Epilepsy & Behavior 100 (2019) 106513

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Psychiatric disorders as predictors of epilepsy surgery outcome

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ARTICLE INFO

Article history:
Received 5 March 2019
Revised 21 August 2019
Accepted 21 August 2019
Available online 19 October 2019

Keywords:
Refractory epilepsy
Epilepsy surgery
Outcome
Psychiatric disorders

ABSTRACT

Objectives: Our aim was to determine if a history of a mental disorder predicts a worst neurological outcome for patients undergoing epilepsy surgery.
Methods: We conducted an ambispective observational study including people with refractory epilepsy who underwent resective surgery. Demographic, psychiatric, and neurological data were collected, before and one year after surgery. Presurgical interviews included a psychiatric evaluation and the determination of prevalent and lifetime psychiatric diagnosis. The one-year postsurgical outcome was classified according to the Engel Outcome Scale. Predictors of postsurgical Engel class were determined using an ordered logistic regression model.
Results: A lifetime history of any mental disorder was a significant predictor of a higher Engel Class ($p = 0.017$).
Conclusion: This study shows that psychiatric lifetime diagnoses are associated with worse surgical outcome and highlighted the importance of the inclusion of these diagnoses in the evaluation of the potential success of the surgery.

1. Introduction

Psychiatric comorbidity is frequent in people with epilepsy [1–3]. There is an association between these types of disorders concerning their severity and probability of occurrence [4–7]. Psychiatric disorders can precede, cooccur, or follow the diagnosis of epilepsy [4]. Previous studies have suggested that there is a bidirectional relationship between mental disorders and epilepsy [8,9].

Some aspects that may explain this association have been postulated. Psychosocial factors may partially explain the high prevalence of depression and anxiety in people with epilepsy. These factors include stigma, poor disease acceptance, and anticipatory anxiety associated with the unpredictable nature and outcome of seizures and the limitations imposed by the disease itself [10]. However, common biological factors may also explain this bidirectional association. Psychiatric disorders and epilepsies may share common genetic mechanisms, such as copy number variants, which seem to act as a nonspecific risk factor for both epilepsy and schizophrenia, autism spectrum disorders, and attention-deficit hyperactivity disorders [11]. A hyperactive hypothalamic–pituitary–adrenal axis has been suggested as another putative mechanism, as an abnormal dexamethasone suppression test has been demonstrated in both primary major depression and in people with epilepsy without depression [9]. Elevated glucocorticoid levels might damage neuronal and cortical function, thereby increasing the synaptic glutamate levels [9]. Dysfunction of glutamate transporter proteins, serotonin, dopamine, and γ-aminobutyric acid transporters, together with reduced levels of serotonin and noradrenaline, might also play a role in the pathogenesis of depression and epilepsy [9,12–14].

People who have mental disorders and epilepsy might have a more global dysfunction of brain networks, neurotransmitter or neuroendocrine systems, or some other general mechanism. Widespread brain abnormalities have been identified in both focal epilepsy and some psychiatric disorders, such as schizophrenia, bipolar disorder, and major depression [15–19].

About one-third of people living with epilepsy have seizures that do not respond to pharmacological treatment [20], and they are considered to have refractory epilepsy [21]. They have an even higher risk for psychiatric disorders [2,22]. Some of these patients may be submitted to surgery (resective or palliative) with different neurological outcomes. Clinical characteristics, such as a history of presurgical secondarily generalized convulsive seizures, learning disability, an extratemporal epileptogenic zone, bilateral hippocampal sclerosis, and bitemporal interictal epileptiform discharge, as well as palliative procedures, have been shown to increase the probability of recurrence of seizures after surgery [23–25]. Inversely, higher age at onset and a shorter duration of epilepsy have been associated with a better postsurgery seizure control [26,27].

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https://doi.org/10.1016/j.yebeh.2019.106513
1525-5050/

Some previous studies have suggested that a lifetime history of psychiatric disorders is also associated with a poor postsurgical seizure outcome [25,28,29]; however, other studies did not confirm this finding [30,31]. Hence, we believe that this important subject deserves further investigation.

People who have mental disorders and epilepsy might have a more global dysfunction of brain networks, neurotransmitter or neuroendocrine systems, and potentially a more serious disorder. Widespread brain abnormalities have been identified in both focal epilepsy and some psychiatric disorders, such as schizophrenia, bipolar disorder, and major depression [15–19].

Considering this hypothesis, the present study postulates that a presurgical lifetime history of mental disorders may be an important predictor of a worst postoperative seizure control.

2. Methods

This ambispective cohort study was conducted at the Neurosciences and Mental Health Department of the Hospital de Santa Maria, between April 2000 and September 2018. Subjects were recruited from both the Refractory Epilepsy Reference Centre and the Epilepsy Surgery Group. Participants were evaluated, before surgery and after 12 months, by one of the psychiatrists belonging to both the Centre and the Group. The diagnosis of refractory epilepsy was based on the definition of the International League Against Epilepsy [21].

Presurgical evaluation routinely included at least a video-electroencephalography (EEG) monitoring, a 3-Tesla brain magnetic resonance with an epilepsy protocol, and a neuropsychological and a psychiatric evaluation. All patients underwent resective surgery.

Data pertaining to demographic (gender, age, employment status, marital status, etiology of epilepsy, the topography of the epileptogenic zone, the age at onset, time to surgery) and Engel Class [32] after surgery were collected during the interviews and from the patient's medical and surgical records. In the presurgical period, patients were taking, at least, two antiepileptic drugs. However, the type, number, and dosages of the medications were not addressed in this study because of the usually broad variability among this population. Nonetheless, patients usually continue to take the same drugs and maintain the same therapeutic schemes for at least 2 years, after surgery, if they stop having seizures.

This study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki, and its later amendments, and it was approved by the Ethics Committee of the Hospital de Santa Maria (CHULN).

2.1. Subjects

Participants older than 18 years, submitted to resective surgery, with a minimum of one year of education were included in the study. Participants that underwent deep brain stimulation (DBS) or vagus nerve stimulation (VNS), and those with other neurological diseases or intellectual disability, were excluded.

A total of 196 consecutive people with refractory epilepsy, who were proposed for presurgical evaluation, were enrolled in the study. Of those, 15 were secondarily excluded because of intellectual disability (intelligence quotient (IQ) <70), 48 were excluded because they did not undergo surgery, 12 were excluded because they underwent DBS or VNS, 1 refused to participate, and 1 died. Thus, a total of 124 individuals were included in the study.

2.2. Psychiatric evaluation

Psychiatric evaluations included a clinical psychiatric history (demographic data, previous psychiatric history, family history, use of substances, as well as other relevant data) and the following psychopathological tests.

2.2.1. The Hamilton Anxiety Rating Scale (HARS)

This scale consists of 14 items and measures both psychic and somatic anxiety [33].

It is scored according to the following cutoffs: 17 = mild; 18–24 = mild to moderate; 25–30 = moderate to severe anxiety [33].

2.2.2. The Hamilton Depression Rating Scale (HDRS)

The version used corresponds to the original 17-item version. It was developed to access the severity of depressive symptoms [34], and the following scores were considered: 0–7 = normal; 8–16 = mild; 17–23 = moderate; >24 = severe depression [35].

2.2.3. Brief Psychiatric Rating Scale (BPRS)

This rating scale is used to measure the change in psychiatric symptoms, particularly, psychotic symptoms. It contains 18 items, each one rated from 1 (absent) to 7 (extremely severe), evaluating positive, negative, and affective symptoms [36]. It ranges from 18 to 126 [37].

2.2.4. Symptom Checklist-90 (SCL-90)

This multidimensional instrument is a 90-item self-report symptom inventory developed to measure psychopathological symptoms and psychological distress. It has been extensively validated. There are three global indices for the SCL-90: 1) Global Severity Index (GSI), which is the average score of 90 items of the questionnaire; it is the best single indicator of the current level of the disorder, 2) Positive Symptom Distress Index, which is the average score of the items scored above zero, and 3) Positive Symptoms Total, which is the number of items scored above zero [38]. A cutoff of 0.57 was proposed [39].

Lifetime psychiatric disorder diagnostics were established according to the International Statistical Classification of Diseases and Related Health Problems (ICD-10) [40], including information provided by the patient and the family member who accompanied the presurgical evaluation.

2.3. Statistical analysis

The statistical analysis was conducted using Stata software (version 14.2; StataCorp, Texas, USA). Descriptive statistics were performed to report the analysis of data presented as mean ± standard deviation or median (minimum-maximum). Student's t-test and the Mann–Whitney U test were used for the parametric and nonparametric data, respectively. A chi-square test, or the Fisher exact test in the case of nonparametric data, was used to compare the categorical variables, which were given as the number of cases or proportions.

The outcome variable considered was the Engel Class, registered 12 months, after surgery. Because this is an ordinal variable, an ordered logistic regression model was used for the univariate and multivariate analysis.

First, a model was developed including lifetime psychiatric diagnosis, analyzed as a binary variable (at least one lifetime diagnosis *versus* no lifetime diagnosis), then as a categorical variable was created, according to the following diagnostic groups: no history of previous mental disorders, history of psychoactive substance use, any psychotic disorder, any mood disorder, any anxiety disorder, any other mental disorder.

Measures of association were expressed as odds ratio (OR); and a p-value ≤0.05 was considered to be statistically significant.

3. Results

3.1. Demographic and clinical findings considering the existence of a lifetime psychiatric diagnosis versus no history of such diagnosis (Table 1)

Comparing patients with and without a history of a lifetime psychiatric disorder, significant differences were found regarding their employment status. Those with a history of some psychiatric disorder

Table 1
Sociodemographical and clinical characteristics of the participants.

	No lifetime psychiatric disorders N = 67	At least one lifetime psychiatric disorder N = 57	p-Value
Age, years	36.9 ± 11.8	40.4 ± 11.7	0.10
Males, n (%)	29 (43.3)	21 (36.8)	0.47
Education, years	11.0 ± 4.4	9.7 ± 4.6	0.11
Active workers, n (%)	53 (79.1)	28 (52.8)	0.009
Married, n (%)	35 (52.2)	27 (49.1)	0.29
Age at onset, years	17.1 ± 11.2	15.3 ± 10.9	0.35
Duration of epilepsy, years	19.9 ± 12.3	25.0 ± 13.7	0.03
Temporal epileptogenic zone, n (%)	61 (91.0)	50 (89.3)	0.74
• Mesial	53 (86.9)	43 (86.0)	
• Neocortical	8 (13.1)	7 (14.0)	
Extratemporal epileptogenic zone, n (%)	6 (9.0)	6 (10.7)	
Side of the epileptogenic lesion			0.007
• Left	39 (58.2)	19 (33.9)	
• Right	28 (41.8)	37 (66.0)	
Type of epileptogenic lesion			0.68
• Sclerosis	40 (65.6)	31 (62.0)	
• Tumors	13 (21.3)	9 (18.0)	
• Dysplasia	2 (3.3)	3 (6.0)	
• Gliosis	2 (3.3)	1 (2.0)	
• Cavernous angioma	2 (3.3)	2 (4.0)	
• Other	2 (3.3)	4 (8.0)	
Number of antiepileptic drugs	2.3 ± 0.6	2.2 ± 0.6	0.39
Epileptic crises per month	6.8 ± 8.6	9.2 ± 16.9	0.48
Engel I	58 (92.1)	39 (75.0)	0.01
Engel II, III, and IV	5 (7.9)	13 (25.0)	

had a lower probability of being active workers ($p = 0.009$). Approximately half of them were unemployed or had retired early. They also tended to have a right epileptogenic zone ($p = 0.007$), a longer duration of disease ($p = 0.03$), and a worse outcome after surgery ($p = 0.01$). Other demographic and clinical characteristics are described in Table 1.

3.2. Lifetime history of mental disorders

Before surgery, a total of 57 candidates (46%) had a lifetime history of at least one mental disorder. The number of patients per diagnosis category is represented in Table 2.

3.3. Psychopathology at the moment of presurgical evaluation

At the presurgical evaluation, surgical candidates had a medium HDRS total score of 7.69 ± 7.56, a medium HARS total score of 8.32 ± 7.09, a medium GSI total score of 0.88 ± 0.56, and a medium BPRS total score of 27.5 ± 9.15.

According to the defined cutoff for HDRS, 7 people had moderate depression and 13 people had severe depression at the moment of evaluation. Two patients had moderate to severe anxiety according to the HARS.

Table 2
Sociodemographical and clinical characteristics of the participants.

No previous diagnosis, n (%)	67 (54.0)
Depressive disorders, n (%)	36 (29.0)
Anxiety disorders, n (%)	6 (4.8)
Psychoactive substance use, n (%)	6 (4.8)
Psychotic disorders, n (%)	3 (2.2)
Other diagnosis, n (%)	6 (4.8)

3.4. Results from the univariate analysis

The lifetime history of any mental disorder was a predictor of higher Engel Class scores one year after surgery (OR: 3.83; confidence interval (CI) 95%: 1.27–11.59; $p = 0.017$).

Considering each group of disorders separately, a previous diagnosis of a psychotic disorder (OR: 35.18; CI 95%: 2.84–436.15; $p = 0.006$) and any substance use disorder (OR: 15.94; CI 95%: 2.89–87.93; $p = 0.001$) were significant predictors of higher Engel Class scores.

4. Discussion

This cohort study was conducted in a reference center for refractory epilepsy using a sample of people who underwent epilepsy surgery. Our aim was to confirm that lifetime psychiatric disorders or psychopathology, detected at the presurgical evaluation, predict a worse postoperative seizure outcome.

Our data showed that 46% of epilepsy surgery candidates had a previous history of mental disorders. This high percentage tracks with previous studies [41,42] and argues for a close relationship between epilepsy and psychiatric disorders.

Further, this study showed that patients with a history of mental disorders tend to have lower levels of success in the control of seizures after surgery. Depression, psychotic disorders, and substance use disorders may have a higher negative impact.

Previous researchers have also investigated the relationship between preoperative psychopathology or major psychiatric disorders and the probability of seizure remission after epilepsy surgery. However, the results were controversial. Koch-Stoecker et al. concluded that a lifetime diagnosis of psychosis, major depression, or personality disorders diminished the probability of complete seizure remission [43]. Additionally, Kanner et al. studied presurgical lifetime history of mood, anxiety, attention-deficit hyperactivity, and psychotic disorders as independent predictors of seizure outcome and suggested that a lifetime psychiatric history may predict worse postoperative seizure control [28]. Adams et al. found no association between psychiatric history and seizure outcome on patients with mesial sclerosis. These contradictions, however, may be due to the analysis of a small sample ($n = 72$). Another potential explanation was provided by the authors, namely that the association found in previous literature may be due to the inclusion of patients with other diseases besides mesial sclerosis in their samples. Lifetime psychiatric disorders would predict worse outcomes in this group of people but not in patients with mesial sclerosis [30]. Our sample includes both patients with and without mesial sclerosis. Lackmayer et al. also found that preoperative depressive symptoms were not predictors of postoperative seizure control in people with temporal lobe epilepsy. However, their sample size was also small ($n = 45$) [31].

The association between preoperative psychiatric lifetime diagnosis and seizure outcome could, as mentioned, be related to psychological factors or common biological mechanisms. Long-lasting refractory epilepsy may cause more brain dysfunction and contribute to both psychiatric disorders and a reduced probability of seizure remission.

Our study has some limitations. This was an observational study with a retrospective component, so some data were missing. Different sources of information were considered in order to confirm clinical information and to complete data as much as possible. Another limitation was that lifetime psychiatric diagnosis may not have been reported for several reasons, some including the fact that some psychopathological symptoms may be considered as a "natural reaction" to epilepsy or because of their fear of not being qualified for surgery. Consequently, this may have affected our results. However, information was, whenever possible, confirmed with family members and other accompanying persons. We did not control for the type of antiepileptic drugs; these may have an impact on mood and behavior. Nevertheless, we do not expect to have significant differences in therapeutic schemes between patients

with and without psychiatric comorbidities as they are mainly determined by their efficacy on the control of epilepsy regardless of this type of comorbidity. We also did not include in our analysis the use of psychiatric medications, although we might expect that all patients with moderate to severe symptomatology were medicated. Finally, we considered the 12-month outcome while a 24-month assessment would be more adequate to evaluate seizure outcome.

Despite these constraints, our study shows a clear relationship between epilepsy and mental disorders, arguing for a bidirectional relationship. Patients with psychiatric disorders and epilepsy may represent a group with more generalized brain dysfunction and a potentially more serious disorder. Previous psychiatric history should always be identified and included in an evaluation protocol that would help clinicians and surgery candidates to have a more accurate prediction of the potential success of the surgery.

Unfortunately, until recent years, psychiatric comorbidities were frequently not considered or treated. The recognition of their impact on the quality of life and on the clinical course of epilepsy has highlighted the need for early identification and treatment of psychiatric disorders [44].

Future studies should focus on the impact of pharmacological or psychosocial treatment of psychiatric comorbidities on the postsurgical course of epilepsy.

Disclosure

The first author is responsible for data collection and integrity.

Funding sources

None.

Author's contributions

The study design was developed by FN and JP. Data collection was made by LCM, MA, SL, and FN. FN was responsible for data collection and data analysis and wrote the manuscript draft. LCM, JP, and MLF reviewed the manuscript draft. All authors have approved the final manuscript.

Declaration of competing interest

None.

Acknowledgments

We sincerely thank all patients for their participation in the study. We gratefully acknowledge Professor Emilia Monteiro for her important contribution to the design of the study. We also thank Professor Ebrahim Barkoudah and Professor Pamela Rist for their support in the statistical analysis. Finally, we thank all members from Refractory Epilepsy Reference Centre and the Epilepsy Surgery Group, of our Institution, for their support in the evaluation of patients and clinical data.

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