Headache was the most common aura in our study. In one previous study [10], the most common underlying etiology for ictal pain was PNES. However, epilepsy and migraine were also associated with this symptom. The authors concluded that, although ictal pain was not a specific or pathognomonic sign for PNES, its presence should raise suspicion for PNES [10]. Maybe, that is why reporting auras in patients with PNES in our study was associated with less probability of being treated by AEDs (since many patients reported headache as their auras). Having said that, we do not have any clear explanation for our observation that reporting auras by the patients with PNES decreased the chance of being treated with AEDs. Urinary incontinence during or after a seizure has often been associated with epileptic seizures, but one previous systematic review showed that urinary incontinence has no value in the differential diagnosis between epileptic seizures and PNES [11]. Therefore, this phenomenon should not be used as a marker for epileptic seizures and should not automatically lead to prescribing an AED for a patient with suspicious paroxysmal attacks.

Dysfunctional family was another factor associated with receiving AEDs in our patients with PNES (though not a strong one). Dysfunctional family may result in poor family support for the patient and may cause a suboptimal communication between physicians and patients (and caregivers); something that is important for taking a detailed history and making an accurate diagnosis by the physician. One previous study showed that patients with an inadequate primary support group and those who had tried many AEDs were most likely to have their diagnosis of PNES delayed by more than two years after the onset [12]. This should be explored in future studies. Longer duration of the condition before the diagnosis was also associated with AED use in patients with PNES (again, not a strong risk factor). It is not clear whether this is the cause or the effect of receiving AEDs in patients with PNES, and future studies should also shed light on this issue.

In conclusion, patients with PNES are at great risk of receiving unnecessary AEDs, and some patients' historical factors (e.g., urine incontinence) have strong association with this practice. Physicians should be aware of this risk and prescribe an AED only after making a definite diagnosis of epilepsy in a patient with a paroxysmal event. Interestingly, in one study of 47 patients with PNES, who were using AEDs, 22 patients (46.8%) reported complete or partial remission of their attacks [13]. Therefore, a favorable response to AEDs may be interpreted as supporting a diagnosis of epilepsy, which is associated with diagnostic delay. Physicians should keep in mind that patients with PNES may be vulnerable to placebo effects [13].

This study has some limitations including its retrospective design and lack of some important data such as psychiatric comorbidities of the patients. In addition, many other factors may play a role in the use of AEDs in patients with PNES (e.g., healthcare system, physicians'

knowledge, psychiatric disorders, etc.); we did not investigate these potential factors in this study.

Conflict of interest

Ali A. Asadi-Pooya, M.D.: Honoraria from Cobel Daru; Royalty: Oxford University Press (Book publication).

Acknowledgments

This study was in part supported by the National Institute for Medical Research Development Grant (No. 971003). We also thank the Neuroscience Research Center, Shiraz University of Medical Sciences for supporting this study.

References

[1] Asadi-Pooya AA, Sperling MR. Epidemiology of psychogenic nonepileptic seizures. Epilepsy Behav 2015;46:60–5.
[2] Kerr MP, Mensah S, Besag F, de Toffol B, Ettinger A, Kanemoto K, et al. International consensus clinical practice statements for the treatment of neuropsychiatric conditions associated with epilepsy. Epilepsia 2011;52:2133–8.
[3] Asadi-Pooya AA, Emami M. Demographic and clinical manifestations of psychogenic non-epileptic seizures: the impact of co-existing epilepsy in patients or their family members. Epilepsy Behav 2013;27(1):1–3.
[4] Asadi-Pooya AA, Emami M, Ashjazadeh N, Nikseresht A, Shariat A, Petramfar P, et al. Reasons for uncontrolled seizures in adults; the impact of pseudointractability. Seizure 2013;22(4):271–4.
[5] Asadi-Pooya AA, Emami M. Reasons for uncontrolled seizures in children; the impact of pseudointractability. Epilepsy Behav 2012;25(3):341–4.
[6] Valente KD, Alessi R, Vincentiis S, Santos BD, Rzezak P. Risk factors for diagnostic delay in psychogenic nonepileptic seizures among children and adolescents. Pediatr Neurol 2017;67:71–7.
[7] Asadi-Pooya AA, Tinker J. Delay in diagnosis of psychogenic nonepileptic seizures in adults: a post hoc study. Epilepsy Behav 2017;75:143–5.
[8] Müller T, Merschhemke M, Dehnicke C, Sanders M, Meencke HJ. Improving diagnostic procedure and treatment in patients with non-epileptic seizures (NES). Seizure 2002;11(2):85–9.
[9] Kerr WT, Janio EA, Le JM, Hori JM, Patel AB, Gallardo NL, et al. Diagnostic delay in psychogenic seizures and the association with anti-seizure medication trials. Seizure 2016;40:123–6.
[10] Asadi-Pooya AA, Asadollahi M, Sperling MR. Ictal pain: occurrence, clinical features, and underlying etiologies. Epilepsy Behav 2016;61:59–62.
[11] Brigo F, Nardone R, Ausserer H, Storti M, Tezzon F, Manganotti P, et al. The diagnostic value of urinary incontinence in the differential diagnosis of seizures. Seizure 2013;22(2):85–90.
[12] Rodríguez-Urrutia A, Toledo M, Eiroa-Orosa FJ, Salas-Puig X, Santamarina E, Fidel-Kinori SG, et al. Psychosocial factors and antiepileptic drug use related to delayed diagnosis of refractory psychogenic nonepileptic seizures. Cogn Behav Neurol 2014;27(4):199–205.
[13] Alessi R, Valente KD. Psychogenic nonepileptic seizures: should we use response to AEDS as a red flag for the diagnosis? Seizure 2014;23(10):906–8.