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Suicide risk, temperament traits, and sleep quality in patients with refractory epilepsy☆

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ABSTRACT

Objectives: The objective of the study was to access the suicide risk (SR) in patients with refractory epilepsy and its association with temperament and sleep quality.
Methods: A total of 50 consecutive patients referred for epilepsy surgery evaluation in the Porto Alegre Epilepsy Surgery Program were included. All patients had a detailed neurologic and psychiatric evaluation, including video-electroencephalogram (VEEG), high-resolution magnetic ressonance imaging (MRI), and neuropsychologic assessment. In addition, structured questionnaires were applied: module C of the MINI-plus (International Neuropsychiatric Interview-Brazilian version 5.0.0), Affective and Emotional Composite Temperament Scale (AFECTS), and Pittsburgh Sleep Quality Index (PSQI).
Results: Ten patients (20.0%) showed an increased SR. The most frequent location of the epileptic focus was in the temporal lobe (50%; n = 25). Final diagnosis on VEEG comprised epilepsy in 74.0% (n = 37), psychogenic nonepileptic seizures (PNES) in 8.0% (n = 4), and both in 12%. Thirty patients (60.0%) received surgery indication. Mood disorders were the main psychiatric diagnosis, found in 19 subjects (70.4%), with major depressive disorder (MDD) encountered in 15 patients (55.6%). In the group, SR was more frequent in patients with sleep disorders ($p = 0.001$) and elevated scores of high emotional sensitivity ($p = 0.003$).
Conclusion: In this cohort of patients with highly refractory epilepsy, there was a significant association between SR, sleep disorders, and high emotional sensitivity. Careful evaluation of these factors should be performed in these patients to fully access SR.

1. Introduction

Psychiatric comorbidities are commonplace in epilepsy, occurring in 10 to 40% of patients [1,2]. Often, psychopathologies are underdiagnosed and remain untreated, leading to significant morbidity [3]. Suicide poses a public health challenge, with over a million suicides worldwide every year. Suicide represents one of the main causes of death in epilepsy, representing 5 to 11% of deaths in this group [4]. In the United States, such numbers are significantly higher than the rate of suicide in the general population (1.5 to 11.6/100.000) [1,2,4]. Since early 2000s, there has been a better understanding in the shared physiopathology of psychiatric disorders and epilepsy [5]. Such relationship is known as the 'bidirectional hypothesis', in which a shared cerebral deregulation that interferes in behavioral functioning and mood regulation, also leads to neuron excitability and an increased risk of seizures. This concept helps understand the high prevalence of psychiatric disorders both prior and after the diagnosis of epilepsy [6].

An increasing amount of evidence suggests an increased risk of suicidal behavior in patients with psychogenic nonepileptic seizures (PNES) [6,7]. Psychogenic nonepileptic seizure is the main differential diagnosis in patients with supposedly refractory epilepsy, and its coexistence with epilepsy, particularly refractory, has been recently recognized as a diagnostic and therapeutic challenge [6]. Mood disorders contribute to four times increase in the risk of suicide in these patients [2,3,8]. Another important factor in patients with epilepsy (PWE) is sleep quality and psychiatric comorbidities, especially related to suicide risk (SR). Evidence suggests a protective effect of sleep in epilepsy, mostly based on the clinical and laboratorial observation of increased seizures and epileptiform discharges after sleep deprivation. Alterations in the sleep–wake cycle may also contribute to an increased risk of suicidal behavior [9,10]. Mood and anxiety disorders are the most frequent psychiatric comorbidities found in epilepsy [9,11]. In these patients, symptoms may not fulfill strict diagnostic

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criteria from International Statistical Classification of Diseases and Related Health Problems (ICD-10) or Diagnostic and Statistical Manual of Mental Disorders (DSM 5), requiring other instruments to fully evaluate their emotional characteristics [2,11,12]. Temperament traits may be evaluated as protective or harmful for suicidal behaviors [13–15]. Lara et al. [11] proposed an alternative instrument of assessment (the so-called Affective and Emotional Composite Temperament (AFECT) model) that integrates emotional temperament (Cloninger) [16] and affective temperament (Kraepelin and Akiskal) [17,18]. Our study aimed to assess SR, temperament traits, and sleep quality in a cohort of patients whose epilepsy is highly refractory evaluated for epilepsy surgery.

2. Methods

We performed a prospective study of all patients admitted for diagnostic and presurgical evaluation of refractory epilepsy at the Epilepsy Monitoring Unit (EMU) of the Porto Alegre Epilepsy Surgery Program (PAESP) from January 2017 to October 2017.

2.1. Inclusion criteria

We screened all patients from 18 to 70 years of age, and all were included after agreeing to participate in the study and signing a written informed consent form.

2.2. Exclusion criteria

Patients were excluded if they had any of the following conditions: 1) Active psychosis; 2) Current drug abuse (i.e., cannabis, alcohol, cocaine…) and drug-related mental illnesses; 3) Severe cognitive impairment; 4) Unable or unwilling to sign the consent form or to participate in the study.

2.3. Ethics

Our study was approved by our Ethics Committee at Pontifícia Universidade Católica do Rio Grande do Sul (CAAE69516317.0.0000.5336). All patients in the study signed a written informed consent form.

2.4. Data collection

All patients had a detained neurologic and psychiatric assessment, as part of their evaluation for possible epilepsy surgery. This included a careful semiological evaluation of the seizure type and epilepsy, as well as a prolonged video-electroencephalographic (VEEG) study and a 3 T brain MRI. In addition, all had thorough neuropsychologic and psychiatric evaluations. We also applied structured validated questionnaires, including the following: a) Standardized sociodemographic questionnaire; b) Module C of the MINI-plus questionnaire (International Neuropsychiatric Interview-Brazilian version 5.0), regarding SR and evaluation [19]. This score ranges from 1 to 33. Scores from 1 to 5 indicate low risk (suicide ideation), 6 to 10 represents moderate risk (suicide plan), and >10 implies high SR (with previous suicide attempt). In our sample, SR were categorized in two groups, according to module C as present (moderate and high scores) or absent (low scores); c) Affective and Emotional Composite Temperament Scale (AFECTS) [11], a self-reporting instrument, developed and validated by Lara et al. This scale is comprised of two parts: 1) Emotional Section divided in nine dimensions: volition, impulse, anger, fear, emotional sensibility, maturity, control, anxiety, and stability; 2) Affective section comprised of brief descriptions of 12 affective temperaments: [depressive, anxious, apathetic (internalizing); cyclothymic, dysphoric, volatile (unstable); obsessive, euthymic, hyperthymic (stable); irritable, unhinged, and euphoric (externalizing)]; d) Pittsburgh Sleep Quality Index (PSQI), a self-reporting instrument, previously validated in Portuguese [20]. This questionnaire evaluates sleep quality over a 1-month period, and it is comprised of 19 self-reported questions and five questions directed to the patient's spouse, composing seven composite scores ranging from 0 (no difficulty) to 3 (severe difficulty). The score is calculated by the sum of all items and ranges from 0 to 21, where lower scores denote 'good sleepers', moderated scores indicate 'poor sleepers' quality, and high scores indicate sleep disorder.

2.5. Statistics analysis

Descriptive data will be reported using Chi-square test and *t*-test analyses. Residue analyses were performed to detect categories with higher-than-expected values. Quantitative variables were analyzed by *t*-student test. Statistical analyses were performed by SPSS software v. 20 (IBM Corp., Armonk, NY). A p value of ≤0.05 was considered statistically significant.

3. Results

A total of 50 patients were included in our study, all of whom consent to participate. Sociodemographic and clinical data are displayed

Table 1
Sociodemographic and clinical data [without SR–with SR (n = 50)].

	Without SR [n (%)]	With SR [n (%)]	Total number [n (%)]	OR (CI:95%)
Gender				
Male	20(50.0)	5(20.0)	25(50.0)	
Female	20(50.0)	5(20.0)	25(50.0)	
Age (mean ± SD)	35.8 ± 12.2	31.80 ± 11.2	34.96 ± 12	
Stable relationship				
No	17(43.6)	5(50.0)	22(44.9)	
Yes	22(56.4)	5(50.0)	27(55.1)	
Education, in years (mean ± SD)	10.1 ± 3.7	11.4 ± 4.4	10.4 ± 3.8	
Employment				
Student	5(12.5)	1(10.0)	6(12.0)	
Working	7(17.5)	2(20.0)	9(18.0)	
Housewife	10(25.0)	4(40.0)	14(28.0)	
Unemployed	7(17.5)	1(10.0)	8(16.0)	
Retired	11(27.5)	2(20.0)	13(26.0)	
Age at epilepsy onset (≤18 years)	30(75,0)	8(80.0)	38(76.0)	
Epileptic focus[a]				
Frontal	4(10.5)	1(12.5)	5(10.9)	
Temporal	19(50.0)	6(75.0)	25(54.3)	
Multiple foci	7(18.4)	1(12.5)	8(17.4)	
Nonlocalizing	3(7.9)	–	3(6.5)	
Others foci	5(13.2)	–	5(10.9)	
Final diagnosis				
Epilepsy	31(77.5)	6(60.0)	37(74.0)	
PNES	2(5.0)	2(20.0)	4(8.0)	
Epilepsy + PNES	4(10.0)	2(20.0)	6(12.0)	
Inconclusive	3(7.5)	–	3(6.0)	
Epilepsy surgery	24(60.0)	6(60.0)	30(60.0)	
Psychiatric diagnosis (ICD-10)				
Yes	19(47.5)	8(80.0)	27(54.0)	OR = 1.68 (0.57–4.95)
No	21(52.5)	2(20.0)	23(46.0)	
Types of psychiatric diagnosis[b]				
Schizophrenia	1(5.3)	–	1(3.7)	
Mood disorders	13(68.4)	6(75.0)	19(70.4)	
Depressive disorder	13(68.4)	2(25.0)	15(55.6)	
Bipolar disorder	1(5.3)	3(37.5)	4(14.8)	
Anxiety disorders	5(26.3)	2(25.0)	7(25.9)	

SR: suicide risk, VEEG: video-electroencephalogram; PNES: psychogenic nonepileptic seizures, SD: standard deviation, OR: odds ratio, CI: confidence interval, ICD: International Statistical Classification of Diseases and Related Health Problems.
[a] This variable is about 46 patients with epilepsy, excluded PNES.
[b] This variable is about 27 patients with psychiatric disorders.

Table 2
Affective temperament and suicide risk [without SR–with SR (n = 50)].

Affective temperament [n (%)]	Without SR	With SR	Total
Internalized	8(20.5)	1(10.0)	9(18.4)
Unstable	7(17.9)	3(30.0)	10(20.4)
Stable	13(33.3)	3(30.0)	16(32.7)
Externalized	11(28.2)	3(30.0)	14(28.6)
Total	39	10	49
SR: suicide risk. p = 0.782			

in Table 1. Sociodemographics and clinical variables did not seem to interfere with SR, showing no significant difference between at risk patients and the rest of the sample (p > 0.05).

Suicide risk, measured by the MINI, was present in 10 patients (20.0%). Twenty -five patients (50%) were female, mainly married (55.1%). Mean age was 34.96 ± 12 years with mean schooling years of 10.3 ± 3.8 years of study. Only 18% of patients with refractory epilepsy were currently employed, and 26% were retired because of disability (Table 1).

Temporal lobe was the main epileptic focus, encountered in 25 patients (54.3%), followed by multifocal foci in 8 patients (17.4%), frontal lobe and other focus with 5 patients (10.9%) in both groups. In addition, three patients were found to have nonlocalizing foci (6.5%). Definite diagnosis was reached in 47 patients, with epilepsy found in 37 patients (74.0%). Other diagnoses were PNES in 4 patients (8%), coexisting PNES and epilepsy in 6 patients (12.0%) and inconclusive in 3 (6.0%). Thirty patients (60%) were considered eligible candidates for epilepsy surgery, having their procedures scheduled over the ensuing months.

Table 3
Emotional temperament and suicide risk [(n = 50)/n(%)].

Temperament	Without SR	With SR	Total	p value	OR (CI95%)
Volition				0.868	
Low	17(43.6)	5(50)	22(44.9)		
Medium	11(28.2)	3(30)	14(28.6)		
High	11(28.2)	2(20)	13(26.5)		
Impulse				0.330	
Low	16(41)	5(50)	21(42.9)		
Medium	17(43.6)	2(20)	19(38.8)		
High	6(15.4)	3(30)	9(18.4)		
Anger				0.854	
Low	14(35.9)	3(30)	17(34.7)		
Medium	13(33.3)	3(30)	16(32.7)		
High	12(30.8)	4(40)	16(32.7)		
Fear				0.444	
Low	22(56.4)	4(40)	26(53.1)		
Medium	14(35.9)	4(40)	18(36.7)		
High	3(7.7)	2(20)	5(10.2)		
Sensitivity				**0.003***	**5.0 (1.13–22.10)**
Low	24(61.5)	1(10.0)	25(51)		
Medium	11(28.2)	4(40)	15(30.6)		
High	4(10.3)	5(50)*	9(18.4)		
Coping				0.637	
Low	11(28.2)	4(40)	15(30.6)		
Medium	18(46.2)	3(30)	21(42.9)		
High	10(25.6)	3(30)	13(26.5)		
Control				0.734	
Low	13(33.3)	4(40)	17(34.7)		
Medium	9(23.1)	3(30)	12(24.5)		
High	17(43.6)	3(30)	20(40.8)		
Anxiety				0.089	1.87 (0.60–5.80)
Low	12(30.8)	3(30)	15(30.6)		
Medium	12(30.8)	0(0)	12(24.5)		
High	15(38.5)	7(70)	22(44.9)		
Stability				0.745	
Low	11(28.2)	2(20)	13(26.5)		
Medium	17(43.6)	4(40)	21(42.9)		
High	11(28.2)	4(40)	15(30.6)		

In bold is the value with difference statistically significant between groups.
SR: suicide risk, OR: Odds ratio, CI: confidence interval. Significant p-values appear to be marked (*).

Psychiatric comorbidities were found in 27 patients (54%). Among those at risk of suicide, a psychiatric diagnosis was reached in 80% [Odds ratio (OR): 1.68 (0.57–4.95); p = 0.085]. The main psychiatric diagnoses were mood disorders (major depressive disorder in 15 and bipolar disorder in 4) in 19 patients (70.4%), followed by anxiety disorders in 7 patients (25.9%).

Most commonly prescribed antiepileptic drugs (AEDs) were carbamazepine in 24 patients (48%) and valproic acid in 11 patients (22%). We analyzed the impact of AEDs in our sample and did not find it to significantly interfere with SR (Table 4). Twenty-two (44%) patients were on any psychotropic drugs, with antidepressants the most commonly prescribed drugs (n = 13; 26%). In Table 4, there is a detailed description about AEDs and psychotropic drugs. Lithium was the only psychotropic drug more frequently prescribed in the group with SR and had statistical significance [OR: 8.00 (1.28–50.04); p = 0.026].

There was a trend of female predominance in patients with PNES, which did not reach statistical significance. In addition, there was no significant difference in SR between PNES and PWE; (p = 0.960).

Structured questionnaires showed a statistically significant association between SR and sleep disorders [OR:10.0 (1.68–59.3); p = 0.001]. Affective temperaments did not seem to play a role in suicidal behavior, as demonstrated in Fig. 1. When assessing specifically the emotional dimensions of temperament, there was a significant association between SR and emotional sensibility [OR:5.0 (1.13–22.10); p = 0.003; Fig. 2]. In Tables 2 and 3, there are the results of temperament evaluation.

In Table 5, there are results about relation between sleep quality and psychiatric diagnosis. Patients with major depressive disorder had higher frequency of 'poor sleeper' quality or sleep disorder (according PSQI).

4. Discussion

Patients with epilepsy are at an increased SR, around 3 to 5 times higher than the general population [21,22]. Our study showed that 20% (n = 10) of a population whose epilepsy is highly refractory displayed SR and 20% (n = 10) reported previous suicide attempt. A recent Croatian study reported 38% of PWE had recurrent death thoughts,

Table 4
Antiepileptic drugs and psychotropic drug classes [without SR–with SR (n = 50)].

	Without SR [n (%)]	With SR [n (%)]	Total number [n (%)]	OD (CI 95%)
Antiepileptic drugs (AEDs)				
Valproic acid	9(22.5)	3(30.0)	11(22.0)	
Carbamazepine	27(67.5)	5(50.0)	24(48.0)	
Phenobarbital	6(15.0)	–	1(2.0)	
Phenytoin	10(25.0)	–	2(4.0)	
Lamotrigine	8(20.0)	3(30.0)	2(4.0)	
Clobazam	24(60.0)	6(60.0)	6(12.0)	
Topiramate	1(2.5)	–	1(2.0)	
Oxcarbazepine	7(17.5)	3(30.0)	3(6.0)	
Others	14(35.0)	3(30.0)	6(12.0)	
Polytherapy AEDs				
1 AEDs	3(75.0)	1(25.0)	4(8.0)	
2 AEDs	12(70.6)	5(29.4)	17(34.0)	
3 AEDs	19(82.6)	4(17.4)	23(46.0)	
≥4 AEDs	6(100.0)	–	6(12.0)	
Median and percentiles (25/75)	3.0(2.0/3.0)	2.0(2.0/3.0)	–	
Psychotropic drug classes (n = 22)[a]				
Antidepressants	8(57.1)	5(33.3)	13(38.2)	2.50 (0.67–9.31)
Antipsychotics	5(26.3)	3(20)	8(23.5)	2.40 (0.49–11.77)
Lithium	2(10.5)	4(36.6)**	6(17.6)	8.00 (1.28–50.04)
Benzodiazepines[b]	3(15.8)	1(6.6)	4(11.8)	1.33 (0.12–14.22)
Hypnotics	1(5.3)	–	1(2.9)	1.29 (0.04–33.89)

SR: suicide risk.
[a] Some patients use more than one psychotropic.
[b] Excluded clobazam.
** p = 0.026.

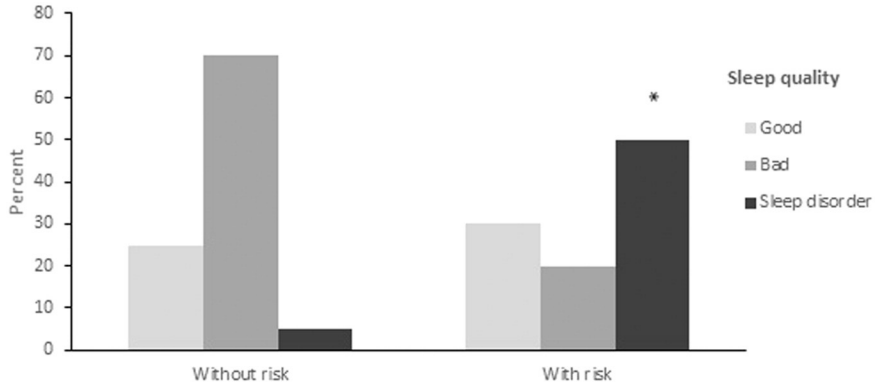

Fig. 1. Sleep quality by groups (without and with suicide risk). *p = 0.001.

and 18% had a previous suicide attempt, comparable with our results [4]. A wide-based population study in England showed that 25% of PWE had suicidal ideation, however, only 10% had a prior suicide attempt [3]. Our study found 80% of patients at risk of suicide fulfilled criteria for a psychiatric diagnosis (p = 0.085; Table 1). Although a high number, statistical significant was not reach because of a small sample, nevertheless, this finding could be clinically relevant.

Mood disorders are the most frequently found psychiatric diagnosis in patients with suicidal tendencies and comorbid epilepsy [5]. A study of 380 patients found a high prevalence of depression (n = 103; 27.1%), with 49 (12.9%) presenting suicidal ideation [22]. In our sample, 19 (37%) patients fulfilled the criteria for mood disorders (depressive and bipolar).

Around 5 to 33% of all patients evaluated to dedicated epilepsy surgery centers end up with a conclusive diagnosis of PNES [5]. Coexistence of PNES and epilepsy varies widely in studies from 5 to 60% [6,7], probably reflecting local referral bias. Our study found 10 patients with PNES, in which 4 (8%) patients had only PNES and 6 (12%) had both PNES and epileptic seizures. There was no significant interaction between final diagnosis of PNES and SR, although our sample did not have the appropriate size to exclude an association. Nonetheless, this association has also been refuted by previous studies [23].

Suicidal patients have been demonstrated to have poor sleep quality compared with nonsuicidal subjects [9]. A systemic review found disturbed sleep to be a risk factor for suicide, regardless of the presence or absence of mood disorders [24]. Sleep architecture is frequently altered in PWE, especially in those with nocturnal seizures or due to effects of AEDs [25]. This is in accord with our findings, in which patients with sleep disorders (PSQI score >10) also displayed a higher risk of suicide.

Lithium was the only psychotropic drug more frequently prescribed in the group with SR with a statistical significance [OR: 8.00 (1.28–50.04); p = 0.026]. The data that show higher lithium use in the group with SR are probably due to a well-known protector effect of lithium against suicide [26].

Patients with epilepsy display different temperament characteristics when compared with subjects without epilepsy [5,13]. A study using the Temperament and Character Inventory developed by Cloninger et al. showed higher scores of Novelty Seeking (similar to Volition in AFECTS) and Reward Dependence (similar to Emotional Sensitivity in AFECTS) in PWE when compared with controls [28]. By using the scale TEMPS-A (Temperament Evaluation of Memphis, Paris Pisa and San Diego), a case–control study showed that the most frequent temperament traits in epilepsy are irritable (15.71%), depressive (10%), anxious (7.14%), and cyclothymic (7.14%) [15]. Our evaluation, through the AFECTS, showed slightly different findings with the most frequent affective temperaments in a highly refractory cohort to be stable (obsessive, euthymic, hyperthymic) and externalizing (irritable, unhinged, euphoric). Affective temperaments did not seem to play a role in SR (p = 0.782). On the other hand, emotional temperament exposed a significant association between high emotional sensibility and SR. This dimension reflects how the subject reacts to stressors such as interpersonal relations (rejection, criticize, offenses) or general events (frustration, pressures, trauma, personal loss) [11]. As such, this may be an intrinsic factor exposing the patient to a higher SR when confronted with a disabling condition (i.e., refractory epilepsy) and shows diminished resilience.

Our study presents several limitations. First, its convenience sample may be skewed by referral bias, therefore, not representing the general population with epilepsy. Then again, it is a fairly representative picture of most EMUs and epilepsy surgery programs, probably reflecting the reality of patients with treatment-refractory seizures in the real world. On the same issue, it is a small sample, and it was not powered enough to uncover associations of SR with PNES. Also, the lack of a control group

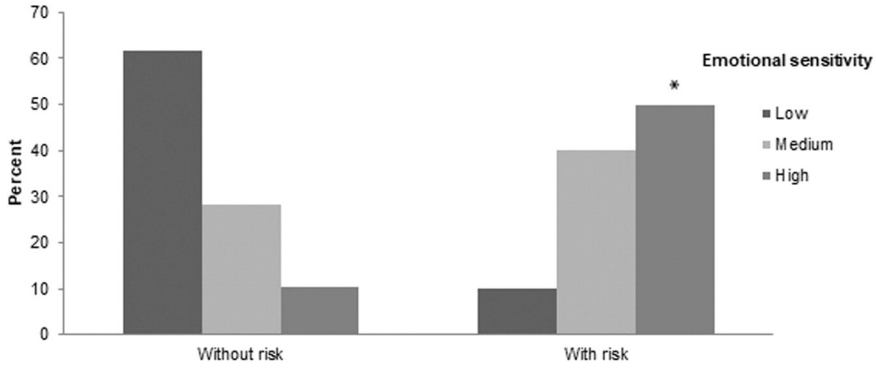

Fig. 2. Emotional sensitivity by groups (without and with suicide risk). *p = 0.003.

Table 5
Sleep quality and psychiatric diagnosis (n = 27).

	Schizo [n (%)]	MD [n (%)]	MDD [n (%)]	BD [n (%)]	AD [n (%)]
Sleep quality					
Good sleepers	–	4(80.0)	7(25.9)	1(3.7)	1(20.0)
Poor sleepers	1(6.3)	10(62.5)	5(18.5)	2(7.4)	5(31.3)
Sleep disorder	–	5(83.3)	3(11.1)	1(3.7)	1(16.7)
Total	1(3.7)	19(70.4)	15(55.6)	4(14.8)	7(25.9)

Schizo: schizophrenia, MD: mood disorder, MDD: major depressive disorder, BD: bipolar disorder, AD: anxiety disorder.

(i.e., healthy population or controlled epilepsy) weakens its power. Nonetheless, the prospective nature of our study overshadows collection biases, allowing for accurate and unbiased first-hand psychiatric diagnosis, prior to final epilepsy diagnosis. This is important, since patients with PNES may have been approached differently if diagnosis had been known. Another strength of our study relies on the structured neurologic and psychiatric evaluation, performed by Board-certified neurologists and psychiatrists. In addition, SR evaluation by a vastly distributed tool helps to confer reproducibility to our results. By last, as already stated, this cohort fairly represents patients with refractory epilepsy commonly referred for epilepsy surgery evaluation.

Despite an extensive literature indicating a higher risk of suicide among PWE, this issue is hardly explored by general physicians or neurologists because of difficulties and prejudice in approaching the subject, as well as detecting and managing the risk [27]. Strategies to enhance physician's abilities in dealing with delicate subjects, such as suicide, are essential for effective prevention. Half of patients who commit suicide and 2/3 of those who attempt it had seen a physician in the prior month [28]. Our data suggest a need for increased awareness to mental health in patients with refractory epilepsy.

Our results highlight the importance of thoroughly evaluating PWE, including temperament traits and sleep quality, since these factors may uncover a higher risk of suicide. The AFECTS and PSQI may be used as complementary tools in the evaluation of PWE.

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Declarations of interest

None.

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