Journal of Psychosomatic Research 111 (2018) 83–88

Contents lists available at ScienceDirect

Journal of Psychosomatic Research

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

Neuropsychiatric features of the coexistence of epilepsy and psychogenic nonepileptic seizures

Gislaine Baroni[a,d,e,*], William Alves Martins[a,d,e], Vitoria Piccinini[d], Marcelo Pereira da Rosa[f], Luciano de Paola[g], Eliseu Paglioli[c,e], Regina Margis[h], André Palmini[a,b,d,e]

[a] Post-Graduate Program in Medicine and Health Sciences, Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Brazil
[b] Department of Neurology, Faculty of Medicine, PUCRS, Brazil
[c] Department of Neurosurgery, Faculty of Medicine, PUCRS, Brazil
[d] Service of Neurology, Hospital São Lucas, PUCRS, Brazil
[e] Service of Neurosurgery, Hospital São Lucas, PUCRS, Brazil
[f] Porto Alegre Epilepsy Surgery Program, Hospital São Lucas, PUCRS, Brazil
[g] Fundação Universitária de Cardiologia, Brazil
[h] Epilepsy and Electrencephalography (EEG) Service, Hospital de Clínicas, Federal University of Paraná, Brazil

ARTICLE INFO

Keywords:
Conversion disorder
Diagnosis
Epilepsy
Psychogenic nonepileptic seizures
Video-EEG

ABSTRACT

Objective: To investigate demographic, epidemiologic and psychiatric features suggestive of the coexistence epilepsy (ES) and psychogenic nonepileptic seizures (PNES) that may contribute to precocious suspicion of the association.

Methods: In this exploratory study, all patients older than 16 years admitted to prolonged video-electroencephalogram monitoring were evaluated about demographic, epileptological and psychiatric features. Detailed psychiatric assessment using M.I.N.I.-plus 5.0, Beck Anxiety Inventory, Beck Depression Inventory and the Childhood Trauma Questionnaire (CTQ) was performed. Data were collected previous to the final diagnosis and patients with ES-only, PNES-only or coexistence of ES/PNES were compared.

Results: Of 122 patients admitted to epilepsy monitoring unit, 86 patients were included and 25 (29%) had PNES. Twelve (14%) had PNES-only, 13 (15%) had ES/PNES and the remaining 61 (71%) had only ES. A coexistence of ES and PNES was associated with clinical report of more than one seizure type ($p^{<}0.001$), non-specific white matter hyperintensities on MRI ($p < .001$) and a past of psychotic disorder ($p = .005$). In addition, these patients had significantly more emotional abuse and neglect ($p < .002$ and 0.001, respectively). Somatization (including conversion disorder) was the most common diagnosis in patients with PNES- only (83%) and co-existing of PNES and ES (69.2%), differentiating both from ES-only patients ($p < .001$).

Conclusion: The high prevalence of this coexistence ES/PNES in this study reinforces a need to properly investigate PNES, especially in patients with confirmed ES who become refractory to medical treatment with antiepileptic drugs. The neuropsychiatric assessment may help to diagnostic suspicion and in the planning of therapeutic interventions.

1. Introduction

Psychogenic nonepileptic seizures (PNES) are paroxysmal episodes without concomitant ictal electrical discharges, caused by a psychological dysfunction. They represent the most common cause of nonepileptic phenomena in adults, can be confused with epilepsy (ES) [1,2] and are categorized by the Diagnostic and Statistical Manual (DSM-5) as a functional neurological disorder of the conversion type [3]. The combination of ES and PNES represents quite well how neuropsychiatric interconnection and biopsychosocial vulnerabilities connect physical and psychological illnesses.

Neurologists need to differentiate epileptic from nonepileptic seizures on a regular basis. For instance, among patients referred for a first episode of loss of consciousness, 57% received a diagnosis of ES, 18% of PNES and 22% of a syncopal episode [4]. The prevalence of coexistence ES/PNES has been estimated to be 5 and 50% [5] and a precise diagnosis of ES, PNES or their coexistence remains a clinical challenge, inasmuch as timely diagnosis reduces chronicity and increases the likelihood of a favorable prognosis [6,7]. Once a diagnosis of PNES is established, accurate treatment may lead to remission or improvement

* Corresponding author at: Porto Alegre Epilepsy Surgery Program, Hospital São Lucas da PUCRS, Avenida Ipiranga 6690, Room 737, Porto Alegre 90610-000, RS, Brazil
E-mail addresses: gisbaroni@gmail.com, gislaine.baroni@acad.pucrs.br (G. Baroni).

https://doi.org/10.1016/j.jpsychores.2018.05.014
Received 14 January 2018; Received in revised form 24 May 2018; Accepted 24 May 2018

in 75–95% of patients, significantly reducing health care costs and overall morbidity [8,9].

Patients with co-existing ES and PNES are often excluded from PNES studies and in the last years only few studies differentiating patients with PNES-only from those with PNES + ES were published [10–15]. They were all retrospective and thus open to selection biases. This study aimed to investigate demographic, epidemiologic and psychiatric features suggestive of co-existing epilepsy (ES) and psychogenic non-epileptic seizures (PNES) that may contribute to precocious suspicion of the association.

2. Methods

2.1. Participants

This is a cross-sectional study. Patients were consecutively recruited from the inpatient VEEG monitoring unit of the Porto Alegre Epilepsy Surgery Program, Hospital São Lucas, PUCRS, between March 2014 and November 2015. Because only few centers in Brazil perform presurgical evaluation and epilepsy surgery through the public health system, referrals of people with refractory epilepsy are from general neurologists all over the country, through a 'high complexity procedure code'.

A total of 122 potential participants were admitted in the V-EEG monitoring unit for (1) diagnostic investigation/classification of seizures; (2) optimization of antiepileptic drugs (AEDs) for refractory ES and (3) evaluation for eligibility to ES surgery.

All patients were approached for participation prior to stabilizing the diagnosis. Twenty-five patients were excluded: ten for significant limitation in adaptive behavior or mental retardation, nine for previous epilepsy surgery, four because of acute psychosis during evaluation and two for severe language deficits. Ninety-seven were evaluated, prior to a diagnosis related to their seizures.

This study was approved by the local ethics committee and written informed consent was obtained from all participants and no monetary incentive was provided for participation.

2.2. Procedures

Participants were informed that this research would evaluate their seizure type(s) and received an explanation about their possible diagnoses (ES, PNES or a combination of both). Two different groups of examiners, who were blind to each other's findings, obtained neuropsychiatric and epileptological data prior to final diagnosis.

Neuropsychiatric evaluation was performed by the senior author (GB), a certified psychiatrist. Demographic variables included gender, age, marital status, ethnics, education and occupation. Age at seizure onset, duration of illness, number and type of antiepileptic drugs (AEDs), as well as description of the type of clinical events were obtained from patients and relatives. Seizure frequency was assessed by historical recall by patients and family members, for whom we asked to perform an estimate of seizure frequency for 3 months prior to the evaluation. Seizure triggers included sleep deprivation, stress, menstrual cycle variation, alcohol and drug use.

The Mini International Neuropsychiatric Interview plus– M.I.N.I. (DSM-IV) 5.0 [16], probed the main psychiatric diagnoses in axis I. In addition, M.I.N.I.-plus tool also analyses presence of antisocial personality disorder, which is the only axis II diagnosis assessed. Beck Anxiety Inventory (BAI) [17] and Beck Depression Inventory II (BDI II) [18] scales evaluated severity of anxiety and depression symptoms. Childhood Trauma was measured using Childhood Trauma Questionnaire (CTQ) [19]. History of seizure triggers, previous personal contact with epilepsy and family history of psychiatric disorders were obtained during interview.

Prolonged V-EEG monitoring was recorded digitally on a 21-channel polygraph (Siemens-Elema), with electrodes placed according to the 10–20 system. Time under Video-EEG monitoring, therefore, varied from each patient, since it is our practice to capture all typical seizures or events reported by the patients and their family members. Duration of recordings ranged from 24 to 178 h and was extended until all typical attacks were registered. Time under Video-EEG monitoring, therefore, varied from each patient. The latter was routinely reviewed with caregivers or relatives to assure a typical spell. During recording, no atypical spells were captured. Activation methods were used in a case-by-case basis, including hyperventilation, photic stimulation, sleep deprivation and partial or total withdraw of AEDs. Verbal suggestion or placebo was not used to induce PNES. If the typical seizures could not be recorded, patients would receive an inconclusive diagnosis and be excluded from the study. Epileptological data included the presence of focal or diffuse background slowing interictal as well as localization ictal epileptiform discharges. These were classified as lobar: frontal, temporal and other. MRI was classified as normal, lesional or presenting nonspecific white matter alterations.

When evaluation was concluded, two senior neurologists (AP, LP) and a senior psychiatrist (GB) reviewed all data. Definitive diagnosis, including putative localization of the epileptogenic zone, when feasible, was based on the convergence of multimodal localizing data, including clinical history, ictal scalp EEG and MRI. Ictal events were classified as epileptic or non-epileptic.

Following this initial selection, we excluded 11 further cases: 8 (8.2%), which did not present a seizure or a typical paroxysmal episode on V-EEG, therefore precluding an unequivocal diagnostic confirmation, and 3 subjects that had documented disorders other than ES or PNES: factitious disorder or syncopal episodes.

All 86 patients, in whom it was possible to establish a diagnosis of PNES-only, ES-only or co-existing ES/PNES, through V-EEG recording of typical episodes, validated by clinical history and confirmed by family members or patients were included.

2.3. Definition of specific groups

- Group ES-only: Diagnosis was made when a patient presented ictal epileptiform discharges during a seizure.
- Group PNES-only: During a typical episode, V-EEG did not show epileptiform discharges or change in baseline background – despite muscle artifacts– nor electroencephalogram (EEG) abnormalities.
- Group co-existing ES/PNES: V-EEG with typically ictal and interictal epileptiform discharges during ES, associated with documentation of at least one PNES, validated as a typical attack.

2.4. Statistical analysis

Data are presented as mean ± standard deviation (SD) or median and interquartile range for continuous variables and as absolute and relative frequencies for categorical variables. For comparison between groups, Chi-square and one-way analysis of variance (ANOVA) adjusted by Bonferroni test or Kruskal-Wallis tests were used. To use the Bonferroni correction in non-parametric data, logarithmic transformation was applied. Statistical analyses were performed by SPSS v 21.0 and statistical significance was set at $p < 0.017$.

3. Results

Demographic characteristics are summarized in Table 1. Mean age at presentation was 33.7 ± 11.5 (16 to 62) years and patients with PNES-only were younger at evaluation than those ES-only ($p = .01$). Female patients comprised 70% of the sample and predominated in both PNES groups ($p = .01$).

Time under V-EEG monitoring did not differ between groups. ES-only were recorded in 61 patients (71%), while the other 25 (29%) had PNES. Thirteen (52%) of the latter had both ES and PNES.

Age at seizure onset did not differ among the groups. Onset of each seizure semiology was assessed. Epileptic seizures preceded PNES in all

Table 1
Demographic characteristics.[a, b, c]

Variables	PNES-only (n = 12)	ES/PNES (n = 13)	ES-only (n = 61)	P
Gender – n (%)				0.01
Male	1 (8.3)	1 (7.7)	24 (39.3)	
Female	11 (91.7)[a]	12 (92.3)[b]	37 (60.7)	
Age at evaluation (years) – mean ± SD	25.4 ± 12.9 *	31.5 ± 10.8	35.8 ± 10.7	0.01
Ethnics – n (%)				> 0.99
Caucasian	8 (66.7)	9 (69.2)	32 (52.5)	
Afro-descendent	1 (8.3)	1 (7.7)	3 (4.9)	
Asiatic	1 (8.3)	1 (7.7)	11 (18.0)	
Mixed	2 (16.7)	2 (15.4)	15 (24.6)	
Occupation – n (%)				
Student	8 (66.7)[c]	1 (7.7)	5 (8.2)	0.001
Housewife	0 (0.0)	2 (15.4)	4 (6.6)	
Unemployed	2 (16.7)	3 (23.1)	13 (21.3)	
Employed	2 (16.7)	4 (30.8)	21 (34.4)	
Disability allowance	0	3 (23.1)	13 (21.3)	
Retired	0	0	5 (8.2)	

ES = epileptic seizures; PNES = psychogenic nonepileptic seizures.
[a] PNES only versus ES.
[b] ES/PNES versus ES.
[c] PNES versus ES only and ES/PNES - statistically significant at the 0.017 level.

Table 2
Epilepsy features.

Variables	PNES-only (n = 12)	ES/PNES (n = 13)	ES-only (n = 61)	P
Age of seizure on set – md (P25 – P75)	16 (11–29)	7 (1–17)	10 (5.5–19)	0.07
Duration of illness – md (P25 – P75)	3.5 (1.3–7.5)[a]	22 (10.5–27)	21 (12 – 31)	< 0.001
Frequency of seizures – n (%)				0.02
Daily	10 (83.3)	9 (69.2)	21 (34.4)	
Weekly	2 (16.7)	1 (7.7)	19 (31.1)	
Monthly	0 (0.0)	3 (23.1)	17 (27.9)	
Very rarely	0 (0.0)	0 (0.0)	4 (6.6)	
More than one type of seizure – n (%)				< 0.001
Yes	3 (25.0)	13 (100)[b]	8 (13.1)	
No	9 (75.0)	0 (0.0)	53 (86.9)	
Focal slowing on interictal EEG – n (%)				< 0.001
Yes	2 (16.7)	6 (46.2)	48 (78.7)[c]	
No	10 (83.3)	7 (53.8)	13 (21.3)	
Seizure localization – n (%)				0.10
Frontal	–	3 (23.1)	9 (14.8)	
Temporal	–	5 (38.5)	42 (68.9)	
Other	–	5 (38.5)	10 (16.4)	
MRI – n (%)				0.001
Lesional	2 (16.7)	4 (30.8)	44 (72.1)[c]	
Non-lesional	6 (50.0)	4 (30.8)	11 (18.0)	
Nonspecific white matter hyperintensities	4 (33.3)	5 (38.5)	6 (9.8)	
Number of AEDs – n (%)				0.46
1	4 (33.3)	2 (15.4)	10 (16.4)	
2	2 (16.7)	6 (46.2)	24 (39.3)	
3	3 (25.0)	2 (15.4)	19 (31.1)	
4 or more	3 (25.0)	3 (23.1)	8 (13.1)	
Polytherapy (two or more AEDs)	8 (66.7)	11 (84.6)	51(83.6)	0.36

AEDs- Antiepileptic drugs; EEG- electroencephalogram; ES- epileptic seizures; MRI-magnetic resonance imaging; PNES- psychogenic nonepileptic seizures; V-EEG- video-electroencephalogram.
[a] PNES only versus ES.
[b] ES/PNES versus ES only and PNES.
[c] ES versus PNES and ES/PNES- statistically significant at the 0.017 level.

patients with co-existing ES and PNES (median 7 × 26.9 years, respectively) and PNES took a mean of 16.5 years to arise after seizure onset. Patients with PNES had seizure onset in early adulthood (16 years). However, time from onset of seizures to specialized care was shorter in patients with PNES-only compared to ES-only and ES + PNES. All 13 with co-existing ES and PNES reported several types of seizures, whereas 56 (87%) with ES-only and 9 patients with PNES-only (75%) reported only one type of attack ($p < .001$). Only two patients had more than two semiologies, one in the ES group and one in the coexisting ES plus PNES group. PNES-only patients had a higher frequency of the seizures than other groups ($p = .02$). Number of AEDs before diagnosis was similar ($p = .36$). Epileptological features are shown in Table 2.

Electroencephalographic abnormalities served as the basis for patient classification. The seizure localization frontal, temporal or other did not differ between the three groups and background slowing helped to discern patients with ES-only from those with PNES-only ($p < .001$).

MRI showed well-defined epileptogenic lesions in 44 (72.1%) patients with ES-only compared to 4 (30.8%) with ES/PNES and 2 (16.7%) with PNES- only ($p < .001$). Furthermore, five additional patients with both diagnoses (38.5%) had non-specific white matter hyper-intensities.

The PNES group showed more psychiatric diagnoses, independent of considering PNES as a core syndrome or as co-morbidity. Patients with ES only had a distinct psychiatric profile from the groups with PNES ($p = .009$), in which 43 (70.5%) had at least one psychiatric diagnosis, predominantly depressive disorder (34.4%). In contrast, a psychiatric disorder was present in all PNES patients, even after excluding somatoform disorders. We used the Childhood Trauma Questionnaire (CTQ) to assess and confirm history of abuse (Childhood emotional neglect, childhood physical negligence, childhood sexual abuse, childhood emotional abuse, childhood physical abuse). Psychiatric and somatic features are shown in Table 3.

Somatization (including conversion disorder) was the most common diagnosis in patients with PNES- only (83%) and co-existing of PNES and ES (69.2%), differentiating both from ES-only patients ($p < .001$). No other conversion disorder was found in our sample (i.e. functional movement disorders). Bipolar disorder ($p = .03$), antisocial personality disorder ($p = 0.04$), posttraumatic stress disorder (PTSD) ($p = .04$) and a past of psychosis ($p = .005$) were more prevalent in co-existing of PNES and ES patients, although only the latter reached our prespecified significance. However, anxiety disorders as a whole were observed in

Table 3
Psychiatric features.

Variables	PNES-only (n = 12)	ES/PNES (n = 13)	ES-only (n = 61)	P
Psychiatric comorbidities (with somatization disorder)-n (%)	12 (100)[a]	13 (100)[b]	43 (70.5)	0.009
Psychiatric comorbidities (without somatization disorder, which was classified as PNES)-n (%)	12 (100)[a]	13 (100)[b]	43 (70.5)	0.009
Depression disorder	2 (16.7)	4 (30.8)	21 (34.4)	
Bipolar disorder	4 (33.3)	5 (38.5)	7 (11.5)	0.03
Panic disorder	3 (25.0)	1 (7.7)	9 (14.8)	
Agoraphobia disorder	1 (8.3)	2 (15.4)	10 (16.4)	
Social phobia disorder	1 (8.3)	1 (7.7)	12 (19.7)	
Specific phobia disorder	1 (8.3)	3 (23.1)	7 (11.5)	
Obsessive-compulsive disorder	1 (8.3)	1 (7.7)	4 (6.6)	
PTSD	1 (8.3)	3 (23.1)	2 (3.3)	0.04
Psychotic disorder, past	1 (8.3)	5 (38.5)[d]	4 (6.6)	0.005
Eating disorders	1 (8.3)	0 (0.0)	0 (0.0)	0.04
Generalized anxiety disorder	5 (41.7)	5 (38.5)	14 (23.0)	
Antisocial disorder	0 (0.0)	2 (15.4)	1 (1.6)	0.04
Somatization disorder	10 (83.3)[a]	9 (69.2)[b]	4 (6.6)	< 0.001
BAI	14(9–22)	21(14–36)	11(6–24)	0.04
BDI II	6(2.5–13)	21 (9–30)	10(4–21.5)	0.03
Number of psychiatric drugs-n (%)				0.002
0	2 (16.7)	4 (30.8)	37 (60.7)[e]	
1	4 (33.3)	2 (15.4)	16 (26.2)	
2	6 (50.0)[a]	5 (38.5)[b]	5 (8.2)	
3 or more	0 (0.0)	2 (15.4)	3 (4.9)	
Classification of psychiatric drugs – n (%)				
Antidepressants	5 (41.7)	8 (61.5)	19 (31.1)	0.11
Antipsychotics	8 (80.0)[c]	6 (66.7)	5 (20.8)	0.002
Childhood trauma				
Emotional neglect	2(16.7)	7 (53.8)[d]	10 (16.4)	0.001
Physical negligence	1(8.3)	4 (30.8)	10 (16.4)	0.31
Sexual abuse	5 (41.7)	6 (46,2)	15 (24.6)	0.19
Emotional abuse	6 (50.0)	8 (61.5)[b]	11 (18.0)	0.002
Physical abuse	1 (8.3)	5 (38.5)	12 (19.7)	0.16
Family history of psychiatric illness – n (%)	6 (50.0)	7 (53.8)	30 (49.2)	
Previous contact with epilepsy – n (%)	7 (58.3)	8 (61.5)	28 (45.9)	
Seizure triggers – n (%)	10 (83.3)	9 (69.2)	42 (68.9)	
Physical symptoms – n (%)	12 (100)	12 (92.3)	42 (68.9)	0.02
Gastrointestinal	6 (50.0)	4 (33.3)	15 (35.7)	
Fatigue	7 (58.3)	7 (58.3)	11 (26.8)	0.04
Chronic pain	11 (91.7)[c]	6 (50.0)	10 (24.4)	< 0.001
Migraine	8 (66.7)	10 (83.3)	30 (73.2)	

Abbreviations: ES = epileptic seizures; BAI = Beck Anxiety Inventory; BDI II = Beck Depression Inventory II; PNES = psychogenic nonepileptic seizures; PTSD = posttraumatic stress disorder.

[a] PNES only versus ES.
[b] ES/PNES versus ES.
[c] PNES versus ES only and ES/PNES.
[d] ES/PNES versus ES only and PNES.
[e] ES versus PNES and ES/PNES- statistically significant at the 0.017 level.

all groups, including a high prevalence of specific phobia (fear of having a seizure), spontaneously reported. Finally, subjects with ES/PNES had the highest load (higher scores in BDI e BAI) of depressive symptoms and higher anxiety levels than the ES-only group. There were no statistical differences among the groups in family history of psychiatric illness, previous contact with ES and seizure triggers.

Most patients with PNES, co-existing with ES or not, were using two or more psychoactive drugs, with antipsychotics as the most common drug, found in 80% of patients with PNES-only (p = .002). Patients with ES-only used less psychoactive drugs (excluding AEDs) than other groups.

Physical symptoms were classified as somatic complaints, present in all patients with PNES (p = .02). Chronic pain was the most common physical complaint and fatigue contributed to differentiate patients with PNES from patients with ES-only.

4. Discussion

PNES remain a common discovery in epilepsy monitoring units and evaluation for ES surgery [20], as shown in our study. Despite meticulous evaluation, around 8% of patients did not reach a final diagnosis, as typical attacks were not recorded, as already reported [21]. PNES were recorded in 29% of patients and coexisted with ES in 15% off all sample, highlighting the relevance of the association.

There seems to be a number of features that suggest a higher probability of the presence of co-existing ES and PNES. Patients with co-existing ES and PNES present more than one well-established seizure pattern, nonspecific white matter hyperintensities on MRI, and established psychiatric diagnoses or symptoms, including bipolar disorder, PTSD, antisocial disorder, a past history of psychosis and more marked levels of anxiety and depression. Because patients with combined ES and PNES variably came from the ES-only or PNES-only groups, this tentative profile emerged from those variables in which patients with combined disorders significantly differed from both only groups (Fig. 1). To our knowledge, this is the first study attempting to characterize patients with co-existing ES and PNES prior to definite diagnosis. Although further studies are needed, the findings provide potential clinical and physiopathologic clues to this comorbidity.

This study has confirmed that PNES predominate in female patients and that although age at evaluation did not set apart patients with ES and co-existing disorders, it did differentiate patients with PNES-only from those with ES-only, the former being in average 10 years younger [10,22].

Epileptological features have proved important to raise suspicion of PNES, isolated or combined with epileptic seizures. Time from onset of seizures to a definite diagnosis was 3.5 years in patients with PNES only. This is similar to some [23,24], but not all previous reports [25]. The relatively short period of time until diagnosis probably reflects a heightened suspicion for PNES and the fact these patients have very frequent seizures despite AED polytherapy. The longer period of time to diagnose co-existing ES and PNES have been described previously, and

ES/PNES: Clinical report of the more than one type of seizure. Psychiatric analysis revealed more common presence of bipolar disorders, PTSD, antisocial personality disorder disorder and past of psychotic disorder and higher depression and anxiety intensities. Also, nonspecific white matter alterations in neuroimaging.

PNES-only: Younger patients at evaluation, less time from onset of seizures to specialized evaluation, daily seizures and physical symptoms more than other groups.

ES-only: Older at evaluation, lentification on EEG, and presence of structural lesions on MRI. Psychiatric comorbidities may be found in up to 70% of patients, however, different ones from PNES patients. Also, there is a lower burden of psychiatric illnesses.

Abbreviations: EEG= electroencephalogram; ES= epileptic seizures; MRI= magnetic resonance imaging; PNES= psychogenic nonepileptic seizures; PTSD= posttraumatic stress disorder.

Fig. 1. Main features of each group.
Abbreviations: EEG = electroencephalogram; ES = epileptic seizures; MRI = magnetic resonance imaging; PNES = psychogenic nonepileptic seizures; PTSD = posttraumatic stress disorder.

it has been stated that ES always start before PNES [26,27].

Clinical information remains relevant and may help distinguish patients with co-existing ES and PNES. Daily seizures despite appropriate AEDs and multiple seizure types may contribute both to the suspicion of PNES and ES as to early referral for V-EEG.

This study does not confirm the association with particular topographic epilepsy diagnosis and combined ES/PNES as Reuber et al. [28] and differs from previous studies pointing either to an association with frontal lobe epilepsy [29] and with right-hemispheric electrographic seizures [13].

Focal neuroimaging abnormalities are one of the hallmarks of focal epilepsies and not surprisingly predominated in patients with ES only. Nonspecific subcortical white matter abnormalities were significantly more frequent in patients with combined ES and PNES. This should, however, be seen with caution, since such white matter abnormalities are very common in MRIs and usually carry little to no clinical significance. However, they were also found in 50% of patients with PNES only, supporting the statement that functional and structural brain abnormalities may be more frequent in patients with PNES-only than in the general population [30,31].

Prevalence of axis I diagnoses was similar in PNES groups, irrespective of the understanding of PNES as an individual entity or a comorbid somatoform disorder. The increased number of psychiatric diagnoses in the co-existing ES/ PNES and PNES-only groups, compared to patients with ES-only, has also been reported [11]. Nevertheless, this study has found that 70% of the latter also had psychiatric comorbidities, strongly supporting that psychiatric disorders should be aggressively sought in people with refractory epilepsies [32].

Both groups of PNES shared a high frequency of the somatoform disorders followed by generalized anxiety disorder, which may be clue for such diagnoses. Interestingly, a past history of psychosis was significantly more frequent in ES/PNES patients. In addition, there was a tendency for the association of bipolar disorder, PTSD and antisocial disorder to the coexistence of ES/PNES, showing the complex interaction of individual vulnerability, impact of epilepsy on brain neurodevelopment and brain risk of neurobehavioral comorbidities [33]. Such associations may be confirmed in larger studies.

Traumatic experiences during childhood and adolescence may trigger maladaptive behaviors, as crucial brain developments are undertaken in these periods [34].Despite historically related to sexual abuse, our finding corroborate to other studies that did not show a direct relation [35,36]. On the other hand, emotional neglect scores were higher in patients with PNES associated with ES. This highlights the need for a thorough assessment of this factor when evaluating and treating such patients. Emotional neglect surprisingly differentiated ES/PNES from other groups and may reflect a lack of emotional support during crucial childhood periods, perhaps triggered by parental overloading due to epilepsy issues or even a higher emotional need from these patients. Further studies may shed light on this finding.

The higher number of psychiatric drugs in PNES patients with and without epilepsy suggests the higher prevalence of psychiatric comorbidities. Co-existing ES and PNES displayed a higher intensity of anxiety and depression in BAI and BDI II scores, in addition to the well-established relationship of hospitalization and anxiety [37]. This reinforced the relevance to assess whether PNES recorded during the V-EEG is similar to other previously presented by the patient monitoring, as done in this study.

Multiple associations of physical symptoms with somatoform disorders, seizure triggers and adverse events of medications make it even more challenging to ascertain about their presence. All these physical complaints were more frequent in patients with PNES only, but only chronic pain significantly distinguished these patients.

Rates of AED polytherapy were similar in the three groups, probably reflecting the variable combination of refractory seizures and the use of some AEDs to treat psychiatric disorders. Thus, facing a diagnosis of PNES it is crucial to define the co-existence of PNES and ES an associated psychiatric diagnosis, which responds to AEDs, before withdrawing these medications.

Our present findings somewhat mirror the ones from our recent systematic review. Factors such as female predominance among both PNES groups, age at presentation (ES/PNES older at evaluation), high prevalence of psychiatric disorders in ES/PNES with predominance for somatoform disorders and generalized anxiety were also found in the present study. There was no association to any epilepsy features that could distinguish ES/PNES from ES, compatible with the contradictory evidence shown in our review [38].

Our study has limitations and strengths. The findings cannot be fully generalized because they apply to a highly selected population seen at a tertiary epilepsy center. However, these are exactly the patients in need of specialized attention and therefore our findings may aid in their management. In addition, this is a small sample of patients with PNES and ES, which implies that further studies will have to confirm our findings. Another issue is the lack of evaluation of Axis II (personality disorders) diagnosis other than antisocial personality disorders. Although recollection of seizure frequency is flawed and may be subject to biases, this is usually the method used to assess seizure control in clinical practice and may therefore reflect reality. Nonetheless, retrospective analysis of seizure frequency is a limitation of our study. On the other hand, the fact that psychiatric and neurological variables were assessed previous to the final diagnosis clearly set this exploratory study apart by limiting selection and interpretation biases.

In conclusion, co-existing ES and PNES should be thought as a diagnostic possibility in patients with seemingly refractory epilepsy. Clues to the association are more than one well-established seizure pattern, a higher burden of emotional symptoms and psychiatric diagnoses may be useful for diagnostic suspicion, including a past history of psychosis and marked levels of anxiety and depression. Conversely, patients with PNES-only are younger, have shorter disease duration and daily seizures. Further developments may help physicians to recognize this association and unveil new therapeutic approaches for co-existing ES and PNES.

Statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflict of interest

None of the authors have financial or other relationships that might lead to a perceived conflict of interest. Drs. Palmini and de Paola have received honoraria from Novartis, Abbott, Janssen-Cilag and UCB for lectures and participation in advisory boards, which do not bear upon this publication. Dra. Margis has received honoraria from Sanofi and EMS for lectures, which do not bear upon this publication. Drs. Baroni, Piccinini, Martins, Rosa and Paglioli have nothing to disclose.

Disclosures

Drs. Palmini and de Paola have received honoraria from Novartis, Abbott, Janssen-Cilag and UCB for lectures and participation in advisory boards, which do not bear upon this publication. Dra. Margis has received honoraria from Sanofi and EMS for lectures, which do not bear upon this publication. Drs. Baroni, Piccinini, Martins, Rosa and Paglioli have nothing to disclose.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Authors' individual contributions

Study concept: AP, GB.
Data collection: AP, GB, LP, WM, VP.
Manuscript drafting for content: AP, GB, MPR, WM.

Manuscript revision for content: GB, EP, RM, LP, VP.
Study supervision: AP.

References

[1] W.C. LaFrance Jr., G.A. Baker, R. Duncan, 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 54 (2013) 2005–2018.
[2] S.R. Benbadis, E. O'Neill, W.O. Tatum, et al., Outcome of prolonged video-EEG monitoring at a typical referral epilepsy center, Epilepsia 45 (2004) 1150–1153.
[3] American Psychiatry Association, Diagnostic and Statistical Manual of Mental Disorders - DSM-5, 5th ed., American Psychiatric Association, Washington, 2013.
[4] I.A. Kotsopoulos, M.C. Krom, F.G. Kessels, et al., The diagnosis of epileptic and non-epileptic seizures, Epilepsy Res. 57 (2003) 59–67.
[5] S.R. Benbadis, V. Agrawal, W.O. Tatum, How many patients with psychogenic nonepileptic seizures also have epilepsy? Neurology 57 (2001) 915–917.
[6] L. Selwa, J. Geyer, N. Nikakhtar, et al., Nonepileptic seizure outcome varies by type of spell and duration of illness, Epilepsia 41 (2000) 1330–1334.
[7] T.S. Walczak, S. Papacostas, D.T. Williams, et al., Outcome after diagnosis of psychogenic nonepileptic seizures, Epilepsia 36 (1995) 1131–1137.
[8] R. Martin, F. Gilliam, M. Kilgore, et al., Improved health care resource utilization following video-eeg-confirmed diagnosis of nonepileptic psychogenic seizures, Seizure 7 (1998) 385–390.
[9] A.B. Ettinger, O. Devinsky, D.M. Weisbrot, et al., A comprehensive profile of clinical, psychiatric, and psychosocial characteristics of patients with psychogenic nonepileptic seizures, Epilepsia 40 (1999) 1292–1298.
[10] J.O. Elliott, C. Charyton, Biopsychosocial predictors of psychogenic non-epileptic seizures, Epilepsy Res. 108 (2014) 1543–1553.
[11] C.A. Galimberti, M.T. Ratti, R. Murelli, et al., Patients with psychogenic nonepileptic seizures, alone or epilepsy-associated, share a psychological profile distinct from that of epilepsy patients, J. Neurol. 250 (2003) 338–346.
[12] K. Turner, A. Piazzini, V. Chiesa, et al., Patients with epilepsy and patients with psychogenic non-epileptic seizures: video-EEG, clinical and neuropsychological evaluation, Seizure 20 (2011) 706–710.
[13] B.D. Wissel, A.K. Dwivedi, T.E. Gaston, et al., Which patients with epilepsy are at risk for psychogenic nonepileptic seizures (PNES)? A multicenter case-control study, Epilepsy Behav. 61 (2016) 180–184.
[14] F. Mari, C. Di Bonaventura, N. Vanacore, et al., Video-EEG study of psychogenic nonepileptic seizures: differential characteristics in patients with and without epilepsy, Epilepsia 47 (2006) 64–67.
[15] S. Chen-Block, B.W. Abou-Khalil, A. Arain, et al., Video-EEG results and clinical characteristics in patients with psychogenic nonepileptic spells: the effect of a co-existent epilepsy, Epilepsy Behav. 62 (2016) 62–65.
[16] D.V. Sheehan, Y. Lecrubier, K.H. Sheehan, et al., The mini-international neuropsychiatric interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10, J. Clin. Psychiatry 59 (1998) 22–33.
[17] A.T. Beck, N. Epstein, G. Brown, et al., An inventory for measuring clinical anxiety: psychometric properties, J. Consult. Clin. Psychol. 56 (1988) 893–897.
[18] A.T. Beck, R.A. Steer, G.K. Brown, Manual for the Beck Depression Inventory-II, Psychological Corporation, San Antonio, 1996.
[19] R. Grassi-Oliveira, J.C. Pezzi, L.M. Stein, Translation and content validation of the childhood trauma questionnaire into Portuguese language, Rev. Saúde Pública 40 (2006) 249–255.
[20] A.M. Strutt, S.W. Hill, B.M. Scott, et al., Motivation, psychopathology, locus of control, and quality of life in women with epileptic and nonepileptic seizures, Epilepsy Behav. 22 (2011) 279–284.
[21] K. Lobello, J.C. Morgenlander, R.A. Radtke, et al., Video/EEG monitoring in the evaluation of paroxysmal behavioral events: duration, effectiveness, and limitations, Epilepsy Behav. 8 (2006) 261–266.
[22] J. Kuyk, W.A. Swinkels, P. Spinhoven, Psychopathologies in patients with nonepileptic seizures with and without comorbid epilepsy: how different are they? Epilepsy Behav. 4 (2003) 13–18.
[23] LaFrance W Jr, Baird GL, Barry JJ, et al. Multicenter pilot treatment trial for psychogenic nonepileptic seizures:a randomized clinical trial. JAMA Psychiatry 2014;71:997–1005.
[24] W. LaFrance Jr., R. Ranieri, Y. Bamps, et al., Comparison of common data elements from the managing epilepsy well (MEW) network integrated database and a well-characterized sample with nonepileptic seizures, Epilepsy Behav. 45 (2015) 136–141.
[25] M. Reuber, G. Fernández, J. Bauer, et al., Diagnostic delay in psychogenic nonepileptic seizures, Neurology 58 (2002) 493–495.
[26] T.R. Henry, I. Drury, Non-epileptic seizures in temporal lobectomy candidates with medically refractory seizures, Neurology 48 (1997) 1374–1382.
[27] O. Devinsky, F. Sanchez-Villasenor, B. Vazquez, M. Kothari, K. Alper, D. Luciano, Clinical profile of patients with epileptic and nonepileptic seizures, Neurology 46 (1996) 1530–1533.
[28] M. Reuber, A. Qurishi, J. Bauer, et al., Are there physical risk factors for psychogenic non-epileptic seizures in patients with epilepsy? Seizure 12 (2003) 561–567.
[29] J.A. Pillai, S.R. Haut, Patients with epilepsy and psychogenic non-epileptic seizures: an inpatient video-EEG monitoring study, Seizure 21 (2012) 24–27.
[30] M. Reuber, G. Fernández, J. Bauer, et al., Interictal EEG abnormalities in patients with psychogenic nonepileptic seizures, Epilepsia 43 (2002) 1013–1020.
[31] H. Merskey, M. Trimble, Personality, sexual adjustment, and brain lesions in patients with conversion symptoms, Am. J. Psychiatry 136 (1979) 179–182.
[32] A.M. Kanner, J. Parra, M. Frey, et al., Psychiatric and neurologic predictors of psychogenic pseudoseizure outcome, Neurology 53 (1999) 933–938.
[33] J.J. Lin, M. Mula, B.P. Hermann, Uncovering the neurobehavioural comorbidities of epilepsy over the lifespan, Lancet 380 (2012) 1180–1192.
[34] C.M.S. Martins, S.M.C. Tofoli, C.V.W. Baes, M.R. Juruena, Analysis of the occurrence of early life stress in adult psychiatric patients: a systematic review, Psychol. Neurosci. 4 (2011) 219–227.
[35] L.M. Arnold, M.D. Privitera, Psychopathology and trauma in epileptic and psychogenic seizure patients, Psychosomatics 37 (1996) 438–443.
[36] J. Jedrzejczak, K. Owczarek, J. Majkowski, Psychogenic pseudoepileptic seizures: clinical and electroencephalogram (EEG) video-tape recordings, Eur. J. Neurol. 6 (1999) 473–479.
[37] N.J. Botega, M.R. Bio, M.A. Zomignani, et al., Mood disorders among inpatients in ambulatory and validation of the anxiety and depression scale HAD, Rev. Saúde Pública 29 (1995) 355–363.
[38] G. Baroni, V. Piccinini, W.A. Martins, et al., Variables associated with co-existing epileptic and psychogenic nonepileptic seizures: a systematic review, Seizure 37 (2016) 35–40.