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Review

Variables associated with co-existing epileptic and psychogenic nonepileptic seizures: a systematic review

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ABSTRACT

Purpose: Epileptic seizures (ES) have many mimickers, perhaps the most relevant being psychogenic nonepileptic seizures (PNES). The picture is even more challenging when PNES are associated with ES in a given patient. The aim of this research paper was to delineate the demographic, epileptological and psychiatric profile of that specific population.

Methods: A systematic review was carried out from 2000 to 2015 for articles in English, French, Italian, Spanish and Portuguese in PUBMED and EMBASE. Cohort or case-control studies reporting prospective or retrospective original data comparing patients with co-existing ES and PNES with those who had PNES only and ES only have been included. In retained studies, the presence of PNES was confirmed by video-electroencephalography (V-EEG). Forty-eight abstracts were identified.

Results: Nine studies were retained. Most showed that female gender predominated in both groups with PNES. Patients with co-existing ES and PNES take higher number of antiepileptic drugs (AEDs) than PNES alone. Two studies showed association of concomitant ES and PNES with earlier age of seizure onset. Localizing EEG features and ES type were evaluated in only two studies and their association with either group was inconclusive. Somatoform, conversion or cluster B personality disorders were more frequent in subjects with PNES than with ES.

Discussion: Patients with concomitant ES and PNES are highly heterogeneous, challenging differentiation on clinical grounds. A diagnosis of conversion or somatoform, anxiety disorders, and the use of a higher number of AEDs than psychiatric medications may have an association with co-existing ES and PNES.

Further studies are warranted to differentiate patients who only have PNES from those with co-existing ES and PNES.

1. Introduction

Epileptic (ES) and psychogenic nonepileptic seizures (PNES) share a number of features, despite distinct mechanisms and clinical meaning. Both lead to physical, social and occupational impairment, meet with significant stigmatization and are associated with a high prevalence of comorbid psychiatric disorder [1,2]. PNES are the most common cause of nonepileptic ictal events and present as unintentional physical symptoms mediated by psychological factors, usually triggered by stressful situations [3,4]. DSM-V has

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PNES as a conversion disorder with functional neurological symptoms and several studies relate PNES to maladaptive behavior, personality traits and major psychiatric comorbidities, particularly depressive, or anxiety and somatoform disorders [4–6]. Thus, PNES are likely to be the result of a complex interaction between psychiatric disorders, coping style and cerebral vulnerability [2,7].

Some patients, however, have both epileptic seizures and PNES. Ictal semiology varies accordingly and a correct differential diagnosis between epilepsy, a psychiatric disorder manifesting PNES or a combination of both is pivotal to their management. Because only ES respond to antiepileptic drugs (AEDs), failing to diagnose PNES or the co-existence of ES and PNES, may lead to unnecessary modifications and/or escalation of AEDs regimens to the point that patients with frequently recurring episodes may be totally sedated. Given such practical relevance, it is somewhat surprising that such association is of uncertain prevalence - reported figures vary widely from 5.3 to 50% of patients with confirmed PNES [8,9] - and the factors associated with the co-occurrence of ES and PNES are far from clear.

To set the stage for future research, we have carried out a systematic review of articles published since the year 2000, which aimed to uncover demographic, epileptological and psychiatric factors suggestive of co-existing ES and PNES in the same patient.

2. Method

2.1. Search strategy and study selection

A systematic review using the methodology outlined in the Cochrane Handbook for Systematic Reviewers was carried out [10]. Data were reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [11]. Several synonyms for PNES were initially identified and then a systematic search for articles in English, French, Italian, Spanish and Portuguese in PUBMED (818 abstracts) and EMBASE (1057) abstracts, from January 2000 to October 2015, was carried out. Search words/terms were pseudoseizure OR pseudoseizures* OR pseudoseizures epilepsy OR psychogenic seizures OR psychogenic non-epileptic OR psychogenic nonepileptic OR psychogenic non-epileptic OR psychogenic nonepileptic seizures OR psychogenic non-epileptic seizures OR psychogenic non-epileptic seizures OR nonepileptic attack disorder AND (epilepsy OR seizures).

The senior author reviewed all abstracts and selected, for further review, those reporting (I) original research (II) related to diagnostic evaluation of (III) adult patients (IV) and the association of ES and PNES. Abstracts thus selected underwent a second round of independent review by the senior author (GB) and the co-author VP to confirm initial findings. When both reviewers agreed that pre-requisites had been met, the abstract was retained. When abstract data were unclear, the full article was assessed for further analysis.

Forty-eight abstracts were identified and then full texts independently reviewed by one certified psychiatrist (GB, senior author) and one certified neurologist (LP). A third reviewer (AP) resolved divergences in data interpretation. Based upon the main goals, these 48 manuscripts were further 'screened' and retained if they (a) reported prospective or retrospective original observational data or were cohort or case-control studies with ten or more subjects; (b) compared patients with co-existing ES and PNES with those with PNES only and ES only; (c) had a confirmation of the diagnosis of PNES by video-electroencephalography (V-EEG) monitoring, with or without induced events. A concomitant diagnosis of ES in these studies was based either upon ictal confirmatory recordings or convergent semiology and interictal epileptic discharges. Nine articles [12–20] met the inclusion criteria. A list of excluded articles can be found as supplementary material (S1). The screening process is described in Fig. 1.

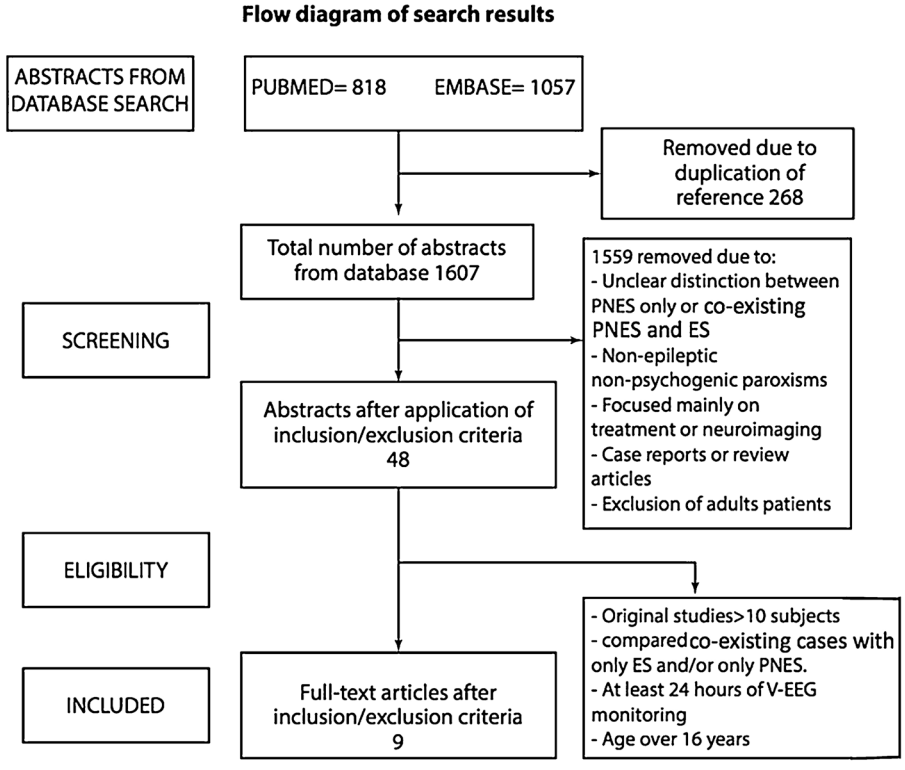

Fig. 1. Psychogenic Nonepileptic Seizure (PNES); Epileptic Seizure (ES).

2.2. Quality of evidence assessment and data collection:

Two independent reviewers (GB and WM) accessed the level of evidence using the Oxford [21] and the Grading of Recommendation Assessment Development and Education (GRADE) [22] criteria for the level of evidence quality. The Oxford criteria is a 5- level-grading system for the scientific literature, with ascending reliability ranging from level 1 through 5 [21]. The GRADE is classified into 4 levels of evidence: A, B, C, and D, with ascending credibility [22]. All reviewed studies had Oxford level 4 evidence for the distinction between mixed seizure types and ES only or PNES only. Three articles met GRADE C and 4 GRADE D level of evidence. Any divergences between the grading of the two reviewers were resolved by a third reviewer. Pediatric studies were excluded.

Data collection was performed independently by GB and WM, and articles were initially divided into three categories: (1) those comparing groups of patients who had associated ES and PNES with those with PNES only [12,14,15,17], (2) those comparing groups of patients who had co-existing ES and PNES with those with ES only [18,19], and (3) those comparing patients with co-existing ES and PNES with those with ES only and PNES only [13,16,20]. Assessed variables included gender, age at evaluation, age at seizure onset, duration of the seizure disorder, time to correct diagnosis, V-EEG localization of the epileptic foci (when applicable), use of AEDs, use of psychiatric medication and comorbidities.

A formal meta-analysis could not be performed due to the extreme heterogeneity of data within the articles. Instead, the studies were analyzed and descriptive and comparative data presented.

3. Results

Nine articles were included and summarized in Table 1. Seven were characterized as observational studies, three prospectives [12–14] and four retrospectives [15–18], and the others are case-control studies [19,20].

3.1. Demographic factors

3.1.1. Gender

Female patients indistinctly predominated in both PNES groups, whether or not co-existing with ES [12,13,15–17], except in the study of D'Alessio et al., [14], in which this predominance was in those with PNES only. In all the studies, women accounted for approximately 70% of the sample in the PNES groups, and when compared with patients with ES only, those in the association ES and PNES group had a clear female predominance ($p < 0.001$) [18]. This differed from a more balanced gender distribution in patients with ES. Male gender, therefore, suggested ES only, but gender alone cannot distinguish PNES from co-existing ES and PNES in female patients.

3.1.2. Age at examination

Seven studies evaluated age at examination and a single study found that patients with co-existing ES and PNES were younger than those with PNES only [17]. Additional demographic factors, including education, marital status and race have been considered but not fully evaluated.

3.2. Epileptological factors

3.2.1. Age at seizure onset

Two studies have linked early onset with co-existing ES and PNES: Galimberti et al., [20] found that ES start earlier ($p = 0.0001$) whilst early onset was a predictor of ES associated with PNES (as opposed to PNES only) and in another study suggesting that seizure onset before age 15 could be a risk factor for either ES only or concomitant ES and PNES [15].

3.2.2. Duration of the seizure disorder or years to diagnosis

Three studies [12,13,20] failed to find an association between the final diagnosis and the duration of the seizure disorder. The others had conflicting results, either finding that shorter [15,17] or longer [14,16] disease duration was associated with a diagnosis of PNES only. Multivariate logistic regression showed that the number of years with events predicted PNES alone, with an escalation of 10% of diagnostic probability for each year before V-EEG diagnostic confirmation [16]. The scant data leads to a confusing picture.

3.2.3. Localization of the irritative and ictal onset zones in the scalp EEG

In a large, controlled study, Reuber and colleagues [18] compared patients with a diagnosis of co-existing ES and PNES and a group with PNES only for physical factors that could be associated with either. There was no predilection of magnetic resonance imaging abnormalities and localization or lateralization of epileptiform EEG abnormalities for one hemisphere in either group [18]. Another study used a case-control strategy to compare ictal and interictal EEG findings in subjects with ES only versus those with association of ES and PNES and has found that the latter tended to have a frontal focus, whereas the former a temporal focus [19].

3.2.4. Antiepileptic drug use

Multivariate logistic regression showed that patients with co-existing ES and PNES are significantly more prone to be treated with more than one AED than patients with PNES only – with an additional odds ratio of 2.55 for each additional AEDs ($p = 0.02$) [15]. A higher number of AEDs in patients with co-existing ES and PNES has also been reported in other studies [12,13,17].

3.3. Psychiatric factors

3.3.1. Psychiatric comorbidity

The extent to which PNES are considered as a diagnosis on its own or a psychiatric comorbidity is debatable. In a study prospectively evaluating patients with DSM IV TR criteria, 52% of those with ES only and 100% of those with PNES had some psychiatric disorder. High prevalence notwithstanding, psychiatric disorders did not contribute to differentiate among the three groups [13]. Many patients with ES only were shown to have anxiety or depressive disorders, whereas dissociative, somatoform or cluster B personality disorders were more frequent in those with PNES. One study found an increased number of psychiatric diagnoses in the combined ES and PNES (mean = 1.47) and PNES only (mean = 1.35) groups, compared with patients with ES only (mean = 1.00) ($p < 0.001$) [20]. Whenever PNES were present, in both ES + PNES and PNES only groups, the most frequent Axis I diagnosis was somatoform disorders followed by anxiety disorders, while on Axis II there was a high incidence of cluster B personality disorders.

In the ES groups, the most frequent diagnoses were mood disorders and cluster C disorders. In the latter, obsessive-compulsive and dependent personality disorders were predominant. Another study has found that at least one DSM IV psychiatric disorder had been diagnosed in patients with PNES [14]. When considering PNES as a nuclear syndrome including both conversion and dissociation, conversion symptoms did not differ between both PNES groups, although dissociative symptoms were more

Table 1
Articles included in our study for review.

Study	Country/ year	Design	Number of patients in each group (%)	Aims
Elliot et al. [16]	USA 2014	Observational retrospective	All = 689 PNES only = 324 (47%) PNES and ES = 84 (12%) ES only= 281 (41%)	To explore/understand of the unique biological -biomedical (gender, number of years with events, history of head injury as well a somatic comorbidities), psychological and social factors (married, history of physical/sexual abuse) associated with a continuous V-EEG confirmed diagnosis of PNES.
Hoepner et al. [15]	Germany 2014	Observational retrospective	All= 114 PNES only= 73 (64%) PNES and ES = 41 (36%)	To analyze clinical data and current medication profiles (AEDs and psychotropic drugs) in a comparatively sample of patients with PNES with and those without additional epileptic seizures.
Asadi-Pooya et al. [12]	Iran 2013	Observational prospective	All = 176 Without ES and family history of ES = 103 (58.5%) With ES but without a family history of ES = 19 (10.8%) With family history of ES but no ES = 54 (30.7%) Excluded patients with both ES and a family history of epilepsy.	To investigate the demographic and clinical manifestations of PNES in patients suffering from PNES alone in comparison with two other groups of patients with PNES: those with concomitant ES and those with a family history of ES. Demographic and clinical factors analyzed: Age, gender, education, age at seizure onset, seizure type and semiology, seizure frequency and associated factors.
Pillai & Haut.19	USA 2012	Retrospective case-control	All = 117 PNES and ES = 39 (33.3%) Controls = 78 (66.6%)	To compare the ictal and interictal EEG characteristics of patients with ES and PNES events and patients ES alone admitted for V-EEG. Examine if specific seizures syndromes were more usually in subjects with ES and PNES.
Turner et al. [13]	Italy 2011	Observational prospective	All = 53 PNES only = 22 (41.5%) PNES and ES = 10 (18,9%) ES only = 21 (39.6%) - Excluded patients with mental retardation.	To compare the prevalence of psychiatric disorder and cognitive deficits in patients with ES and PNES and patients with ES without PNES.
Mari et al. [17]	Italy 2006	Observational retrospective	All = 110 PNES only = 85 (87.3%) PNES and ES = 25 (22, 7%)	To define the differential clinical characteristics between patients with PNES and patients with ES and PNES. Variables reviewed: Age, gender, clinical features, antiepileptic therapy, age of onset, time to diagnosis, pathological history.
D'Alessio et al. [14]	Argentina 2006	Observational prospective	All = 43 PNES only = 24 (55.8%) PNES and ES = 19 (44.2%) - Excluded patients with mental retardation.	To describe similarities and differences in epidemiological, psychiatric and semiological variables between patients with PNES only and patients with ES and PNES.
Reuber et al. [18]	Germany 2003	Retrospetive case-control	All = 300 PNES only = 210 (70%) PNES and ES = 90 (30%)	To examine which biological or epileptological factors affect the risk of PNES in patients with concurrent epilepsy.
Galimberti et al. [20]	Italy 2003	Observational prospective	All: 138 PNES only = 31 (22.5%) PNES and ES = 38 (27.5%) ES = 69 (50%) - Excluded patients with mental retardation.	To identify a psychological profile of patients with psychogenic nonepileptic seizures (PNES) that is possibly distinct from that of subjects affected by epileptic seizures (ES) alone and to detect the possible differences between the clinical features and psychological profile of patients affected by PNES alone and those of subjects in whom PNES are associated with epileptic seizures (ES/PNES patients).

Psychogenic Nonepileptic Seizure (PNES), Epileptic Seizure (ES) Video-electroencephalography (V-EEG).

frequent in those who had PNES only. When analyzing current or past comorbidities one or more Axis I diagnoses were present in 88% of the sample, particularly somatoform (such as chronic pain and autonomic dysfunction), affective and post-traumatic stress disorders. Clusters B and C personality disorders were also highly prevalent in both groups. However, patients who had only PNES were more severely affected than patients with co-existing ES and PNES, as indexed by the need for psychiatric medication and hospital admission [14].

On the other hand, studies focused on retrospective analyses of medical charts showed similar psychiatric profiles between mixed and PNES only patients, particularly the total number of psychiatric comorbidities and the presence of depressive disorders [15,16]. In fact, the only psychiatric predictor of 'pure PNES' was anxiety disorder [16].

3.3.2. Use of psychiatric medication

The number of psychiatric medications apparently added to the distinction. Patients with both conditions were prescribed less

psychotropic medication compared to those with PNES only [12,14]. In one study, one third of patients used psychiatric medication, and the number tended to increase toward those with PNES only [15]. Moreover, multivariate logistic regression found that the difference between the number of AEDs and psychiatric drugs had a strong predictive value: patients with co-existing ES and PNES use a higher number of AEDs than psychiatric drugs (OR = 6.77; 95% CI = 1.06-43.2; $p = 0.04$) [15].

3.4. Level of evidence

Summary of the level of evidence can be seen in Table 2.

4. Discussion

It was not possible to find any systematic review leading to clinical data that might characterize the association of ES and PNES. Thus, it proved challenging to review the putative distinctive features of patients with co-existing ES and PNES that could distinguish this population both from patients with ES only and, more importantly, from those with PNES only. We did identify papers describing clinical features that could raise suspicion of mixed pictures, yet a traditional meta-analysis was not feasible due to lack of standardization of the data. Our main finding was that available data are insufficient to delineate sets of demographic, epileptological and psychiatric variables that could reliably single out patients with concomitant ES and PNES. However, reports in these last 15 years have provided some suggestive factors that could be starting points for future research.

From a host of demographic factors, only gender suggested an association. Women with ES have an additional risk to also have PNES, confirming the overall higher prevalence of PNES in women [23,24]. However, because such predominance was equally seen in patients with PNES only and in those with co-existing ES and PNES, gender alone does not help to single out the latter in women.

Incidence peaks are distinct in ES and PNES. Whereas that of ES is bimodal, peaking in both children and elders, PNES is more common between the second and fourth decades [3]. This notwithstanding, our review produced only one study in which age was associated with concomitant ES and PNES [15]. Specifically, onset of seizure before age 15 was a risk factor for the co-existing pictures. A study published prior to this review also found earlier age of onset in patients with ES, either alone or combined with PNES [25].

The extreme variability excludes time to diagnosis as a reliable diagnostic clue, as refractoriness is a hallmark of PNES and thus may lead to faster V-EEG referral, the availability of which, however, can vary substantially in resource-limited countries. This does not allow taking this variable into account [12,20].

A recent case-control study by Pillai and Haut [19] has found an association between frontal lobe epilepsy (FLE) and combined ES and PNES in contrast with patients with a temporal focus, who tended to have ES only. This finding was not independently confirmed [18] and could be related to ascertainment bias, as patients with co-existing ES and PNES were specifically searched over a period of ten years in the epilepsy monitoring unit database, whereas the ES only group consisted of consecutive admissions to the unit over a much shorter period. Furthermore, because comorbid anxiety and depression are more common in temporal lobe epilepsy than in FLE [26], the suggestion of a preferential association between FLE and PNES should be regarded with caution. In fact, our review indicates that it is not currently possible to establish any reliable association between PNES and the topography of epileptic abnormalities.

Another aspect analyzed in some studies was the predictive value of number of AEDs. It emerged that patients with associated ES and PNES tended to use more AEDs [12,13,15,17]. In contrast, although frequent, the use of psychiatric medications less impressive in mixed than in 'pure PNES' patients [12,14]. Furthermore, there are data suggesting a strong predictive value for an additional diagnosis of ES in patients with PNES when the number of AED is higher than that of psychiatric medication [15]. This obviously should not be used diagnostically, but rather be seen as a preliminary finding that could help in the suspicion of combined ES and PNES. Specific studies adjusting for the duration and severity of both the epilepsy and the psychiatric disorders associated with PNES are needed. Moreover, this finding may reflect the specialty to which the patient was initially referred to primary diagnosis of a psychiatric disorder may raise suspicion of a diagnosis of PNES when the patient also presents with ES, thus potentially limiting the introduction of additional AEDs. Likewise, from the neurologist's perspective, recurrent seizures will often lead to AED escalation, even when breakthrough spells actually represent PNES. In short, our review has found a suggestion that the amount of psychiatric medication *per se* is not helpful in the distinction between ES only and co-existing ES and PNES. However, the use of a higher absolute number of AEDs than of psychiatric medications may suggest that, in addition to comorbid psychiatric disorders of ES, such patients also have PNES.

Finally, although psychiatric comorbidities are common in ES [27,28], patients who also have PNES have an even higher burden of psychiatric disabilities. There are multiple potential mechanisms underlying PNES, leading to its conceptualization as a heterogeneous entity [29]. Having epilepsy may actually be a 'risk factor' for PNES, due to psychosocial factors and a high prevalence of psychiatric disorders [23]. Thus, we frame PNES in a continuum ranging from a single psychiatric disorder with a predominance of conversion or dissociative symptoms to a broader neuropsychiatric disorder with a complex interrelation between brain abnormalities related to epilepsy – including the often comorbid mood and anxiety disorders – and the somatic, conversion and dissociative symptoms prominent in PNES.

Because the prevalence of comorbid psychiatric disorders in epilepsy is high – greater than 50% in one study [13], even the impressive finding that at least one psychiatric disorder was present in all patients with PNES [13,14,20] does not define the presence of a psychiatric disorder *per se* as a risk factor for co-existing ES and PNES.

Neurobehavioral comorbidities of epilepsy have been recently reviewed [26]. Although psychiatric symptoms are often associated with temporal lobe epilepsy, these authors point out that they are also seen in other epileptic conditions and that abnormalities in brain structure may increase risk not only for ES, but also for other cognitive and psychiatric disorders. Additional factors are also relevant to understand the relation between vulnerability and co-existing PNES. For instance, learning difficulty, often associated with earlier ES onset also increases the risk for combined ES and

Table 2
Oxford and GRADE level of evidence.

Reference	Study type	Oxford [21] level of evidence	GRADE [22] level of evidence
D'Alessio et al. [14]	Prospective case series	3b	C
Mari et al. [17]	Retrospective case series	4	D
Turner et al. [13]	Prospective cohort	3b	C
Pillai &Haut [19]	Retrospective case-control	4	D
Asadi-Pooya et al. [12]	Prospective cohort	3b	C
Hoepner et al. [15]	Retrospective case series	4	D
Elliot et al. [16]	Retrospective case series	4	D
Reuber et al. [18]	Retrospective case-control	4	D
Galimbert et al. [20]	Prospective case-control	3b	C

PNES [30]. Furthermore, when both entities co-exist, ES almost always precede the onset of PNES [23] raising important issues related to physiopathological mechanisms underlying psychiatric comorbidities of epilepsy. Crucial issues are the determinants of which psychiatric comorbidity will prevail in a given epileptic patient and what is the putative role of localization of epileptic abnormalities and etiology in this presentation We believe these considerations illustrate a pressing issue in neuropsychiatric interface that may shed light on why patients with a given disorder can develop another. Specifically related to the topic reviewed here, prospective studies analyzing the three distinct groups (ES only, PNES only and combined ES/PNES) from a developmental, neurological and behavioral perspective may advance physiopathological mechanisms.

In conclusion, just a few studies spanning the last 15 years have attempted to seek for variables associated with co-existing ES and PNES and compare these to patients with PNES alone and ES alone. Case ascertainment and the variables explored were highly heterogeneous among studies, precluding the identification of specific sets of demographic, epileptological and psychiatric variables that could solidly suggest an association between ES and PNES. However, taking a more optimistic perspective, this systematic review sets the stage and advances some factors that should be further explored and expanded in future research. Advances in this field will be most welcome, as they could potentially streamline patient selection for costly V-EEG monitoring and better inform neurologists and psychiatrists in the diagnostic conundrum represented by the intricacies between ES, PNES and their association.

Conflict of Interest

Disclosures: Dr. Palmini has received honoraria from Novartis, Abbott, Eli Lilly and Janssen-Cilag for lectures and participation in advisory boards, which do not bear upon this publication. Dra Margis has received honoraria from Sanofi for lectures, which do not bear upon this publication. Drs. Baroni, Piccinini, Martins, De Paola and Paglioli have nothing to disclose.

Authors' individual contributions to the manuscript

Study concept: GB
Data collection: GB, WM
Manuscript drafting for content: AP, GB
Manuscript revision for content: GB, EP, LP, RM, VP
Study supervision: AP

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.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.seizure.2016.02.003.

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