

Psychogenic non-epileptic and epileptic seizures: clues for a differential diagnosis. Findings from a Colombian study

Esteban Jaramillo-Jiménez, Cristian Vargas-García, Iader Rodríguez-Márquez, Juliana Sandoval-Barrios, María A. Vélez, Juan F. Álvarez, Norma L. Muñoz, Alex R. Flórez, Mónica Massaro-Ceballos, Marta E. Jiménez-Jaramillo

Introduction. Psychogenic non-epileptic seizures (PNES) are paroxysmal changes in behavior that resemble epileptic seizures, although they have no electrophysiological correlation or clinical evidence of epilepsy.

Aim. To compare clinical and sociodemographic characteristics of patients diagnosed with PNES-alone and PNES-and-epilepsy.

Patients and methods. A cross-sectional study of consecutive patients diagnosed with PNES in a 20-month period was carried out. A video-EEG was performed in all patients. Socio-demographical, clinical and semiological characteristics were compared between those patients with and without concomitant epilepsy.

Results. Sixty-five patients were included, 35 (53.9%) had PNES-alone and 30 (46.1%) had PNES-and-epilepsy. The proportion of women in the study was 70.8%. The median age at seizure onset was 16 years. A late start was recorded in PNES-alone group (23 years) compared to PNES-and-epilepsy group (11 years), however, it was not significant. There was a lower frequency of antiepileptic drugs use in the PNES-alone group compared with the PNES-and-epilepsy group. The most frequent semiological features were the gradual onset of events (69.2%) and the duration longer than two minutes (63.1%).

Conclusion. The waxing and waning pattern during paroxysmal events suggest a non-epileptic origin. However, it is not uncommon to find patients with concomitant epileptic seizures.

Key words. Conversion disorder. Electroencephalography. Epilepsy. Neurologic manifestations. Psychogenic non-epileptic seizures. Seizures.

Introduction

An epileptic seizure is defined as a transient occurrence of signs and/or symptoms due to an abnormal excessive or synchronous neuronal activity in the brain. A seizure can be categorized as epileptic or non-epileptic, the latter includes psychogenic 'non-epileptic' seizures (PNES) which are episodes of altered movement, sensation or experience similar to epilepsy that are not caused by abnormal electrical discharges in the brain, but rather by psychological processes [1].

PNES are paroxysmal changes in behavior that resemble epileptic seizures, although they have no electrophysiological correlation or clinical evidence of epilepsy. Evidence suggests psychogenic factors as possible causes for seizures [2]. The majority of PNES are considered as beyond patient's voluntary control [3]. These episodes of paroxysmal impairment of self-control are associated with a range of motor, sensory, and mental manifestations, which represent an experiential or behavioral response to emotional or social distress [4]. They are generally

considered as a psychiatric diagnosis characterized by physical symptoms and complaints for which an organic disorder cannot be identified [5]. Distinguishing between these entities is essential not only to provide an adequate treatment to the patient, but also to avoid the overwhelming cost associated with an incorrect diagnosis [6].

The incidence of PNES has been reported from 1.4-3/100,000 people-year and the prevalence has been estimated between 2-33/100,000 people, occurring in up to 10-20% of patients with presumed medically intractable epilepsy cases referred to epilepsy centers [7,8]; Such crisis typically start is the second or third decade of life, with predominance of the female gender [9]. 23% of patients with supposed refractory status epilepticus have a 'pseudo-status' [10]; Additionally, failure to recognize 'pseudo-status' epilepticus has a potential hazard of intuition and its associated morbidity and mortality.

The electroencephalogram (EEG) is an effective tool to identify an epileptic seizure. However, is not adequate for the diagnosis of PNES for which the use of video electroencephalogram (VEEG) has been

University of Western Australia; Perth, Australia (C. Vargas-García). Neurophysiology Unit (E. Jaramillo-Jiménez, J.F. Álvarez, N.L. Muñoz, A.R. Flórez, M.E. Jiménez-Jaramillo); Department of Neurology (I. Rodríguez-Márquez); Instituto Neurológico de Colombia. Universidad CES (E. Jaramillo-Jiménez, M.A. Vélez, J.F. Álvarez, M. Massaro-Ceballos, M.E. Jiménez-Jaramillo). Universidad Pontificia Bolivariana (J. Sandoval-Barrios). Medellín, Antioquia, Colombia.

Corresponding author: Esteban Jaramillo-Jiménez MD. Neurophysiology Unit. Department of Neurology. Instituto Neurológico de Colombia. Calle 55, no. 46-36. Medellín, Colombia.

E-mail: esteban.jaramillo@neurologico.org.co

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effectively implemented. Monitoring for 24 to 144 hours has been shown to improve diagnostic accuracy compared with conventional EEG [11]. Long-term VEEG is the gold standard for the diagnosis of epileptic seizures and PNES in drug resistant patients, primarily by correlating electrographic changes with clinical events, with respect to patient responsiveness [12].

PNES constitute one of the most important differential diagnosis of epilepsy [13], however, our understanding of the etiology, underlying mental processes, and subsequently sub-differentiation and treatment remains seriously deficient [9]. Studies has shown that there is a large degree of confusion not only among patients with PNES and their families, but also within primary care physicians [14,15]. Failure to recognize the psychological nature of these seizures also delays implementation of appropriate psychological treatment [16]. Most studies have focused on PNES as a differential diagnosis of epilepsy [5,17-20], when in fact they can be manifested simultaneously, making it a diagnostic challenge.

The aim of the present study is to describe and compare sociodemographic and clinical characteristics of patients along with psychiatric comorbidities in two study groups –PNES-alone and PNES-and-epilepsy– at a tertiary care center in Colombia.

Patients and methods

Study design and Setting

A cross-sectional study of consecutive patients diagnosed with PNES using VEEG from April 2011 to December 2012 was completed at the Instituto Neurológico de Colombia, in Medellín, Colombia. Sociodemographical and clinical characteristics along with event semiology were compared between patients with and without concomitant epilepsy.

Ethical approval for this study was obtained from our institutional review board and all included subjects or caregivers provided written informed consent prior to the VEEG monitoring.

Eligibility criteria

All patients suspected of having VEEG-recorded PNES, previously confirmed as to represent their usual events were included. The population studied included both adult and pediatric patients. Patients with EEG-negative sensory events (eg, tingling, numbness) were excluded since scalp EEG tracings may not definitively rule out subtle epileptiform ac-

tivity. Also, EEG-confirmed epileptic auras were excluded to prevent bias from over representing isolated sensory events as of an epileptic origin.

Variables and data sources

Sociodemographic (age at diagnosis, age of seizure onset, gender, education level, employee, residence), clinical (personal history of anxiety, personal history of depression, ictal event type, anatomical structure of affliction, seizure frequencies, years between seizure onset and a correct diagnosis, number of antiepileptics used) and semiological (gradual onset, side-to-side head shaking, closed eyes on event onset, duration > 2 minutes, rhythmic pelvic movements, asynchronous limb movements) variables were included. A standard interview focused on epilepsy and its differential diagnosis was conducted as part of the routine process of admission to the neurophysiology unit. Most of the data obtained derived from such interview or from information collected during the VEEG evaluation period. Medical records were reviewed for demographic data and any preexisting psychiatric assessments and related diagnosis.

A patient was defined as having PNES-alone when all types of events described by the patient and eyewitnesses were correctly recorded and identified, along with an adequate electro clinical correlation (discarding interictal epileptiform abnormalities on VEEG recordings of up to 168 hours), as well as having a formal conversion disorder diagnosis by a psychiatrist. In contrast, it was defined that patients had PNES-and-epilepsy if epileptiform abnormalities were recorded during seizures or the interictal period along with paroxysmal events. Results of previous tests, such as scalp EEG and magnetic resonance imaging, were included for the analysis when available.

PNES ictal semiology was divided between ‘convulsive seizures’ (including partial or generalized activity), and ‘non-convulsive seizures’ (including alterations in sensation and unresponsiveness). We classified VEEG-positive events as epileptic seizures if the neurophysiologist documented the presence of an ictal epileptiform correlate on EEG tracings. We categorized the remaining VEEG-negative events as PNES if semiology and EEG/electrocardiogram tracings could not explain a physiologic etiology (eg, migraine, syncope, and positional vertigo). Regarding differential diagnosis, sleep recordings and special VEEG montages including oculogram and chin electrodes were used when needed, if suspicion for an alternative diagnosis.

Based on published data available to date concerning PNES, we listed six semiological signs reported to potentially distinguish PNES from epileptic seizures [21]. After identifying patients previously diagnosed with PNES, a second review was conducted by a neurophysiologist who did not know patients diagnosis nor EEG tracings, independently reviewing the semiology of the events and for each event documenting the presence or absence of each of the semiological signs.

Statistical methods

A descriptive analysis was performed in PNES-alone and PNES-and-epilepsy patient groups. For qualitative variables, absolute and relative frequencies were estimated. The normality of quantitative variables was assessed using the Shapiro-Francia test.

A bivariate analysis was performed between sociodemographic and clinical characteristics in PNES-alone and PNES-and-epilepsy groups. Qualitative variables were analyzed using Chi-square independence test and Fisher's exact test when the expected value was less than or equal to five. For quantitative variables within subgroups the Mann-Whitney *U* test was applied for median comparison. For education level, we used test for trends across ordered groups developed by Cuzick [22]. Additionally, univariate and bivariate analyses were performed in the female subgroup. A value of $p < 0.05$ was considered statistically significant. The statistical package Stata v. 14 was used.

Results

During the selected period 773 patients were referred to VEEG, of which 10.6% had at least one paroxysmal non-epileptic event with or without a concomitant epileptic seizure. We excluded five patients with onanism, four patients with parasomnias, three patients with migraine and five patients with other clinical conditions. Age at diagnosis, age of seizure onset, seizure frequency, years between seizure onset and a correct diagnosis and the number of antiepileptic used had a non-normal distribution ($p < 0.05$). Sixty-five patients were included, of which 53.9% ($n = 35$) were diagnosed as PNES-alone and 46.1% ($n = 30$) as PNES-and-epilepsy. Of note, 97% of the final sample required up to 120 VEEG monitoring hours in order to determine an accurate classification, only two patients needed longer studies.

The proportion of women in the sample was 70.8% ($n = 46$) and 70.8% of the patients had a me-

Table. Characteristics of patients diagnosed with PNES-alone and PNES-and-epilepsy.

	All ($n = 65$)	PNES ($n = 35$; 53.9%)	PNES-and-epilepsy ($n = 30$; 46.1%)	<i>p</i>	
Age at diagnosis (years) ^a	33 (17-53)	32 (17-50)	43 (15-59)	0.298 ^b	
Age of seizure onset (years) ^a	16 (5-35)	23 (9-40)	11 (2-32)	0.104 ^b	
Gender (female)	46 (70.8%)	23 (65.7%)	23 (76.7%)	0.333 ^c	
Education level	Without education	3 (4.6%)	1 (2.9%)	2 (6.7%)	0.060 ^d
	Elementary school	16 (24.6%)	7 (20%)	9 (30%)	
	Middle & high school	30 (46.2%)	15 (42.9%)	15 (50%)	
	Superior education	16 (24.6%)	12 (34.3%)	4 (13.3%)	
Employed	22 (33.9%)	16 (45.7%)	6 (20%)	0.029 ^c	
Residence	Rural	9 (13.9%)	7 (20%)	2 (6.7%)	0.161 ^e
	Urban	56 (86.2%)	28 (80%)	28 (93.3%)	
History of anxiety	16 (24.6%)	8 (22.9%)	8 (26.7%)	0.722 ^c	
History of depression	23 (35.4%)	11 (31.4%)	12 (40.0%)	0.471 ^c	

PNES: psychogenic 'non-epileptic' seizures. ^a Median (interquartile range); ^b Mann-Whitney *U* test; ^c χ^2 test of independence; ^d Test for trend across ordered groups; ^e Fisher's exact test.

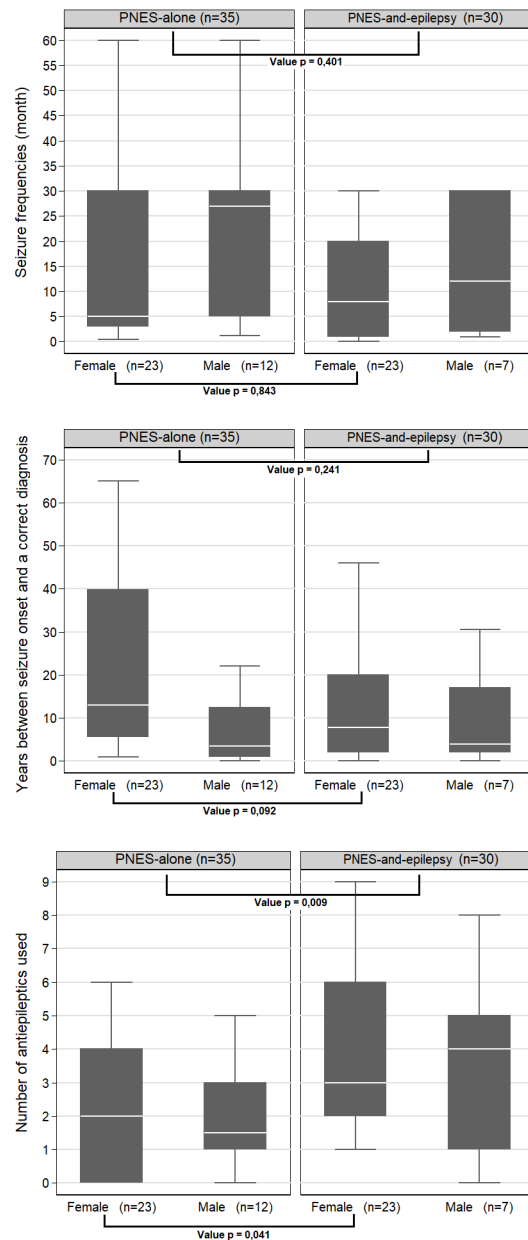
dium and higher level education (Table). The median age of the patients at the start of the VEEG was 33 years (IQR: 17-53) and the median age of seizure onset was at 16 years (IQR: 5-35). A late start was recorded in PNES-alone group (23 years; IQR: 9-40) when compared to PNES-and-epilepsy group (11 years; IQR: 2-32), however, it was not statistically significant (Mann-Whitney *U* test; $p = 0.103$).

The majority of patients lived in urban areas (86.2%) and one third of the sample was unemployed. This proportion was up to 80% in the PNES-and-epilepsy subgroup, being significantly higher than the 54.3% of the patients diagnosed with PNES-alone (χ^2 test of independence; $p = 0.029$). In addition, 24.6% and 35.4% of patients reported a personal history of anxiety and depression, respectively. There were no statistically significant differences between the subgroups concerning their backgrounds.

In the subgroup of PNES-and-epilepsy, 86.7% of patients presented focal ictal events and 10% generalized ictal events. The anatomical structure of greater affliction was the temporal lobe (50%), followed by the frontal lobe (20%) and parietal lobe (16.7%).

Figure 1 shows the frequencies of some seizure characteristics between groups according to gen-

Figure 1. Seizure characteristics in PNES-alone and PNES-and-epilepsy by gender (Mann-Whitney *U* test).



der. Women with PNES-alone presented a lower monthly seizure median (median: 5; IQR: 3-30) than women with PNES-and-epilepsy (median: 8; IQR: 1-20). However, this difference was not statistically significant (Mann-Whitney *U* test; $p = 0.843$). A higher seizure frequency was noted in men with

PNES-alone (median: 27; IQR: 5-30). In contrast, a higher latency between symptoms onset and the confirmation of diagnosis occurred in the group of women with PNES-alone, with a median of 13 years (IQR: 5.5-40); and median of 3.5 years (IQR: 1-12) for men. These findings were not significant (Mann-Whitney *U* test; $p = 0.241$).

When comparing patients with PNES, the frequency of antiepileptic drugs use was significantly higher in patients with PNES-and-epilepsy (Mann-Whitney *U* test; $p = 0.009$). Such difference continued being significant when comparing only the group of women (Mann-Whitney *U* test; $p = 0.041$), although, the male group diagnosed with PNES-and-epilepsy had a greater use of antiepileptic drugs (median: 4; IQR: 1-5).

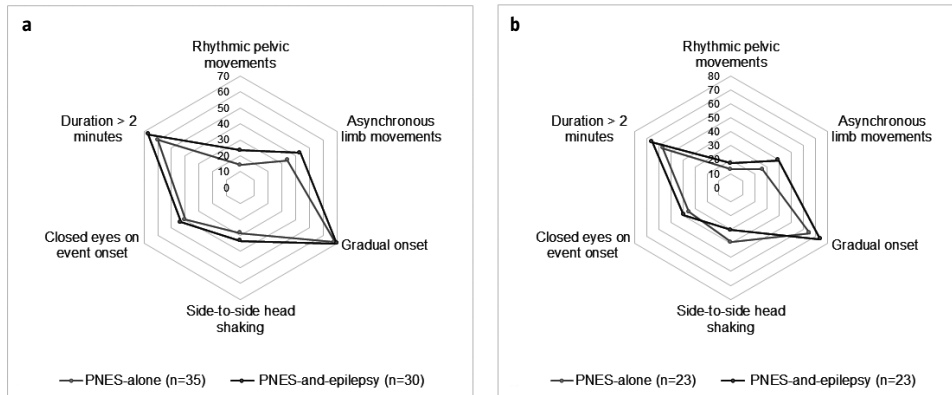
The most frequent features were gradual onset of the crisis with 69.2% and periods greater than two minutes with 63.1%. Rhythmic pelvic movements occurred less often (18.5%). Similarly, in the female subgroup, the most frequent features were gradual onset in 73.9% of PNES-and-epilepsy and 65.2% in PNES-alone patients. The less frequent semiological sign among women were rhythmic pelvic movements with a value of 13% in PNES-alone and of 17.4% in PNES-and-epilepsy patients (Fig. 2).

Discussion

This study compared sociodemographic, clinical and semiological characteristics between two patient groups, the first one with the diagnosis of PNES-alone and the other one with PNES-and-epilepsy. One of the aims of the study was to compare key features between paroxysmal epileptic and non epileptic crisis, which can be expressed simultaneously.

Out of 773 patients referred for VEEG, 10.6% reported at least one non-epileptogenic event, of whom, approximately half of the patients also had epilepsy. O'Sullivan et al [15] reported similar findings with coexistence of PNES-and-epilepsy of up to 43%. Another study reported wider ranges that fluctuated between 5% and 40% in patients initially diagnosed as refractory epilepsy and subsequently referred to epilepsy centers [16]. These data may reflect lack of key features when making the diagnosis of patients with PNES.

In general, the study participants were young adults. However, for the majority, seizures started in their adolescence. This trend was more notorious in the group of PNES-and-epilepsy. A study made in Iceland [8] reported a higher incidence of psychogenic seizures between 15 and 24 years of age.

Figure 2. Seizure semiology (%): a) All participants; b) Female subgroup.

Another study found an average age of patients with PNES of 40 ± 16 years, a similar result to the one found in the present study, nevertheless, these patients reported seizure onset at a later age (mean: 34 ± 16 years) [23]. The age of seizure onset is usually earlier in the PNES-and-epilepsy group; however, the correct diagnosis is made earlier in the PNES-alone group [17]. This could be explained by the fact that when epilepsy is associated with PNES, a correct diagnosis can be more complex.

In terms of gender, women had a higher frequency in both PNES-alone and PNES-and-epilepsy; Asadi-Pooya and Sperling [18], reported a similar finding. Another study made in South Africa found that 73% of PNES occurred in women [20]. A hypothesis that could explain this situation is that there are differences between genders in relation to their emotional and cognitive processes which would lead to a greater predisposition in women to PNES [24]. Females tend to have a more affective response when processing negative emotional experiences [25].

With regards to education level, a large proportion of the population was able to reach a middle education level and had high unemployment rates, the most affected corresponded to PNES-and-epilepsy group. Another issue has been raised on how the education and employment opportunity is affected by the stigma that exists towards patients with PNES [26]. It has been described that a low school performance was more frequent in young patients with PNES [18]. Women with PNES tend to show greater difficulties to perform tasks that involve working memory and attention [27]. All this could explain poor academic and work performances.

The most frequent psychiatric comorbidities described in medical literature in these patients are personality disorders (62%), post-traumatic stress (49%), anxiety (47%) and major depression (47%) [28]. This study explored depression and anxiety. It has been described that explicit anxiety is significantly more frequent in PNES alone. Additionally, there is a positive correlation between the frequency of seizures and anxiety traits [29]. Patients with PNES are characterized for having a prior history of sexual abuse and personality traits with a high degree of emotional instability with a low level of awareness of the problem, restricting their coping skills [30]. These findings justify the evaluation, treatment and follow-up by a multidisciplinary team, including the department of neurology, neuropsychology and psychiatry, among others.

Most patients exhibited a delay of several years between seizure onset and a correct diagnosis. Such finding is consistent with another study which reported a latency until the diagnosis of 5.6 ± 8 years [23]. A delayed diagnosis of PNES results in uncertainty, poorer outcomes, unnecessary prescription of antiepileptic drugs, and unnecessary interventions [31]. In the present study, it was established that men with PNES had higher frequency of seizures and, in turn, higher consumption of antiepileptic drugs. This could be explained in part by the fact that men are more likely to have motor-type PNES, making the prescription of antiepileptic drugs more likely [19].

In regards to seizure semiology, the most common manifestations were a gradual onset of the seizure and a prolonged course, both in the PNES-

alone group and in PNES-and-epilepsy. As mentioned by Reuber et al [13] who reported prolonged duration as a particular feature of PNES. Furthermore, different reports conclude that one of the semiological signs with greater specificity in PNES is prolonged duration (> 90%).

This study poses some limitations. The generalization of the results is restricted because patient data came from clinical records of a single institution. Similarly, the retrospective nature of the study contributed to selection bias and measurement bias regarding age of seizure onset and the frequency of seizures. Of note, most studies set comparisons between PNES and epilepsy. This study allowed comparing patients with PNES-alone, and PNES-and-epilepsy, being the latter a diagnostic challenge that requires further investigations. It is recommended for future investigations to include a greater number of institutions, to actively search for male patients, to identify additional prognostic factors for PNES and to consider psychiatric comorbidities, seizure semiology and VEEG findings.

In conclusion, the patients with PNES-and-epilepsy could have a clinical debut at a younger age than patients with PNES-alone and would be characterized by having a higher rate of unemployment. In relation to the clinical characteristics, the prescription of antiepileptic drugs was higher in the PNES-and-epilepsy group. From the semiological perspective it was not possible to conclude relevant differences between the subgroups. The above findings could be useful in clinical neurological practice.

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Crisis psicógenas no epilépticas y crisis epilépticas: pistas para un diagnóstico diferencial. Hallazgos de un estudio colombiano

Introducción. Las crisis psicógenas no epilépticas (CPNE) son cambios paroxísticos en el comportamiento que se asemejan a las crisis epilépticas, aunque no tienen correlación electrofisiológica ni evidencia clínica de epilepsia.

Objetivo. Comparar las características clínicas y sociodemográficas entre pacientes diagnosticados con CPNE, con y sin epilepsia concomitante.

Pacientes y métodos. Estudio transversal de pacientes consecutivamente diagnosticados de CPNE durante un período de 20 meses. A todos los participantes se les realizó un videoelectroencefalograma (video-EEG). Se compararon las características sociodemográficas, clínicas y semiológicas entre los que presentaban y los que no presentaban epilepsia concomitante.

Resultados. Se incluyó a 65 pacientes, 35 con CPNE (53,9%), y 30 con CPNE y epilepsia (46,1%). La edad mediana en el inicio del video-EEG fue de 33 años, y un 70,8% eran mujeres. La edad mediana de inicio de las crisis fue de 16 años. En el grupo de CPNE hubo un inicio más tardío (23 años) en comparación con el grupo de CNPE y epilepsia (11 años), pero la diferencia no fue significativa. La proporción de pacientes en terapia con fármacos antiepilépticos fue significativamente mayor en el grupo con CPNE y epilepsia comparado con el grupo con CPNE. Las características semiológicas más frecuentemente encontradas fueron el inicio gradual de las crisis (69,2%) y una duración de más de dos minutos (63,1%).

Conclusión. La variabilidad en los síntomas sugiere un origen no epiléptico de los eventos paroxísticos, los cuales se presentan frecuentemente en pacientes con epilepsia.

Palabras clave. Crisis psicógenas no epilépticas. Crisis epilépticas. Electroencefalografía. Epilepsia. Manifestaciones neurológicas. Trastornos de conversión.