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Psychiatric and psychological assessment of Spanish patients with drug-resistant epilepsy and psychogenic nonepileptic seizures (PNES) with no response to previous treatments

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ABSTRACT

Objective: Psychogenic nonepileptic seizures (PNES) are common imitators of epileptic seizures. Refractoriness to antiseizure medication hinders the differential diagnosis between ES and PNES, carrying deleterious consequences in patients with PNES. Psychiatric and psychological characteristics may assist in the differential diagnosis between drug-resistant epilepsy (DRE) and PNES. Nevertheless, current comprehensive psychiatric and psychological descriptive studies on both patient groups are scarce and with several study limitations. This study provides a comprehensive psychiatric and psychological characterization of Spanish patients with DRE and PNES.

Method: A cross-sectional and comparative study was completed with 104 patients with DRE and 21 with PNES. Psychiatric and psychological characteristics were assessed with the HADS, SCL-90-R, NEO-FFI-R, PDQ-4+, COPE, and QOLIE-31 tests. Parametric and non-parametric tests were used, and regression models were fit to further explore factors affecting patients' life quality.

Results: Patients with PNES had greater levels of somatization and extraversion and were associated with benzodiazepine intake. Patients with DRE showed greater narcissistic personality disorder symptoms than those with PNES. In patients with DRE, difficulty in performing basic needs-related tasks and greater psychological distress severity and seizure frequency were associated with poorer life quality. In contrast, being a woman, having a psychiatric disorder history, and greater psychiatric symptoms' intensity were associated with poorer life quality in patients with PNES.

Conclusion: Patients with DRE and PNES share similar psychiatric and psychological characteristics, with only very few being significantly different.

1. Introduction

Epilepsy is a chronic, severe, and heterogeneous neurological disorder characterized by an enduring predisposition to generate epileptic seizures (ESs). ESs are transient paroxysmal events caused by abnormally excessive and hypersynchronous neuronal activity in the brain. ESs can occur at any time, and there is no control on the onset of seizures, last less than 5 minutes, and usually end spontaneously and without intervention [1]. The etiology of seizures is extensive and does not always reside in abnormally excessive and hypersynchronous neuronal activity in the brain. Therefore, their occurrence does not necessarily confirm the epilepsy diagnosis [2].

Drug-resistant epilepsy (DRE) involves the occurrence of uncontrolled seizures despite the use of two or more tolerated and adequately chosen antiseizure medication (ASM) [3]. In addition to higher rates of psychiatric and medical comorbidities, stigmatization, social exclusion, and mortality [4], patients with DRE often

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experience accelerated brain and nervous system damage [5]. Further, after admission to epilepsy units for a comprehensive seizure evaluation, a notable proportion of patients with DRE are found to have nonepileptic seizures (2–71% misdiagnosis), with nonepileptic paroxysmal events (NEPE) being among the most common imitators [6,7].

NEPE are associated with a group of disorders characterized by motor, behavioral, and sensory activity alterations that resemble epilepsy but are not related to EEG neurophysiological dysfunction as observed on EEG. Within NEPEs, psychogenic nonepileptic seizures (PNES) are acute episodes of involuntary movement, sensation, or behavior that mimic ESs [8]. While ESs and PNES can coexist, PNES distinguish from ESs by being episodic, variable duration, and stereotypical profile [9]. PNES's main psychological risk factors are acute or persistent stress, childhood sexual or physical abuse [9,10]. Making PNES's differential diagnosis includes psychiatric interviews, parental reports, imaging tests (e.g., MRI), and video-electroencephalogram (EEG) monitoring [9].

Despite relevant advances in diagnostic techniques, the accurate diagnosis of PNES remains challenging, even for experienced clinicians [7]. PNES misclassification rates as DRE is 5–10% [11] among primary care physicians [12,13]. Failing to diagnose PNES delays the correct diagnosis 7–9 years from the first critical episode [14,15], resulting in deleterious consequences for patients, including increased hospitalization, stigma, and employment restrictions. More importantly, PNES misdiagnosis results in unnecessary ASM treatments and associated side effects, which worsens patients' mental health and life quality [7].

The challenges encountered in the PNES diagnosis, together with the high prevalence of patients facing undesired consequences and scarcity of rapid and affordable diagnostic instruments [13,16], suggest exploring alternative and auxiliary diagnostic methods [12], among which are psychiatric and psychological characteristics [14]. Nevertheless, research with a recent and extensive description of patients with DRE and PNES is scarce and presents relevant methodological limitations [17–19], especially concerning Spanish patients [19].

The aim of this study was to provide a comprehensive characterization of Spanish patients with DRE and PNES, presenting current data on their sociodemographic, clinical, psychiatric, and psychological characteristics. Then, Spanish patients with DRE and PNES are compared across sociodemographic, clinical, psychiatric, and psychological characteristics.

2. Material and methods

2.1. Study design

This is a cross-sectional and comparative study with patients with DRE and PNES at the Epilepsy Unit of the Neurology Department (HCP).

All study procedures complied with the Helsinki declaration for research and received approval from the Ethics Committee Board of the Hospital Clinic of Barcelona (HCP). All patients signed the informed consent for participation.

2.2. Setting and subjects

This study was conducted at the Epilepsy Unit of the Neurology Department (HCP) between March 2017 and November 2019. Patients with DRE and PNES were recruited after an invitation for a one-week protocolized study of their seizures by continuous video-EEG monitoring.

Inclusion criteria were patients with (1) seizure episodes or disconnection from the environment, (2) refractoriness to ASM, (3) admission to the Epilepsy Unit of the Neurology Department (HCP), (4) age over 18 years, and (5) completion of written consent to participate. Exclusion criteria were (1) history of severe medical pathology except for epilepsy, (2) cognitive impairment (i.e., IQ < 70), (3) presence of previously diagnosed dementia, (4) prior diagnosis of schizophrenia or other chronic psychosis, (5) history of nonepileptic seizures of non-psychogenic etiology, (6) history of surgery for seizure control, and (7) history of phobia of closed-in spaces (claustrophobia).

Refractoriness to ASM was established according to the parameters outlined at the HCP [20].

2.3. Clinical assessment

A senior psychiatrist conducted the clinical interviews. Clinical interviews included a thorough explanation of the study purpose and the psychiatric and psychological assessment planned within the one-week protocolized study of their seizures. Clinical interviews also included sociodemographic data collection and psychiatric and psychological assessments, which a senior psychiatrist and fellow psychologists conducted, respectively.

2.4. Neurological assessment

Senior neurologists and psychiatrists conducted the neurological exploration. The neurological exploration included diagnosing DRE or some other etiology causing paroxysmal motor events (PNES) and the intellectual quotient (QI) assessment. The neurological exploration was conducted following the epilepsy surgery protocol established at the HCP [21].

2.5. Data collection and assessment instruments

- **Sociodemographic characteristics.** These were assessed with the sociodemographic form. The form included data regarding age, gender, degree of schooling, history of dropping out of school due to seizures, work status, disability pension status, current living situation, difficulties in performing domestic-, basic needs-, and care-related tasks, and difficulties in performing tasks that require mental effort.
- **Clinical characteristics.** These were assessed with the Structured Clinical Interview for DSM-IV (SCID-CV; Spanish Version) [22]. The clinical characteristics evaluation also consisted of gathering data regarding the seizures: frequency during the last 6 months and at onset, age at onset; age at onset of ASM treatment; history of and present psychiatric disorders; personality disorders; other current psychopharmacological treatment; and present medical illness.
- **Depression and anxiety (psychological distress)**. These were assessed with the Hospital anxiety and depression scale (HADS) [23]. The HADS is a 14-item scale comprised of two subscales: seven items evaluate depression (HAD-D) and the other seven evaluate anxiety (HAD-A). Scoring for each item ranges from zero to three on a 4-point Likert scale basis, the maximum total score is 21 for each subscale and a total of 42 for the overall test. The recommended cutoff point in both subscales (HAD-A and HAD-D) is 8–10 in doubtful cases and $\geq$ 11 for definite cases.
- **Interictal psychiatric disorders.** These were assessed with Blumer's classification for interictal psychiatric disorders [24,25]. The interictal dysphoric disorder is defined by the significantly bothersome presence of at least three of the following affective-somatic symptoms: depressive mood, anergia, irritability, pain, insomnia, fears, anxiety, and euphoric mood. Symptoms tend to be intermittent (lasting from hours to a few days). The interictal psychotic disorder is characterized by a pre-existing and concomitant severe dysphoric disorder where psychotic symptoms

(hallucinations, paranoia, delusions, and/or bizarre behavior) must be present in a persistent (not days or weeks) and not fleeting manner.

- **Somatization level and current psychopathology.** These were assessed with the Symptom Checklist-90-revised (SCL-90-R) [26]. The SCL-90-R is a 90-item self-administered questionnaire that evaluates somatization and psychopathology symptoms on a 0 (absence of symptoms) to 4 (maximum discomfort) scale. The SLC-90-R 90 items are grouped into 9 subscales, evaluating somatic, obsessive–compulsive, interpersonal sensitivity, depressive, anxious, hostility, phobic anxiety, paranoid ideation, and psychoticism symptoms. The SCL-90-R also includes three global indices of psychological distress: Global severity index (GSI), Positive symptom distress index (PSDI), and Positive symptom total (PST).
- **Personality traits.** These were assessed with the NEO Personality Inventory-Revised (NEO-FFI-R) [27]. The NEO-FFI-R is a self-administered questionnaire based on the comprehensive model of general personality traits: the Five-Factor Model [28]. The NEO-FFI-R, a reduced version of the NEO-PI-R inventory [29], consists of 60 items based on a five-point Likert scale response (i.e., Strongly disagree to Strongly agree) that assess five personality dimensions: Neuroticism, Extraversion, Openness to Experience, Agreeableness and Conscientiousness.
- **Coping strategies**. These were assessed with the Coping Orientation to Problems Experience inventory (COPE) [30]. The COPE inventory is a multidimensional 60-item self-reported test that evaluates usage of 15 theory-based coping strategies on a 4-point Likert scale ("I never do this" to "I do this very often). The COPE coping strategies can be grouped into three factorially based dimensions (except Humor): Engagement [E], Disengagement [D], and Help-seeking [HS] [31]. Higher scores suggest higher use of the coping strategies.
- **Life quality**. These were assessed with the Quality of Life in Epilepsy Inventory-31 (QOLIE-31) [32]. The QOLIE-31 is a self-administered questionnaire that evaluates patients' life quality over the last 4 weeks. The QOLIE-31 involves two main factors (emotional and psychological effects and medical and social effects) divided into seven subscales with a total of 31 items. Scoring is based on a 4- to 6-point Likert scale, with a maximum total score of 100. Higher scores suggest a better quality of life.
- **Personality disorders**. These were assessed with the Personality Diagnostic Questionnaire 4+ (PDQ-4+) [33]. The PDQ-4+ is a self-report 99-item questionnaire, which screens for personality disorders described according to DSM-IV criteria [34]. The PDQ-4+ items are distributed at random across 12 subscales: 10 subscales measure symptoms of DSM-IV Axis II personality disorders, while another 2 subscales measure symptoms of DSM-IV Appendix B personality disorders. The PDQ-4+ items follow a true/false response format, with each item referring to a DSM-IV diagnostic criterion.

2.6. Procedures

Patients with DRE and PNES were recruited at the Epilepsy Unit of the Neurology Department (HCP). Both patient groups volunteered for an initial visit with the neurologist to evaluate their seizures. At that time, none of the patients had a confirmed diagnosis of their seizures.

If, during the first visit, the neurologist suspected DRE or some other etiology causing paroxysmal events, patients were invited for a one-week protocolized study of their seizures at the same hospital facilities (HCP) [20].

Alongside the hospitalization week, the Epilepsy Committee board evaluated the compliance of each patient with the study inclusion and exclusion criteria. Patients who met the inclusion criteria were invited to participate in the study by signing the informed consent form. Then data collection and psychiatric and psychological assessments took place. Fig. 1 shows the study procedures.

2.7. Statistical analysis

The mean and standard deviation, in the case of continuous variables, and percentages, in the case of categorical variables, were used for the descriptive statistical analysis of the sample.

The Mann–Whitney U test was used to compare patients with PNES and DRE across sociodemographic, clinical, psychiatric, and psychological continuous study variables. The Chi-square test for Association was used to examine the associations between the patient groups and the sociodemographic, clinical, psychiatric, and psychological categorical study variables. Post hoc Chi-square tests with the Bonferroni correction were used to determine which categories were statistically significant. Fisher's exact test (FET) was used when the Chi-square test for Association's assumptions were not met (e.g., $\leq$5 observations for a group).

A multiple regression analysis was conducted to examine the independent effects of different sociodemographic and clinical variables on quality of life of patients with DRE and PNES, separately: gender, age, working status, difficulty in performing domestic-, basic needs- and care-related tasks, and difficulties in performing tasks that require mental effort, sleeping difficulties, age at onset of ASM treatment, frequency of seizures within the last 6 months, past and present psychiatric disorders, other current psychopharmacological treatment, anxiety and depression (HADS), somatization (SCL-90), overall psychological distress severity (GSI, SCL-90), psychiatric symptom intensity (PSDI, SCL-90), personality traits (NEO-FFI-R), and coping strategies (COPE). The backward elimination, in terms of the lowest AIC value, was used to fit the models.

Study variables such as past and present psychiatric disorders were unified to increase the statistical power and prevent Type I error due to having small subgroup sizes [35].

The SPSS v26 for MAC program was used for all data analyses. All results were interpreted with a 95% confidence interval (CI) and a significance level (p-value) of 0.05. Adjusted estimates were used when reporting the regression models.

3. Results

3.1. Sociodemographic and clinical characteristics

3.1.1. Sociodemographic and clinical characteristics

The final analysis included 104 patients with DRE and 21 patients with PNES. Four patients with no psychiatric history nor psychiatric disorders at baseline were excluded due to non-complete questionnaires. Statistical analysis revealed no significant differences between included and excluded patients ($p > 0.05$). All the sociodemographic and clinical characteristics at baseline are shown in Table 1.

The analysis conducted on sociodemographic characteristics revealed no statistically significant differences between DRE and PNES, except in sleeping difficulties ($\chi^2 = 8.760$, df = 2, $p = 0.013$). Subsequent post hoc tests revealed that patients with PNES were significantly more associated with very frequent sleeping difficulties than patients with DRE ($p = 0.007$).

The analyses conducted on clinical characteristics showed statistically significant differences between patients with DRE and PNES in other current psychopharmacological treatment ($p < 0.001$, FET). The post hoc test conducted revealed that patients with PNES were significantly more associated with benzodiazepines intake ($p < 0.001$) than patients with DRE. Differences in the age at onset of seizures ($U = 414.50$, $p < 0.001$) and age of initiation of ASM treatment ($U = 329.5$, $p = 0.001$) were statistically significant, occurring earlier in patients with DRE than in patients with PNES.

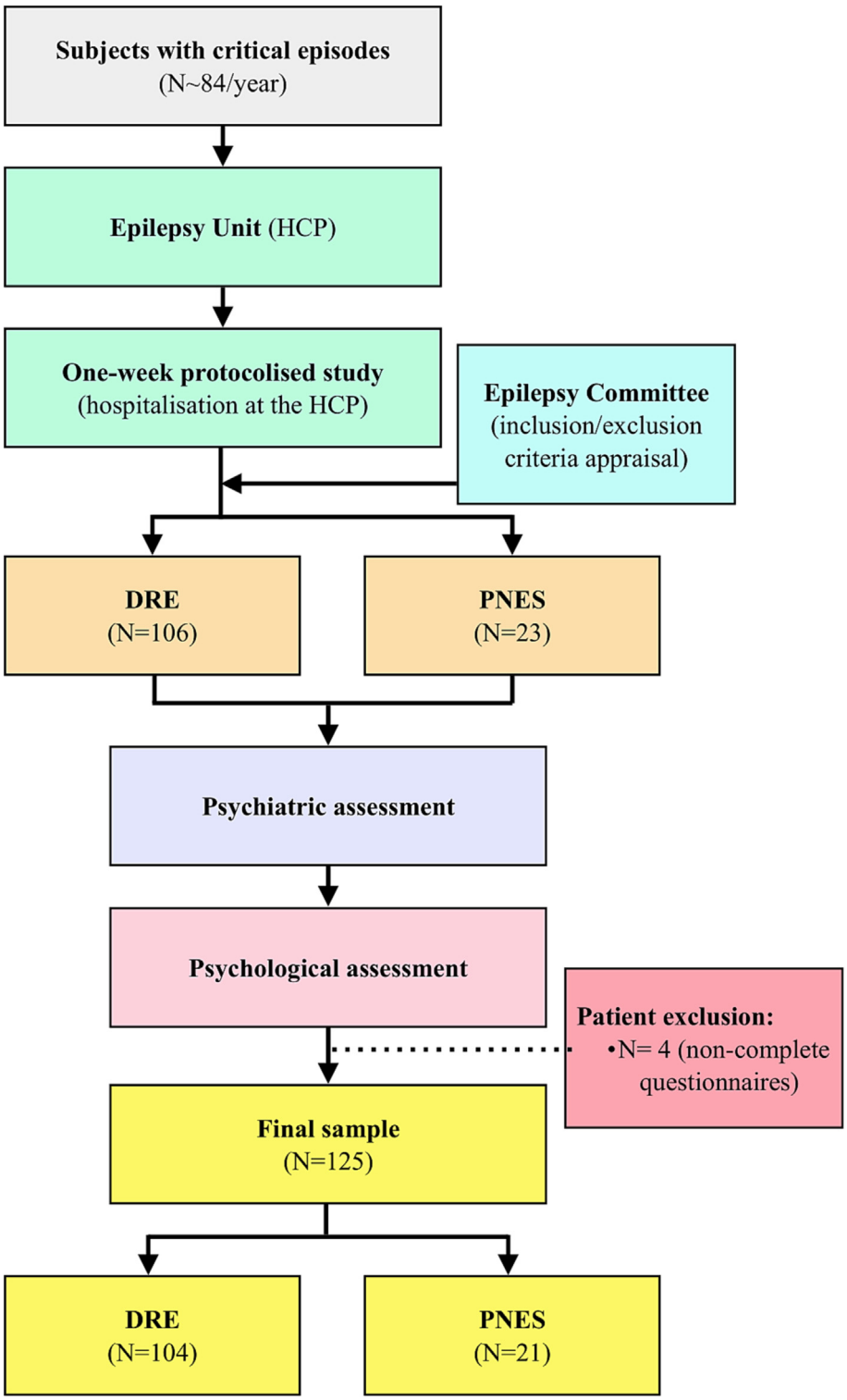

Fig. 1. Study flowchart.

3.2. Quantitative psychiatric and psychological assessment

3.2.1. Anxiety and depression (HADS) and interictal psychiatric characteristics

The HADS test results (Table 2) across patients with DRE and PNES were similar ($p > 0.05$) and below the cutoff point for doubtful cases of anxiety and depression [23].

Most patients did not meet the diagnostic criteria for the interictal dysphoric disorder (69.6%) nor interictal psychotic disorder (95.2%). Although patients with PNES accounted for most interictal dysphoric (38.10%) and psychotic (19.05%) disorder cases, no statistically significant differences were found between patient groups ($p > 0.05$) (Table 2).

3.2.2. Psychopathological (SLC-90 & PDQ) characteristics

Comparisons for the SCL-90-R test (Table 2) showed that patients with PNES had higher scores in all the psychopathological symptoms domains compared to patients with DRE. However, the

Table 1
Sociodemographic and clinical characteristics of the sample and comparisons between patients with DRE and PNES.

	Total (N = 125)		**DRE (N = 104)**		**PNES (N = 21)**		
	N (%)	**M (S.D.)**	**N (%)**	**M (S.D.)**	**N (%)**	**M (S.D.)**	***p-value***
Sociodemographic characteristics							
Age		37.6 (11.9)		38.2 (12.3)		34.5 (9.03)	*0.230*
Gender:							*0.305*
Men	50 (40.0)		39 (37.5)		11 (52.4)		
Women	75 (60.0)		65 (62.5)		10 (47.6)		
Degree of schooling							*0.659*
Elementary school	25 (20.0)		21 (20.2)		4 (19.0)		
Primary school	51 (40.8)		45 (43.3)		6 (28.6)		
Secondary school	34 (27.2)		26 (25.0)		8 (38.1)		
Vocational training	9 (7.2)		7 (6.7)		2 (9.5)		
Higher education (University, PhD, etc.)	6 (4.8)		5 (4.8)		1 (4.8)		
Dropping out of school due to seizures							*0.834*
Yes	24 (19.2)		21 (20.2)		3 (14.3)		
No	101 (80.8)		83 (79.8)		18 (85.7)		
Working status							*0.656*
Active	47 (37.6)		40 (38.5)		7 (33.3)		
Non-active	78 (62.4)		64 (61.5)		14 (66.7)		
Dropping out of the job due to seizures							*0.731*
Yes	47 (37.6)		38 (36.5)		9 (42.9)		
No	78 (62.4)		66 (63.5)		12 (57.1)		
Disability pension scheme							*0.585*
Yes	41 (32.8)		35 (33.7)		6 (28.6)		
No	84 (67.2)		69 (66.3)		15 (71.4)		
Current living situation							*0.342*
With parents	44 (35.2)		38 (36.5)		6 (28.6)		
With relatives	9 (7.2)		6 (5.8)		3 (14.3)		
With partner	55 (44.0)		46 (44.2)		9 (42.9)		
Alone with children in their care	5 (4.0)		4 (3.8)		1 (4.8)		
Alone	6 (4.8)		5 (4.8)		1 (4.8)		
Friends	4 (3.2)		4 (3.8)		0 (0.0)		
Others	2 (1.6)		1 (1.0)		1 (4.8)		
Difficulty in domestic-related tasks							*0.564*
Never	67 (53.6)		58 (55.8)		9 (42.9)		
Occasionally	44 (35.2)		35 (33.7)		9 (42.9)		
Very frequent	14 (11.2)		11 (10.6)		3 (14.3)		
Difficulty in basic needs-related tasks (e.g., personal errands, shopping)							*0.097*
Never	57 (45.6)		51 (49.0)		6 (28.6)		
Occasionally	49 (39.2)		36 (34.6)		13 (61.9)		
Very frequent	19 (15.2)		17 (16.3)		2 (9.5)		
Difficulty in tasks that require mental effort							*0.613*
Never	24 (19.2)		21 (20.2)		3 (14.3)		
Occasionally	70 (56.0)		56 (53.8)		14 (66.7)		
Very frequent	31 (24.8)		27 (26.0)		4 (19.0)		

(*continued on next page*)

Table 1 (*continued*)

	Total (N = 125)		**DRE (N = 104)**		**PNES (N = 21)**		
	N (%)	**M (S.D.)**	**N (%)**	**M (S.D.)**	**N (%)**	**M (S.D.)**	***p-value***
Difficulty in personal care-related tasks							*0.550*
Never	95 (76.0)		80 (76.9)		15 (71.4)		
Occasionally	23 (18.4)		18 (17.3)		5 (23.8)		
Very frequent	7 (5.6)		6 (5.8)		1 (4.8)		
Sleeping difficulties							
Never	65 (52.0)		56 (53.8)		9 (42.9)		*0.013*
Occasionally	38 (30.4)		32 (30.8)		6 (28.6)		
Very frequent	22 (17.6)		16 (15.4)		6 (28.6)		
Clinical characteristics							
Age at onset of seizures (in months)		218.21 (161.56)		198.80 (160.74)		329.33 (117.74)	*<0.001*
Age at onset of ASM treatment (in months)		242.52 (153.22)		225.38 (152.12)		348.80 (115.32)	*0.001*
Seizures frequency (last 6 months)							*0.177*
Less than 1 per month	6 (4.8)		5 (4.8)		1 (4.8)		
1–5 per month	42 (33.6)		37 (35.6)		5 (23.8)		
5 or more per month	77 (61.6)		62 (59.6)		15 (71.4)		
Seizure frequency at onset							*0.933*
Less than 1 per month	20 (16.0)		17 (16.3)		3 (14.3)		
1–5 per month	48 (38.4)		39 (37.5)		9 (42.9)		
5 or more per month	57 (45.6)		48 (46.2)		9 (42.9)		
SCID - Psychiatric disorders (history)							*0.418*
No history	67 (53.6)		59 (56.7)		8 (38.1)		
MD episode	18 (14.4)		14 (13.5)		4 (19.0)		
Recurrent depression	6 (4.8)		3 (2.9)		3 (14.3)		
Dysthymia	7 (5.6)		6 (5.8)		1 (4.8)		
Bipolar disorder	1 (0.8)		1 (1.0)		0 (0.0)		
Other psychosis	5 (4.0)		5 (4.8)		0 (0.0)		
Other anxiety & anxious adjustment disorders	11 (8.8)		8 (7.7)		3 (14.3)		
Phobias	1 (0.8)		1 (1.0)		0 (0.0)		
Eating disorder	1 (0.8)		1 (1.0)		0 (0.0)		
Dependence OH/Abuse	1 (0.8)		1 (1.0)		0 (0.0)		
Other substance abuse dependence	2 (1.6)		1 (1.0)		1 (4.8)		
Adaptive depressive disorder	3 (2.4)		3 (2.9)		0 (0.0)		
Behavioral disorder	2 (1.6)		1 (1.0)		1 (4.8)		
SCID - Psychiatric disorders (history), *in groups*							*0.678*
No history	67 (53.6)		59 (56.7)		8 (38.1)		
Affective disorders	35 (28.0)		27 (26.0)		8 (38.1)		
Anxiety disorders	12 (9.6)		9 (8.7)		3 (14.3)		
Other disorders (psychosis/dependence/behavioral)	11 (8.8)		9 (8.7)		2 (9.5)		
SCID - Psychiatric disorders (present)							*0.479*
No history	78 (62.4)		66 (63.5)		12 (57.1)		
MD episode	13 (10.4)		9 (8.7)		4 (19.0)		
Recurrent depression	3 (2.4)		3 (2.9)		0 (0.0)		
Dysthymia	7 (5.6)		7 (6.7)		0 (0.0)		
Bipolar disorder	1 (0.8)		1 (1.0)		0 (0.0)		
Other psychosis	4 (3.2)		3 (2.9)		1 (4.8)		
Other anxiety & anxious adjustment disorders	14 (11.2)		10 (9.6)		4 (19.0)		
Phobias	1 (0.8)		1 (1.0)		0 (0.0)		
Eating disorder	0 (.)		0 (.)		0 (0.0)		
Dependence OH/Abuse	0 (.)		0 (.)		0 (0.0)		
Other substance abuse dependence	0 (.)		0 (.)		0 (0.0)		
Adaptive depressive disorder	3 (2.4)		3 (2.9)		0 (0.0)		
Behavioral disorder	1 (0.8)		1 (1.0)		0 (0.0)		
SCID - Psychiatric disorders (present), *in groups*							*0.317*
No history	78 (62.4)		66 (63.5)		12 (57.1)		
Affective disorders	27 (21.6)		23 (22.1)		4 (19.0)		

Table 1 (*continued*)

	Total (N = 125)		DRE (N = 104)		PNES (N = 21)		
	N (%)	M (S.D.)	N (%)	M (S.D.)	N (%)	M (S.D.)	*p-value*
Anxiety disorders	15 (12.0)		11 (10.6)		4 (19.0)		
Other disorders (psychosis/dependence/behavioral)	5 (4.0)		4 (3.8)		1 (4.8)		
Pharmacological treatment							*<0.001*
No treatment	92 (73.6)		84 (80.8)		8 (38.1)		
Antidepressants	26 (20.8)		17 (16.3)		9 (42.9)		
Neuroleptics	5 (4.0)		3 (2.9)		2 (9.5)		
Benzodiazepines	2 (1.6)		0 (.)		2 (9.5)		
Medical illness (present) - Axis III							*0.231*
Yes	40 (32.0)		30 (28.8)		10 (47.6)		
No	85 (68.0)		74 (71.2)		11 (52.4)		
Intellectual quotient (QI)							*0.692*
Normal	111 (88.8)		91 (87.5)		20 (95.2)		
Limit	3 (2.4)		3 (2.9)		0 (0.0)		
Mental deficiency	11 (8.8)		10 (9.6)		1 (4.8)		

statistical analysis only revealed that patients with PNES had greater somatization than patients with DRE (U = 541, $p < 0.001$).

Patients with DRE had higher mean scores in 8 out of the 12 PDQ-4 + test subscales compared to patients with PNES (Table 2), but with only a statistically significant difference in the narcissistic subscale ($U = 498$, $p = 0.031$).

3.2.3. Personality (NEO-FFI-R) and coping (COPE) characteristics

The personality assessment results (Table 2) showed that patients with PNES had slightly higher mean scores than patients with DRE in all the NEO-FFI-R test personality dimensions, except in openness to experience. However, the analysis revealed a significant difference only for extraversion (U = 186.5, $p < 0.001$), favoring patients with PNES.

Regarding the COPE inventory results (Table 2); although patients with PNES appeared to have overall higher mean scores across all the COPE inventory coping strategies compared to patients with DRE, no statistically significant differences were found between patient groups ($p > 0.05$).

3.2.4. Life quality (QOLIE-31) characteristics

Patients with DRE and PNES seemed to have similar results in the QOLIE-31 (Table 2). The statistical analysis conducted on the data did not show significant differences in life quality between the two patient groups ($p > 0.05$).

3.2.5. Effects of sociodemographic and clinical characteristics on life quality of patients with DRE and PNES (based on the QOLIE-31 results)

After adjusting for age and gender, the multiple regression analysis conducted to examine the independent effects of study variables on the life quality of DRE [$F(8, 95) = 30.128$, $p < 0.001$; $R^2 = 0.717$] and PNES [$F(6,14) = 10.641$, $p < 0.001$; $R^2 = 0.780$] patients revealed statistically significant results (Table 3).

Overall psychological distress severity (GSI), difficulty in performing basic needs-related tasks, seizure frequency within the last 6 months, depression (HAD-D), agreeableness and openness to experience (NEO-FFI-R), and engagement (COPE) had significant effects on life quality of patients with DRE. On the other hand, psychiatric symptoms intensity (PSDI) history of psychiatric disorder, gender, and neuroticism (NEO-FFI-R) had significant effects on life quality of patients with PNES.

4. Discussion

To the best of our knowledge, our study is the first to provide current, comprehensive, and consistent data on the sociodemographic, clinical, psychiatric, and psychological characteristics of Spanish patients with DRE and PNES with no response to previous treatments.

After extensive assessment, this study found that patients with DRE and PNES had similar depression and anxiety levels. While patients with DRE had higher morbidity compared to patients without DRE [36], previous research has shown that patients with PNES had greater anxiety and depression than patients with epilepsy [19,37,38]. A reasonable explanation for this discrepancy may be the fact that the previous studies used different psychometric instruments to evaluate psychological distress compared to the present study. Additionally, these previous studies mostly assessed patients with epilepsy without refractoriness [19,39,40].

Interictal psychiatric disorders are frequent in DRE [41]. Interictal dysphoric disorder is recognized as the most common presentation of depression in patients with epilepsy (20–70%) [42], whereas the prevalence of interictal psychotic disorder is 3–27% [43,44]. The prevalence of depressive and psychotic disorders in patients with PNES is described as higher and lower, respectively, compared to patients with epilepsy [45]. Consistent with recent findings, our study found no significant differences between patients with DRE and PPNES regarding interictal psychiatric disorders [45,46].

In previous research, patients with PNES had higher rates of psychopathological comorbidity than patients with epilepsy. This includes posttraumatic stress (PTSD), somatic, anxiety, affective, and even personality disorders. While our results seemed to align with early research [47,48], it is important to highlight that psychopathological comorbidity was similarly present in patients with DRE as patients with PNES [39,49]. SCL-90-R test results showed that somatic symptoms were significantly higher in patients with PNES compared to patients with DRE [48,50]. These latter results were not surprising [8], as high somatic symptoms have been associated with traumatic experiences, a risk factor for PNES onset [51].

The PDQ-4+ test results showed that the prevalence of personality disorders was not significantly different in patients with DRE compared to patients with PNES, except for Narcissistic personality disorder. These results are consistent with previous findings [47], although limitations due to the use of different and non-DSM-

Table 2
Results of the psychiatric and psychological assessment for the sample and across patients with DRE and PNES.

	Total (N = 125)	DRE (N = 104)	PNES (N = 21)	
	N (%)			*p-value*
Interictal dysphoric disorder				
Yes	38 (30.4)	30 (28.8)	8 (38.1)	*0.547*
No	87 (69.6)	74 (71.2)	13 (61.9)	
Interictal psychotic disorder				
Yes	6 (4.8)	2 (1.9)	4 (19.0)	*0.082*
No	119 (95.2)	102 (98.1)	17 (81.0)	
	M (S.D.)			***p-value***
HADS				
Anxiety	4.79 (4.50)	4.81 (4.53)	4.71 (4.50)	*0.449*
Depression	7.20 (4.28)	7.08 (4.23)	7.94 (4.63)	*0.844*
SLC-90-R				
SOMA	1.24 (0.86)	1.13 (0.83)	1.81 (0.80)	*<0.001*
OCD	1.68 (0.87)	1.66 (0.87)	1.77 (0.87)	*0.529*
INT	1.09 (0.72)	1.13 (0.74)	0.90 (0.63)	*0.246*
DEPR	1.32 (0.82)	1.30 (0.82)	1.41 (0.84)	*0.617*
ANX	1.13 (0.74)	1.08 (0.72)	1.38 (0.79)	*0.112*
HOST	0.90 (0.77)	0.86 (0.71)	1.08 (1.01)	*0.550*
PHOB	0.83 (0.84)	0.78 (0.84)	1.06 (0.85)	*0.159*
PARA	1.16 (1.63)	1.06 (0.78)	1.69 (3.70)	*0.480*
PSYC	0.71 (0.62)	0.72 (0.61)	0.63 (0.64)	*0.400*
ADD	1.19 (0.76)	1.16 (0.77)	1.34 (0.68)	*0.225*
GSI	1.14 (0.64)	1.12 (0.63)	1.27 (0.65)	*0.212*
PSDI	2.00 (0.52)	1.97 (0.53)	2.12 (0.48)	*0.252*
PST	48.7 (19.1)	48.1 (19.2)	51.7 (18.6)	*0.338*
PDQ-4+				
Paranoid	33.6 (24.9)	33.8 (24.4)	32.2 (28.7)	*0.623*
Schizoid	29.4 (19.1)	30.4 (18.8)	24.1 (20.7)	*0.161*
Schizotypal	28.1 (21.6)	28.3 (20.4)	27.0 (28.1)	*0.523*
Histrionic	27.5 (17.5)	28.5 (17.4)	22.1 (17.9)	*0.092*
Narcissistic	23.4 (18.8)	25.0 (19.0)	14.4 (15.4)	*0.031*
Borderline	29.2 (20.8)	28.0 (18.6)	36.0 (30.3)	*0.413*
Antisocial	12.3 (15.8)	12.1 (14.8)	13.4 (21.1)	*0.724*
Avoidant	33.1 (22.3)	33.5 (21.5)	30.4 (27.1)	*0.487*
Dependent	25.0 (24.1)	25.9 (24.0)	19.7 (24.6)	*0.164*
Obsessive-compulsive	42.8 (24.3)	44.2 (23.9)	34.6 (25.7)	*0.137*
Negativistic	31.1 (23.5)	31.1 (23.3)	31.3 (25.7)	*0.972*
Depressive	45.9 (28.8)	45.3 (28.3)	49.1 (32.5)	*0.595*
Cluster A	31.0 (17.6)	31.4 (16.9)	28.6 (21.5)	*0.484*
Cluster-B	23.4 (14.2)	23.6 (13.6)	21.8 (17.8)	*0.466*
Cluster-C	33.4 (18.1)	34.4 (17.4)	27.9 (21.5)	*0.140*
PDQ Total score	29.9 (15.1)	30.3 (14.4)	27.6 (19.3)	*0.499*
NEO-FFI-R inventory				
Neuroticism	24.9 (7.50)	24.8 (6.61)	25.4 (11.8)	*0.692*
Extraversion	27.3 (5.52)	26.4 (5.16)	32.4 (4.83)	*<0.001*
Openness to experience	26.6 (6.02)	26.7 (6.15)	26.1 (5.36)	*0.485*
Agreeableness	32.9 (5.92)	32.5 (6.05)	34.9 (4.80)	*0.183*
Conscientiousness	32.0 (6.69)	31.9 (6.37)	32.6 (8.62)	*0.736*
COPE inventory				
Active coping [*E*]	52.2 (18.1)	50.9 (18.3)	59.2 (15.8)	*0.079*
Planning [*E*]	52.0 (20.8)	52.0 (21.9)	51.6 (14.8)	*0.986*
Seeking instrumental support [*HS*]	59.3 (21.2)	58.0 (20.6)	66.3 (23.0)	*0.125*
Suppression of competing activities [*E*]	49.4 (19.6)	48.1 (19.2)	55.8 (21.0)	*0.179*
Restraint [*E*]	49.3 (19.5)	48.2 (19.3)	54.8 (20.5)	*0.162*
Seeking emotional support [*HS*]	59.9 (20.9)	59.4 (20.0)	62.7 (25.6)	*0.639*
Positive reinterpretation [*E*]	65.7 (17.3)	64.8 (17.6)	70.2 (15.1)	*0.287*
Turning to religion [*D*]	25.8 (29.8)	27.7 (29.5)	16.1 (29.8)	*0.062*
Acceptance [*E*]	61.8 (22.3)	60.3 (21.7)	69.7 (24.3)	*0.088*
Humour [*]	27.5 (22.1)	25.5 (19.8)	37.8 (30.2)	*0.159*
Venting of emotions [*HS*]	39.0 (18.9)	38.3 (18.6)	42.7 (21.0)	*0.573*
Denial [*D*]	20.1 (14.6)	20.3 (14.3)	19.2 (16.5)	*0.442*
Mental disengagement [*D*]	39.0 (18.9)	38.3 (18.6)	42.7 (21.0)	*0.573*
Behavioral disengagement [*D*]	26.5 (16.7)	25.7 (16.3)	30.4 (18.4)	*0.278*
Alcohol & drug use [*]	1.69 (8.60)	2.02 (9.38)	0.00 (0.00)	*0.267*
Engagement [*E*]	55.1 (14.2)	54.1 (14.6)	60.2 (10.5)	*0.469*
Disengagement [*D*]	27.8 (11.6)	28.0 (11.9)	27.1 (10.7)	*0.268*
Help-seeking [*HS*]	54.6 (16.3)	53.4 (15.6)	60.0 (19.0)	*0.945*
QOLIE-31 inventory				
SWT	42.6 (9.72)	42.8 (9.64)	41.4 (10.3)	*0.586*
OQLT	45.0 (9.85)	45.3 (10.1)	43.2 (8.77)	*0.340*
EWT	44.9 (10.0)	44.9 (10.2)	45.1 (9.38)	*0.928*
EFT	48.9 (9.71)	49.4 (9.70)	46.3 (9.64)	*0.212*
COGT	45.9 (10.8)	46.2 (10.8)	44.5 (11.0)	*0.534*
MET	47.0 (9.22)	47.2 (9.10)	45.7 (10.0)	*0.547*

Table 2 (*continued*)

	Total (N = 125)	DRE (N = 104)	PNES (N = 21)	
	N (%)			***p-value***
SFT	43.0 (9.64)	43.6 (9.55)	40.4 (9.96)	*0.207*
QOLIE-31 total score	42.9 (10.4)	43.4 (10.3)	40.2 (10.4)	*0.222*

Abbreviations: *SOMA: Somatization; OCD: Obsessive-compulsive disorder; INT: Interpersonal sensitivity; DEPR: Depression; ANX: Anxiety; HOST: Hostility; PHOB: Phobic anxiety; PARA: Paranoid ideation; PSYC: Psychoticism; GSI: Global severity index; PSDI: Positive symptom Distress Index; PST: Positive symptom total. Cluster A: paranoid, schizoid, schizotypal; Cluster B: Antisocial, Borderline, Histrionic, Narcissistic; Cluster C: Obsessive-compulsive, Avoidant, Dependent.*

Table 3
Regression coefficients of the sociodemographic and clinical characteristics with a significant effect on life quality of patients with DRE and PNES (based on the QOLIE-31 results).

	DRE						PNES				
Predictors	**B**	**95% CI**	**ß**	**t**	***p***	**Predictors**	**B**	**95% CI**	**ß**	**t**	***p***
GSI	−3.990	−6.547, −1.434	−0.240	−3.099	*0.003*	PSDI	−15.527	−21.272, −9.782	−0.745	−5.761	*<0.001*
Difficulty in basic needs-related tasks (e.g., personal errands, shopping), *Yes*	−3.743	−5.375, −2.110	−0.267	−4.551	*<0.001*	SCID – Psychiatric disorders (history), *Yes*	− 10.052	−16.075, −4.029	−0.511	−3.558	*0.003*
Seizures frequency (last 6 months)	−2.219	−4.193, −0.246	−0.124	−2.233	*0.028*	Gender, *Women*	−6.047	−11.888, −0.206	−0.310	−2.207	*0.043*
HAD-D	−0.805	−1.139, −0.471	−0.353	−4.787	*<0.001*	Neuroticism	−0.448	−0.807, −0.089	−0.458	−2.662	*0.018*
Agreeableness	338	0.141, 0.536	0.216	3.400	*<0.001*						
Openness to experience	−0.252	−0.432, −0.073	−0.167	−2.788	*0.006*						
Engagement	−0.109	−0.185, −0.033	−0.163	−2.835	*0.006*						

Note. *CI, confidence interval for B.*
Abbreviations: GSI: Global severity index; PSDI: Positive symptom Distress Index.

based structured clinical interviews and assessment instruments should be considered [47,52,53]. Nevertheless, as with the SCL-90-R test results discussed above, it is important to recall that recent research emphasizes that personality disorders are present in both PNEs and patients with epilepsy, which is consistent with our study results [52].

Although very few works conducted on patients with epilepsy and PNES have based their personality assessment on the Five-Factor Model [28], our NEO-FFI-R inventory results are consistent with the existing literature [54,55]. That is, patients with PNES scored relatively high on all NEO-FFI-R inventory personality dimensions than patients with DRE, with a significantly higher mean score on Extraversion [39]. Mean scores of both patient groups across all the NEO-FFI-R personality domains were also notably higher compared to normative values, especially neuroticism [56]. Considering that high neuroticism is related to mental disorders [27,57,58], the delay or failure to diagnose these patients may precede a worsening of the underlying symptomatology (e.g., psychological discomfort, psychopathological and personality disorders) [47,59–61].

Both patients with epilepsy and PNES face a wide range of psychological and social demands [62]. Together with seizures, these can seriously compromise their well-being [63]. While patients with PNES have been described as having fewer efficient coping strategies than patients with epilepsy [62,63], our study demonstrated the use of engagement (i.e., adaptive) coping strategies over disengagement (i.e., maladaptive) coping strategies in patients with DRE and PNES. The use of adaptive coping strategies over maladaptive coping strategies has been related to positive outcomes in chronically ill patients [64,65]. In epilepsy, adaptive coping strategies over maladaptive coping strategies have been related to lower self-perceived seizure severity and better mental health [66,67].

Comparative studies with patients without DRE have demonstrated greater life quality than patients with PNES [68–70]. While the scarcity of literature comparing patients with DRE and PNES is still limited, our QOLIE-31 test results seemed to deviate from previous findings, showing that both patients with DRE and patients with PNES reported similar low life-quality levels. Not surprisingly, energy-fatigue and medication effects were the most reported QOLIE-31 domains interfering with life quality in both patient groups [68,71].

Regarding the regression analysis, greater psychological distress severity and depression were associated with poorer life quality in patients with DRE. This is not surprising, and extensive literature already relates psychological distress with increased institutionalization, de novo psychiatric disorders, seizure frequency, and suicide rates [47,72–74]. Difficulties in performing basic needs-related tasks were also associated with poorer life quality in patients with DRE. Although people with epilepsy are encouraged to continue with their everyday lives, many withdraw and even isolate themselves due to the seizures' occurrence and their consequences (e.g., physical injuries, burns, decease) [75–77]. Therefore, as expected, higher seizure frequency, especially within the last 6 months, was associated with poorer life quality [78].

The regression model also showed that higher openness to experience and use of engagement coping strategies were associated with poorer life quality. While McCrae and Costa [79] stated that openness to experience is not directly related to well-being but may have both positive and negative effects on this, we found

that the results regarding the engagement coping strategies were rather contrary to the current evidence [64,65]. High agreeableness, the interpersonal tendency toward altruism and willingness to cooperate with others, was found to be associated with better life quality [80].

The regression analysis conducted among patients with PNES showed that a psychiatric disorder history and an increase in the psychiatric symptom intensity were associated with a diminished life quality [68]. Female patients with PNES demonstrated poorer life quality than male patients with PNES. This latter difference may be related to trauma, with women experiencing significantly higher sexual abuse and assault rates than men, thus leading this group to higher dissociation and sexual disturbances in turn impacting quality of life [81]. Lastly, an increase in neuroticism, that is the tendency to experience negative affect, was associated with poorer quality of life, which is consistent with previous research [82,83].

The analysis also showed significant differences in sociodemographic and clinical characteristics already documented in the literature. Namely, patients with PNES were more associated with very frequent sleeping difficulties than patients with DRE [84]. Patients with PNES were also associated with intake of benzodiazepines, a group of psychoactive drugs common in severe epilepsy [85] but also extensively used in patients with seizures of unknown nature unresponsive to usual ASM (i.e., PNES) [86]. Seizure onset [1,14,87] and seizures' first psychiatric treatment [14,15,88] started earlier in patients with DRE compared to patients with PNES.

This study had some limitations: firstly, the cross-sectional nature of the study design. This together with the inclusion of Spanish patients only prevented establishing the whole causality and temporality of the results obtained [89]. The study also excluded patients with coexistent ESs and PNES, which were expected to differ in psychological and psychiatric characteristics compared to those with only epilepsy or PNES [90–92]. Lastly, the small study sample and the patient ratio 4:1 (DRE:PNES). Although a larger sample size and equal size between patient groups would have benefited our results' statistical power, the ratio fell within what is expected in epilepsy units' admissions annually [93]. Altogether, considering that the literature available on this topic is limited, with methodological limitations [17,47], the study findings provide valuable input on this topic, especially concerning Spanish patients.

5. Conclusion

By providing a comprehensive characterization of Spanish patients with DRE and PNES, the present study constitutes a key milestone in the understanding of the psychiatric and psychological characteristics of Spanish patients with DRE and PNES. Beyond the age at onset of seizures and somatization symptoms, patients with DRE and PNES are two patient groups with similar psychiatric and psychological characteristics.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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