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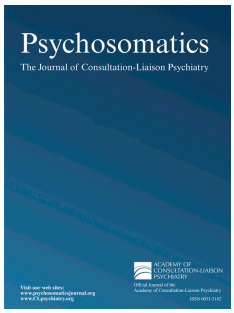

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Differential semiology based on VEEG monitoring between psychogenic non-epileptic seizures and temporal lobe epileptic seizures

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Abstract

Introduction

Psychogenic non-epileptic seizures (PNES) are disruptive changes in behavior without ictal correlate of epileptic activity and high prevalence of psychiatric morbidity. Differential diagnosis is difficult particularly with TLE (temporal lobe epilepsy), which is also associated with high prevalence of psychiatric comorbidity. Although Video-EEG (VEEG) is the gold standard for differential diagnosis, clinical semiology analysis may help the clinician in general medical practice. In this study the differential semiology based on VEEG, between PNES and TLE seizures was analysed.

Methods

The VEEG of patients with diagnosis of PNES and TLE were reviewed and compared between groups. Clinical semiology of all episodes recorded by VEEG in each patient was analyzed and classified according to

the presence of: behavioral arrest, motor hyperkinetic activity, impaired awareness, aura and automatisms. Chi square test and binary logistic regression were determined.

Results

Thirty-two patients with PNES (32 ±11 years) and 34 with TLE (32 ±12 years) were included. Female patients were predominant in PNES group ($p<0.05$). Mean time duration of episodes was 6,8 ±10 minutes in PNES and 1,6±0,8 minutes in TLE ($p<0.05$). Impaired awareness (OR= 24.4, CI 95% 3.79-157.3, $p<0.01$), automatisms (OR= 13.9 CI, 95% 2.1-90.5, $p<0.01$) and shorter duration of the events (OR = 2.261, CI 95% 1.149- 4.449, $p=0.018$), were found as independent factors for detecting TLE seizures comparing PNES.

Conclusion

Clinical semiology analysis may orientate the differential diagnosis in general medical practice, between PNES and TLE seizures. Further studies comparing PNES semiology with other subtypes of epilepsies may complete these preliminary findings.

Key Words: clinical semiology, automatisms, impaired awareness, differential diagnosis, psychiatric disorders.

1. Introduction

Psychogenic non-epileptic seizures (PNES) are diagnosed when disruptive changes in behavior, thinking or emotion, that resemble epileptic seizures (ES), are present without any ictal correlate of epileptogenic brain activity. Usually PNES represent an underlying psychiatric disorder, classified in Axis I of DSM-IV as conversion disorder and/or dissociative disorder. More recently, DSM-5 categorized PNES as a functional neurological disorder ([1–5]). Psychogenic factors like sexual abuse, trauma and posttraumatic stress disorder (PTSD) have been associated with PNES occurrence ([6,7]).

PNES accounts for approximately 20-30% of patients referred to epilepsy centers with suspicion of resistant epilepsy ([1,5]). Additionally, an important delay in the recognition of PNES, between seven to eleven years, has been reported in the international literature and also in previous studies performed by our group ([1,4,8,9]). The diagnostic delay could be in part accounted by difficulties in accessing VEEG (Video-electroencephalography), the gold standard to achieve PNES diagnosis. This is possibly related to both economic and availability factors; indeed, only a limited number of specialized centers have access to these diagnostic tools. Diagnostic delay implies unnecessary exposure to antiepileptic drugs and, in turn, a postponement of the appropriate treatment implementation (psychiatric treatment and psychotherapy) ([8,10–12]).

PNES are frequently confused with epileptic seizures, particularly with TLE (temporal lobe epilepsy), which is the most frequent subtype of epilepsy and is also frequently associated with psychiatric comorbidity, making differential diagnoses even more complex ([4,13]). Although VEEG is the gold standard method in establishing differential diagnosis between PNES events and epileptic seizures ([14,15]), descriptive semiology

may help in patients with suspected PNES in general hospitals, in epilepsy units and/or in mental health departments. Several studies analysed the clinical features of PNES semiology ([16,17]) but only a few studies compared specifically the subtypes of epilepsies with PNES semiology ([1,18,19]). In a previous study performed by our group, we analysed the presence of psychiatric disorders in patients with PNES and in patients with drug resistant epilepsy, finding a high prevalence of depression in both groups while trauma and post-traumatic stress disorder were more frequent in PNES patients ([4]). In the present study we aim to compare the clinical semiology detected during VEEG monitoring between PNES and TLE.

2. Material and methods

2.1. Patient selection

The VEEG records of a selected subgroup of patients with a confirmed diagnosis of PNES or TLE, which were, completed all the mental health protocol and signed the informed consent, were retrospectively reviewed. Selected patients were admitted to the VEEG unit of Ramos Mejía Epilepsy Center. In the PNES group patients were admitted to the VEEG from 2006 until 2016 and some of them (n=14) were included in a previous study about psychiatric aspects of PNES [(4)]. In the TLE group patients were admitted from 2012 until 2015 and some of them (n=16) were included in a previous study about the quality of life of patients with drug resistant epilepsy [(2)]. Thus, the number of patients included in this exploratory study does not reflect the prevalence of PNES or TLE among the total population admitted to the VEEG unit. The approval of the Ethics Committee of Ramos Mejía Hospital was obtained to conduct the study in accordance with the ethical standards established in the 1964 Declaration of Helsinki.

2.2 Diagnosis of PNES events and TLE seizures: Inclusion and exclusion criteria

All patients included in this study underwent a medical assessment according to a standardized protocol including clinical history, neurological evaluation, MRI and completed a psychiatric assessment protocol. The diagnosis of PNES events and/or TLE was made by two epileptologists based on VEEG monitoring. The diagnosis of PNES according to VEEG was complemented by the psychiatric evaluation to support the psychogenic origin of PNES.

In this study two groups of patients were selected and grouped according the presence of PNES or TLE.

PNES events diagnostic criteria were: atypical paroxysmal behavioral episodes recorded by VEEG monitoring, without any electroencephalographic ictal activity (at least one attack recorded) with no existing clinical or electroencephalographic evidence suggestive of epilepsy; neither neurological nor medical disorder that explains the atypical paroxysmal behavior (exclusion criteria). Patients were included in PNES group, when at least one PNES event was recorded during VEEG. Exclusively patients with only PNES recorded during VEEG in which the documented seizures were similar from their usual and current episodes were included in this group.

Temporal lobe epileptic seizures diagnostic criteria were: characteristic clinical events recorded with simultaneous ictal EEG abnormalities during VEEG localized in temporal lobe. The subtype of epileptic syndrome was diagnosed according to ILAE nomenclature guidelines ([20,21]) and temporal lobe epilepsy was

diagnosed according to clinical semiology and ictal VEEG results ([20,21]). Patients were included in TLE group, when at least one TLE event was recorded during VEEG. Exclusively patients with only TLE events recorded in VEEG were included in this group.

Exclusion criteria were: Patients with both types of seizures (PNES and epileptic seizures) registered during VEEG were excluded. Additionally, patients with doubts about epileptogenic zone or patients with other subtype of epilepsy registered during VEEG were excluded of the group of TLE. Patients who did not complete all diagnostic steps, paroxysmal events of other medical aetiology, (e.g., transient ischemic attacks, vasovagal syncope, sleep disorders and non-epileptic myoclonus), and patients who did not sign the informed consent were also excluded. If the documented seizures differed from their usual episodes, and patients with purely subjective phenomena during the events were excluded from the study.

2.3 Video-Electroencephalography (VEEG)

For VEEG monitoring (5 days period), a Stellate-Bioscience EEG machine at a 200-Hz sample rate was used. All ictal recordings were obtained using the international 10–20 system with the addition of temporal electrodes of the 10–10 system. Referential montages as well as longitudinal–bipolar and transverse bipolar montages were used for the analysis. VEEG is usually indicated in order to determine the possibility of epilepsy surgery and/or to confirm the differential diagnosis between epilepsy and PNES. A routine practice during the ictal and post-ictal period includes systematic patient assessment performed by qualified technical staff and, at the same time, patients are instructed to promptly advise the staff whenever they experience an aura. For the purpose of this study, all video-EEG recordings were retrospectively reviewed by three qualified readers, trained and experienced in video-EEG interpretation. Seizure onset was defined as the first electrical change seen in the EEG rhythm as compared to baseline or at any clinical sign or symptom indicating seizure onset.

2.4 Psychiatric assessment

Psychiatric assessment protocol was performed by 2 trained psychiatrist based on a standardized protocol previously applied in our population in other studies ([1,]). Psychiatric history was obtained. All patients underwent the Structured Clinical Interview for DSM IV Axis I disorders (SCID I), a semi-structured interview for major DSM IV Axis I diagnoses and the SCID II, which is a semis-structured interview for DSM IV Axis II personality disorder diagnoses (Spanish Clinical Version of SCID I and SCID II). Patients with mental disabilities were excluded from the psychiatric data analysis.

2.5 Magnetic Resonance Imaging

All patients had magnetic resonance imaging (MRI) 3T, with a temporal lobe epilepsy protocol [(22).] The sequences used were the following: Sagittal plane T1-weighted image for the purpose of detecting the hippocampus in the parasagittal slices; inversion-recovery (IR) pulse sequence, fluid- attenuated IR (FLAIR), and three-dimensional gradient echo sequence (volumetric), perpendicular to the long axis of the hippocampus, and T2-weighted axial sequence parallel to the long axis of the hippocampus.

2.6 Semiological analysis of PNES events and TLE seizures recorded during VEEG

The VEEGs of patients included in this study were reviewed, and all the episodes of PNES and TLE recorded in each group of patients were examined and classified depending on the presence of the following signs and symptoms [(1)]. 1- Behavioral arrest: detention of activities, immobility and/or freezing [(20,23)]. 2- Motor/Hyperkinetic activity: active movements of fluctuating intensity involving the limbs, head and trunk ([13,25-27]). 3- Impaired awareness: this was considered when the patient did not contact (i.e eye contact), listen, neither answer, nor remember during all the episode's duration since the beginning of the seizure (after aura) until the end. Fluctuations of awareness during the episode were not considered total impaired awareness ([1,20,23]). 4- Presence of aura: we included subjective symptoms and/or sings when they were clearly manifested before seizures started. We included somatic aura, presence of clinical symptoms (pain, autonomic symptoms, headache, dizziness, etc.), sensorial aura (different types of hallucinations or illusions) and psychic aura (psychological symptoms such as anxiety, fear, other emotions, etc.) ([1,20,23]). 5- Presence of automatisms: a coordinated, repetitive and stereotyped motor activity, affecting facial and/or distal movements ([20,23]).

2.7. Statistical analysis

All the variables studied were compared between groups. Chi-square test and binary logistic regression were determined to compare clinical semiology between patients with TLE and PNES ($p<0.05$ was considered significant). Two-tailed Student *t* test was used for continuous data. SPSS for Windows was used.

3. Results

In this study we included 32 patients with PNES (women n=26, men n=6; mean age= 32±11) and 34 patients with TLE (women=16, men=18; mean age=32±12). Sociodemographic and clinical data is summarized in Table 1. A higher prevalence of female sex and a higher age of onset were found in PNES group comparing to TLE group ($p<0.05$).

The presence of aura, behavioral arrest, automatisms and impaired awareness, were significantly more frequent in TLE group, compared to PNES (Chi Square test, $p<0.05$). On the contrary, hyperkinetic seizures and the absence of impaired awareness were more frequently found in the PNES group (Chi Square test, $p<0.05$ (Figure 1). Mean seizure duration of episodes was 1.72±0.9 minutes in TLE group and 3.98±3.1 minutes in PNES group ($p<0.001$)(Figure 2).

According to logistic regression analysis, impaired awareness (OR= 0.050, CI 95% 0.004-0.6343, p=0.021), the presence of automatisms (OR= 0.032, CI 95% 0.003-0.306, p=0.003) and the shorter duration (OR = 2.261, CI 95% 1.149- 4.449, p=0.018), were found as independent factors for detecting TLE compared to PNES (Table 2).

4. Discussion

In this study we examined and compared the frequency of presentation of the main semiological sings detected during VEEG, between PNES and TLE seizures ([1,9]). The semiological classification used in this analysis was restricted to a limited number of specific semiological signs, usually described in epileptic seizures and previously reported by our group ([1]). However other broader semiological stereotyped classifications were proposed in the literature to describe PNES in detail ([26–29]). Nevertheless, in this preliminary study we focused on TLE (a very frequent syndrome among patients with resistant epilepsy admitted to epilepsy centres), which is also frequently associated with psychiatric comorbidity, making differential diagnoses even more difficult ([26–28]). In this analysis, we used common linguae to neurologists for describing seizures, with the aim to improve the communication between neurologists and psychiatrists, enhancing a prompt diagnosis. This also may provide standardization across future studies that compare epileptic seizures versus PNES.

According to the literature ([1,8]) the 20-30% of patients referred to epilepsy centers with suspicion of resistant epilepsy, have PNES; so semiological data may be crucial to speed up the differential diagnosis. In the present study we found differences in TLE semiology comparing with PNES events. The presence of automatisms was found an independent factor for differentiating TLE from PNES. Although automatisms are widely described phenomena in TLE, it is interesting to point out, that in this study the presence of automatisms allowed us to strongly differentiate TLE from PNES. Other publications obtained a similar results, finding that automatisms, referred as "focal signs", "minor motor seizures"([26,27]), are less frequent in PNES ([1,17,30,31]) and predominate in TLE seizures ([20,32]). Nevertheless, these studies did not compare the clinical semiology of PNES specifically with TLE.

Total impaired awareness during all the episode's duration was also found as an independent factor, according to logistic regression, and constitutes as a useful clinical manifestation for differentiating TLE seizures from PNES. Similar to our results, consciousness alterations have been previously reported as a key clinical feature for TLE diagnosis ([20,32,33]). Additionally, other publications and previous reports published by our group ([1]), found that impaired awareness was less frequently in PNES compared to epileptic seizures ([25,26]). However, as far as our knowledge, there is no data available about comparisons between PNES and TLE regarding semiological aspects.

Other semiological signs such as hyperkinetic seizures were more frequently found among PNES patients. Nevertheless, in this study we did not distinguished between different subtypes of hyperkinetic seizures. Similar to our results, other studies found that hyperkinetic seizures, also named in the literature as "motor seizures" or "hypermotor seizures"([27]) are characteristic of PNES ([1,3,17,19,27,31,34]). Still, hyperkinetic seizures are also frequently described among frontal epilepsies, which have been not analysed in this preliminary study ([35]). On the other side, behavioral arrest, also described in the literature as "psychogenic atonic seizures", "dialeptic" or "pseudosyncope" ([27]), was more frequently found in TLE patients in this study. Similarly, other reports described behavioral arrest as a common sing of epileptic seizures ([20]), especially TLE seizures ([32]). This clinical manifestation seemed to be rarely found in PNES ([1,3,17,19,31,34]). Regarding aura, it was more frequently found in TLE seizures. The presence of aura is classically described in TLE seizure semiology ([20,32,33]), and not so frequently described in PNES ([1,3,17,19,31,34]).

A classical sign which has been considered an important semiology factor useful for differentiation PNES versus epileptic seizures, is the time duration of the events ([1,3,17,19,32,36]). In agreement with the literature we found a significant higher duration of seizures among PNES patients compared with TLE. We also found that patients with TLE seizures presented a significantly younger seizures' age of onset in comparison to PNES, similarly to other studies ([17,19,30,32–34]). Additionally, we found an over representation of female in PNES group ([1,3,17,19,36,37]).

In this study we found semiological signs that could help the clinicians to differential diagnosis between PNES and TLE. PNES diagnostic delay in Latin America, particularly in Argentina, is very high, ranging between 7 to 11 years ([1,4]). Although, other international studies also reported a high diagnosis delay, similar to ours, but, in our country we have to additionally consider the difficulties in accessing to VEEG ([8,38,39]). This is possibly related to both economic and availability factors. Besides, only a limited number of specialized centers in the whole country have access to this diagnostic tool. Additionally, the misdiagnosis in clinical practice is bidirectional, PNES may be confused with epilepsy and epilepsy (i.e TLE), may be confused with PNES. According to this study, the presence of impaired awareness, automatisms and a shorter duration, are suggestive of TLE comparing PNES, reinforcing the idea of epileptic origin. On the contrary, longer duration of the events may be considered as independent factor for diagnosis PNES.

Some limitations of this study must be mentioned; this is a small and exploratory study, which compared the clinical semiology between PNES and TLE. We found differences on TLE patients useful to differentiate from PNES but larger studies, using more detailed classifications and including other subtypes of epilepsies (i.e frontal epilepsy), should be made in the future to find clinical differences in PNES to differentiate from epilepsy. As well as VEEG is the gold standard for differential diagnosis, clinical semiology may help the clinician (neurologists and psychiatrists) in differential diagnosis, may reduce the diagnosis delay time and may accelerate a correct treatment instauration. In PNES patients psychiatric treatment and psychotherapy is the treatment of choice, and an early differential diagnosis may help in reducing the risks of unnecessary antiepileptic drugs use.

5. Conclusion

In this preliminary study we found semiological signs that may orientate the differential diagnosis between PNES and TLE. The presence of automatisms, impaired awareness and a shorter duration of the events were more frequently found in TLE, comparing to PNES. Clinical semiology information constitutes a useful tool for differential diagnosis between TLE and PNES and may help neurologists and mental health professionals (psychiatrists, psychologists), to differentiate PNES from TLE seizures, and also to consider an early request of VEEG. Further studies comparing PNES semiology with other subtypes of epilepsies using large and detailed classifications will complete these preliminary findings.

Disclosures

The authors do not declare any conflict of interest.

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Figure 1

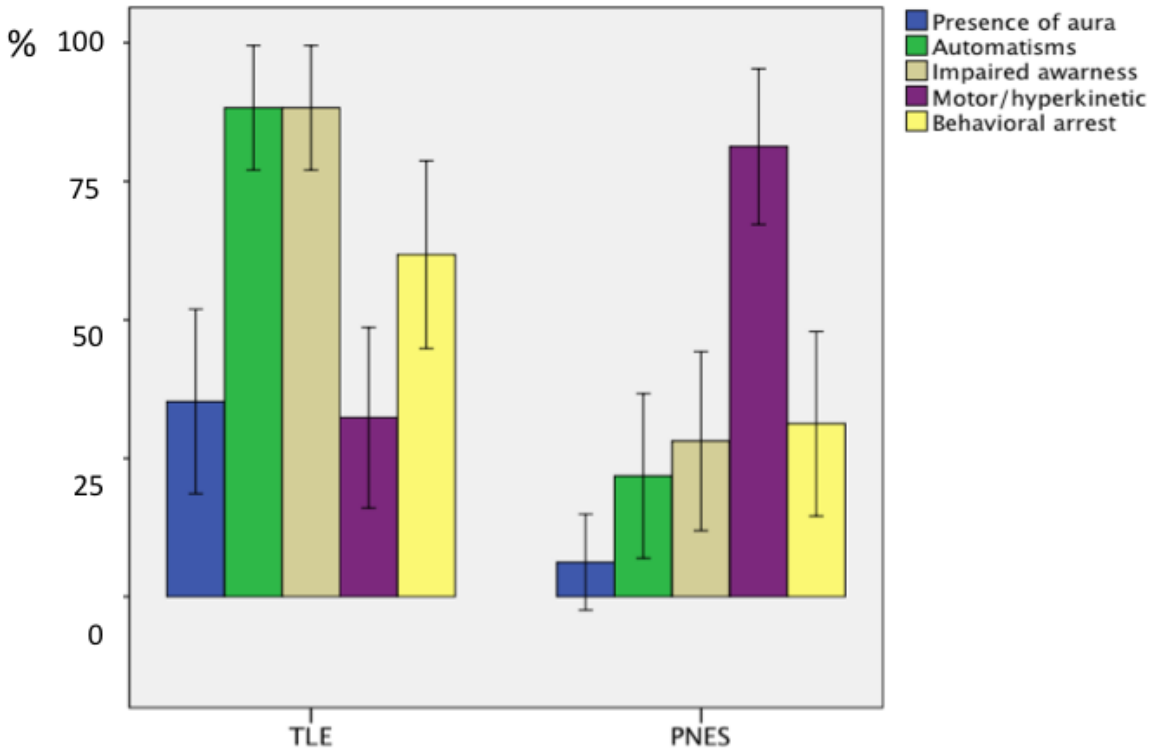

Figure 2

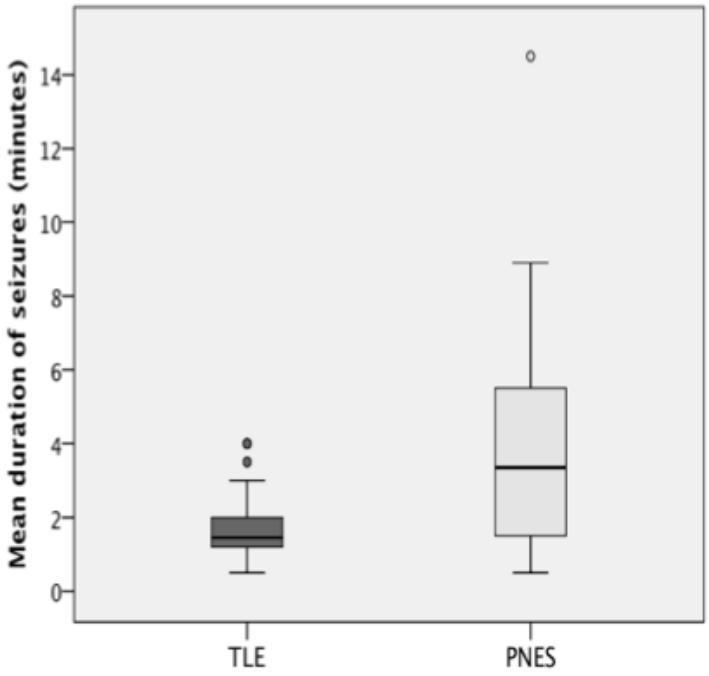

Table 1. Demographic Data

	TLE	**PNES**	***p* value**
Female	16	26	0.004
Male	18	6	
Age (years)	32(±12years)	32(±11years)	0.872
Age of Seizures' Onset	13(±9years)	19(±11years)	0.012
Occupation			
Unemployed	51.6%	27.3%	0.531
Underemployed	29.0%	45.5%	
Active Work	9.7%	13.6%	
Student	3.2%	4.5%	
Disability Pension	6.5%	9.1%	
Civil Status			
Single	56.3%	44.4%	0.489
Married/Couple	40.6%	55.6%	
Divorced	3.1%	- -	
Location			
Buenos Aires City	18.5%	38.1%	0.336
Great Buenos Aires	33.3%	33.3%	
Buenos Aires Province	14.8%	14.3%	
Rest of the Country	33.3%	35.0%	
Education			
Less than 12 years	44.4%	41.2%	0.831
More than 12 years	55.6%	58.8%	

Table 2. Logistic regression analysis of semiological symptoms recorded during VEEG

	Odds Ratio	95% CI for Odds Ratio	*p* value
Automatisms	0.050	0.004 - 0.634	0.021
Impaired Awareness	0.032	0.003 - 0.306	0.003
Mean time duration (minutes)	2.261	1.149 - 4.449	0.018
Aura	0.916	0.035-23.80	0.958
Hyperkinetic	2.571	0.169-39.00	0.496
Behavioral Arrest	0.224	0.027-1.857	0.166

Results of the logistic regression analysis, clinical semiology between TLE seizures and PNES events were compared. The presence of automatisms, the impaired awareness ant the shorter time duration, was found as independent factors for detecting TLE compared to PNES.