Original article

Epileptic Disord 2019; 21 (2): 192-6

Loss of responsiveness in psychogenic non-epileptic seizures

Ali A. Asadi-Pooya [1,2], Zahra Bahrami [1]

[1] Neuroscience Research Center, Shiraz Medical School, Shiraz University of Medical Sciences, Shiraz, Iran
[2] Jefferson Comprehensive Epilepsy Center, Department of Neurology, Thomas Jefferson University, Philadelphia, Pennsylvania, PA, USA

Received December 11, 2018; Accepted February 19, 2019

ABSTRACT – *Aims*. The aim of this study was to investigate the frequency of loss of responsiveness (LOR) in patients with psychogenic non-epileptic seizures (PNES) and to characterize the patients' clinical variables that may be associated with such a manifestation.
Methods. In this retrospective study, all patients with documented PNES, who were investigated at Shiraz Comprehensive Epilepsy Center at Shiraz University of Medical Sciences, from 2008 to 2018, were investigated.
Results. During the study period, data was available for 324/325 patients with PNES. In total, 275 patients (85%) reported LOR during their seizures, but this was not the case for 49 patients (15%). The model, generated by regression analysis, was shown to be significant (p=0.0001) and LOR could be predicted in 84% of the patients. Closed eyes during seizures (OR: 4.4; 95% CI: 2.101-9.235; p=0.0001) and seizure-associated injury (OR: 3.5; 95% CI: 1.402-8.686; p=0.007) were significantly associated with LOR based on the model.
Conclusion. Patients with PNES may frequently report LOR, which is significantly associated with seizure-related injuries. Therefore, it is important to apply appropriate management strategies for patients with PNES and LOR in order to prevent or decrease the possibility of any associated consequences, including ictal injury.

Key words: responsiveness, psychogenic, PNES, seizure, semiology

Transient loss of responsiveness (LOR) is a common presentation in primary care settings and emergency departments. Over 90% of instances of LOR are associated with either epileptic seizures, syncope, or psychogenic non-epileptic seizures (PNES); misdiagnosis rates are as high as 30% (Wardrope *et al*., 2018). Psychogenic non-epileptic seizures comprise paroxysmal changes in responsiveness, movements, or behaviour that seemingly look like epileptic seizures, but lack a neurobiological origin comparable to that of epileptic seizures and are not associated with electrophysiological epileptic changes (Asadi-Pooya and Sperling, 2015). Psychogenic non-epileptic seizures and epilepsy have different distinguishing signs and symptoms, but none are pathognomonic to either epilepsy or PNES (Müller *et al*., 2002; Asadi-Pooya and Emami, 2013; Asadi-Pooya and Sperling, 2015).

Correspondence:
Ali A. Asadi-Pooya
Neuroscience Research Center,
Shiraz Medical School,
Shiraz University of Medical Sciences,
Shiraz, Iran
<aliasadipooya@yahoo.com>

doi:10.1684/epd.2019.1044

In a previous study from the USA, 66% of the patients (47 out of 71) had LOR during their seizures (Baslet *et al*., 2017).

The aim of this study was to investigate the frequency of LOR in patients with PNES and to characterize the patients' clinical variables that may be associated with such a manifestation. We hypothesized that some clinical variables may affect the presence of LOR in patients with PNES (*e.g*. a family history of seizures may provide a basis for model learning [Reuber, 2009]). Determining the prevalence of LOR in PNES has significant clinical and diagnostic implications, as LOR may be used as a marker for epileptic seizures (mistakenly) in practice (Wardrope *et al*., 2018). In addition, the presence of LOR with seizures may be associated with an increased risk of morbidity (*e.g*. physical injury).

Materials and methods

Studied population

In this retrospective database study, all patients with documented PNES, who were evaluated and diagnosed at Shiraz Comprehensive Epilepsy Center at Shiraz University of Medical Sciences, from 2008 to 2018, were investigated. This is the only Comprehensive Epilepsy Center in south Iran and delivers services to a large number of people (a population of more than 11 million), both adults and children. In this centre, the epileptologist makes the diagnosis through a careful clinical assessment and ictal recording during video-EEG monitoring. A diagnosis of PNES is made if the detailed clinical history is compatible with diagnosis; seizures witnessed by the epileptologist showing semiology typical of PNES during video-EEG monitoring, and no epileptiform activity detected immediately before, during, or after the attack, captured on ictal video-EEG recording. We also routinely obtain a detailed clinical history in order to investigate the existence of concomitant epileptic seizures in patients (*e.g*. presence of other seizure types, different from those captured during video-EEG monitoring, if their description is compatible with epileptic seizures). We reviewed the recorded EEG of patients with documented PNES carefully to search for any possible epileptiform discharges. Patients with concomitant epilepsy or abnormal EEG were not excluded. The epileptologist examined all the patients and information was registered in a database and used according to consent.

Studied factors

Demographic variables (*i.e*. age, gender, marriage status), seizure characteristics (*i.e*. semiology and frequency, onset, and duration), ictal injury (any physical injury resulting as a direct consequence of seizures), factors potentially predisposing to PNES (history of physical abuse, sexual abuse, child abuse, dysfunctional family [*i.e*. divorce, single parent, significant family disputes, *etc*.], academic failure [school dropout or repeated grades], any medical comorbidities, and family history of seizures), and video-EEG recording of all patients were registered routinely. These data were obtained through a face-to-face interview with the patients and their care-givers; seizure characteristics (*e.g*. LOR) were corroborated by analysing ictal recordings during video-EEG monitoring.

Statistical analysis

Patients were divided into two groups based on their responsiveness at the time of the captured seizure during their video-EEG monitoring (if it was typical of their habitual seizures). Demographic variables and relevant clinical variables were summarized descriptively in order to characterize the study population. Initially, we performed univariate analyses using the Pearson Chi-square, Mann-Whitney, Kolmogorov-Smirnov, and t-test. Variables that were significant ($p<0.05$) based on univariate analyses were assessed according to logistic regression. Odds ratio (OR) and 95% confidence interval (CI) were calculated. P value less than 0.05 was considered as significant. This study was conducted with the approval of the Shiraz University of Medical Sciences Review Board.

Results

During the study period, data were available for 324 patients with PNES (out of 325), and these patients were studied further. Two hundred and seventy-five patients (84.8%) reported LOR during their seizures but this was not the case for 49 patients (15%). LOR was associated with two variables (*i.e*. closed eyes during seizures and ictal injury) based on univariate analyses (*table 1*). We then performed a logistic regression analysis to assess these two variables. The model, that was generated by regression analysis, was shown to be significant (p=0.0001) and LOR could be predicted in 84% of the patients. Based on the model, closed eyes (OR: 4.4; 95% CI: 2.101-9.235; p=0.0001) and ictal injury (OR: 3.5; 95% CI: 1.402-8.686; p=0.007) retained their significance.

Sixty-five patients had comorbid epilepsy (21 [32%] had idiopathic generalized epilepsy syndromes and 44 [68%] had focal epilepsies). When we excluded those with comorbid epilepsy, 221 patients out of 259 (85.3%) had LOR with their seizures; ictal injury

Table 1. Factors associated with loss of responsiveness during psychogenic non-epileptic seizures based on univariate analyses.

	Loss of responsiveness (275 patients) (*n*)	**Preserved responsiveness (49 patients) (*n*)**	***p* value**
Sex ratio (female: male)	176: 99	35: 14	0.3
Age (years)	29 ± 10	28 ± 12	0.7
Age at onset (years)	24 ± 10	24 ± 13	0.9
Duration of the condition (years)	5 ± 7	5 ± 7	0.6
Aura	170	36	0.1
Eyes closed during attacks	234	32	0.0001
Urinary incontinence	32	3	0.3
Generalized motor seizures	242	39	0.2
Akinetic seizures	25	8	0.1
Ictal injury	91	7	0.01
Seizure frequency per month	33 ± 65	43 ± 42	0.3
Nocturnal seizures	102	12	0.07
History of head injury	14	1	0.7
Family history of seizures	88	12	0.3
History of physical abuse	33	7	0.6
History of child abuse	29	3	0.4
History of sexual abuse	20	6	0.2
Dysfunctional family	99	12	0.1
Academic failure	23	2	0.3
Married	143	21	0.3
Medical comorbidities	70	18	0.1
Comorbid epilepsy	54	11	0.6
Taking antiepileptic drugs	178	30	0.6

(OR: 5.3; 95% CI: 1.567-18.250; p=0.007) and closed eyes during seizures (OR: 4.1; 95% CI: 1.778-9.765; p=0.001) were significantly associated with LOR (data on the entire population were similar; *see above*).

Discussion

In this study, we observed that 85% of the patients with PNES from Iran reported LOR associated with their seizures; this is a significantly higher rate than that reported in the study from the USA (Baslet *et al*., 2017) (66%; p=0.0002). Altered responsiveness during PNES is hypothetically a marker of lower emotional resilience or an inability to tolerate emotions among these patients (Baslet *et al*., 2017). Therefore, it is possible that the observed significant difference in the frequency of LOR among patients with PNES from Iran compared with those from the USA reflects their cultural differences and their different abilities to manage their emotions. However, since we do not know other potential differences between these two

populations (*e.g.* socio-demographic, economical, *etc.*), we cannot draw a firm conclusion. This should be studied in future well-designed international cross-cultural studies.

Video-EEG monitoring with ictal recording is the current gold standard test for the investigation of ictal alterations of responsiveness and for the differential diagnosis between epilepsy and PNES (Eddy and Cavanna, 2014). LOR should not be used as a marker for making a diagnosis of epileptic seizures. In order to make a documented diagnosis of PNES, history should be compatible with the diagnosis; seizures should be witnessed by a physician experienced in the diagnosis of paroxysmal events (with or without LOR), showing semiology typical of PNES during video-EEG monitoring, and no epileptiform activity should be detected immediately before, during, or after the event (Avbersek and Sisodiya, 2010; LaFrance *et al*., 2013).

The authors of the US study (Baslet *et al*., 2017) observed that married or partnered patients were more represented in the altered responsiveness group; this was not observed in our study. In addition, in the US study, patients with altered responsiveness were more likely to have a family history of seizures and LOR associated with traumatic brain injury (Baslet *et al*., 2017); such observations were also not observed in our study. While these differences could be due to socio-cultural factors, they might be clinically important and suggest the possibility that various psychopathological mechanisms account for the development of PNES in a Middle-Eastern country compared with those in a Western country. For example, the presence of *FKBP5* gene variants and early-life stress may increase the risk of stress-associated disorders (*e.g.* post-traumatic stress disorder) (Wang *et al*., 2018) and there might be genetic differences between patients from Iran compared with those from the USA. This should be investigated in future international genetic studies.

In the current study, we observed that most patients with LOR had closed eyes during their seizures (OR: 4.4) and that they were more likely to experience ictal injury (OR: 3.5). The first observation (*i.e.* closed eyes) is very much expected in patients with LOR and does not have a great clinical significance. However, ictal injury is a significant and serious consequence of PNES (Asadi-Pooya *et al*., 2014). Therefore, it is important to apply appropriate management strategies for patients with PNES and LOR in order to prevent or decrease the possibility of any associated consequences, including ictal injury. It has been suggested that "emotion management" may be an important therapeutic target for patients with PNES and LOR (Baslet *et al*., 2017).

In conclusion, patients with PNES may frequently report LOR, which may have important consequences, such as injuries. This study has some limitations including its retrospective design as well as a lack of some important data, such as psychiatric comorbidities of the patients. □

Acknowledgements and disclosures.

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.

Ali A. Asadi-Pooya MD has received honoraria from Cobel Daruo and royalties from Oxford University Press (book publication). Zahra Bahrami MD has no conflict of interest to declare.

References

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: 1-3.

Asadi-Pooya AA, Sperling MR. Epidemiology of psychogenic nonepileptic seizures. *Epilepsy Behav* 2015; 46: 60-5.

Asadi-Pooya AA, Emami M, Emami Y. Ictal injury in psychogenic non-epileptic seizures. *Seizure* 2014; 23: 363-6.

Avbersek A, Sisodiya S. Does the primary literature provide support for clinical signs used to distinguish psychogenic nonepileptic seizures from epileptic seizures? *J Neurol Neurosurg Psychiatry* 2010; 81: 719-25.

Baslet G, Tolchin B, Dworetzky BA. Altered responsiveness in psychogenic nonepileptic seizures and its implication to underlying psychopathology. *Seizure* 2017; 52: 162-8.

Eddy CM, Cavanna AE. Video-electroencephalography investigation of ictal alterations of consciousness in epilepsy and nonepileptic attack disorder: practical considerations. *Epilepsy Behav* 2014; 30: 24-7.

LaFrance WC, Baker GA, Duncan R, *et al*. Minimum requirements for the diagnosis of psychogenic nonepileptic seizures: a staged approach; a report from the International League Against Epilepsy Nonepileptic Seizures Task Force. *Epilepsia* 2013; 54: 2005-18.

Müller T, Merschhemke M, Dehnicke C, *et al*. Improving diagnostic procedure and treatment in patients with non-epileptic seizures (NES). *Seizure* 2002; 11: 85-9.

Reuber M. The etiology of psychogenic non-epileptic seizures: toward a biopsychosocial model. *Neurol Clin* 2009; 27: 909-24.

Wang Q, Shelton RC, Dwivedi Y. Interaction between early-life stress and FKBP5 gene variants in major depressive disorder and post-traumatic stress disorder: a systematic review and meta-analysis. *J Affect Disord* 2018; 225: 422-8.

Wardrope A, Newberry E, Reuber M. Diagnostic criteria to aid the differential diagnosis of patients presenting with transient loss of consciousness: a systematic review. *Seizure* 2018; 61: 139-48.

TEST YOURSELF

(1) What are the possible reasons for loss of responsiveness during psychogenic non-epileptic seizures?

A. Lower emotional resilience.
B. Reduced ability to tolerate emotions.
C. The socio-cultural background.
D. All of the above.

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".