Epilepsy & Behavior 90 (2019) 204–208

Contents lists available at ScienceDirect

Epilepsy & Behavior

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

Predicting *de novo* psychopathology after epilepsy surgery: A 3-year cohort study

Filipa Novais [a,*], Luís Câmara Pestana [a], Susana Loureiro [a], Mafalda Andrea [a], Maria Luísa Figueira [a], José Pimentel [b]

[a] Psychiatry Department, Santa Maria Hospital, Faculty of Medicine, University of Lisbon, Portugal
[b] Neurology Department, Santa Maria Hospital, Faculty of Medicine, University of Lisbon, Portugal

ARTICLE INFO

Article history:
Received 3 October 2018
Revised 28 November 2018
Accepted 29 November 2018
Available online 17 December 2018

Keywords:
Epilepsy
Refractory epilepsy
Surgery epilepsy
Psychopathology

ABSTRACT

Objective: The aim of this study was to determine the potential risk factors for *de novo* psychiatric syndromes after epilepsy surgery.

Methods: Refractory epilepsy surgery candidates were recruited from our Refractory Epilepsy Reference Centre. Psychiatric evaluations were made before surgery and every year, during a 3-year follow-up period. Demographic, psychiatric, and neurological data were recorded. The types of surgeries considered were resective surgery (resection of the epileptogenic zone) and palliative surgery (deep brain stimulation of the anterior nuclei of the thalamus (ANT-DBS)). A survival analysis model was used to determine pre- and postsurgical predictors of *de novo* psychiatric events after surgery.

Results: One hundred and six people with refractory epilepsy submitted to epilepsy surgery were included. Sixteen people (15%) developed psychiatric disorders that were never identified before surgery. Multilobar epileptogenic zone ($p = 0.001$) and DBS of the ANT-DBS ($p = 0.003$) were found to be significant predictors of these events.

Conclusion: People with more generalized epileptogenic activity and those who undergo ANT-DBS seem to present an increased susceptibility for the development of mental disorders, after neurosurgical interventions, for the treatment of refractory epilepsy. People considered to be at higher risk should be submitted to more frequent routine psychiatric assessments.

1. Introduction

More than 50 million people around the world have epilepsy [1], a debilitating neurological disorder associated with several comorbidities, particularly, psychiatric conditions [2]. Indeed, it is estimated that up to 60% of this population suffer some psychiatric disorder, and the risk of death from suicide may be 5.8 times higher than in the general population [3,4].

About one-third of people with epilepsy do not respond to adequate antiepileptic drug treatment [5]; they are considered to have refractory epilepsy and may be candidates for epilepsy surgery. Resective surgery is the most common procedure for those who have a well-localized epileptogenic zone, and about 70% of those submitted to this procedure became seizure-free [6]. The most common type of localized epileptogenic zone affects the temporal lobe, particularly, mesial structures. A smaller proportion affects neocortical zones [7,8].

Those who are not candidates for resective surgery, generally, because of multiple epileptogenic zones or lack of an identifiable epileptogenic zone, may undergo palliative surgery, such as neuromodulation interventions. Vagus nerve stimulation (VNS), or more recently, cortical responsive stimulation (CRS) or deep brain stimulation (DBS), targeting the anterior nucleus of the thalamus (ANT), bilaterally, are currently the most frequently employed techniques.

Despite the high rates of success of resective surgery in the control of epileptic seizures, about 20% of people with refractory epilepsy may develop *de novo* psychopathology after surgery [9], most commonly, adjustment disorders and depression [10].

Few studies have focused on predictors of *de novo* adverse psychiatric events after resective surgery, such as major depression, mania, and psychosis. Some have found that receiving psychiatric treatment or a history of mental illness, namely, depression or anxiety, before surgery, was a risk factor for psychopathology after resective surgery [11,12]. However, this association may only reflect the natural history of previous disorders. Other potential risk factors include higher prevalence of mood disorder among first- and second-degree relatives [13], preoperative bilateral electroencephalogram (EEG) abnormalities [14],

* Corresponding author.
E-mail address: fnovais@campus.ul.pt (F. Novais).

https://doi.org/10.1016/j.yebeh.2018.11.037
1525-5050/

preoperative history of secondarily generalized tonic–clonic seizures [15], persistence of seizures after resective surgery, history of fear auras [16], and temporal *versus* extratemporal surgery [17].

Concerning ANT stimulation, the most common modality of DBS (ANT-DBS), some studies suggest that it might have a positive impact on mood [18,19] while others found worse depression scores after this procedure [20,21].

Establishing potential risk factors for *de novo* psychopathology would allow clinicians to inform people with refractory epilepsy better before surgery and to be more attentive to those presenting these factors.

We aimed to study the potential risk factors for *de novo* psychopathology following epilepsy surgery, either resective surgery or DBS of the anterior nucleus of the thalamus (DBS-ANT).

2. Methods

This ambispective cohort study was conducted at the Neurosciences' Department that includes the Psychiatric, the Neurological, and Neurosurgical Departments of Hospital de Santa Maria (Lisbon), between May 2004 and May 2018. Subjects were recruited from the Refractory Epilepsy Reference Centre and the Epilepsy Surgery Group of our institution. The considered total follow-up period was 36 months, after surgery, although not all subjects were followed during this entire period because of loss of follow-up. Patients were evaluated by the psychiatrist belonging to both the center and group before surgery and after 12, 24, and 36 months. Follow-up time was measured in months. The diagnosis of refractory epilepsy was made according to the International League Against Epilepsy [22].

Presurgical surgery evaluation, in our group, includes at least a video-EEG monitoring, a 3-Tesla brain magnetic resonance with epilepsy protocol, and neuropsychological and psychiatric evaluation. Our reference center includes patients with temporal and extratemporal epileptogenic zones. The location of the epileptogenic zone is determined using surface preoperative magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), and positron emission tomography scans and video–EEG. In our institution, the majority of people with refractory epilepsy who underwent surgery are submitted to resective surgery, a smaller proportion of VNS or ANT-DBS. People submitted to VNS will not be included in this study given the lack of enough follow-up data.

Data concerning demographic (gender, age, employment status, marital status, etiology of epilepsy, the topography of the epileptogenic zone, the age of onset, time to surgery) and Engel Class [23] after surgery were collected during interviews and from medical and surgical records. In the presurgical period, patients were under, at least, two antiepileptic drugs, but their type and dosages were not addressed in this study because there was considerable variability between patients as it is usually in people with refractory epilepsy. However, in our center, patients keep the same antiepileptic drugs and therapeutic schemes for at least 2 years after surgery.

During follow-up, patients were seen regularly by the members of the Epilepsy Surgery Group and referred to psychiatry if they develop *de novo* psychopathology after surgery. Information concerning the referral to psychiatry was also registered.

This study has been performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments and was approved by the Ethics Committee of Santa Maria Hospital. All participants evaluated prospectively signed an informed consent.

2.1. Subjects

Participants older than 18 years, submitted to resective surgery or DBS, were included in the study. Patients with other neurological diseases or intellectual disability were excluded from the analysis. One hundred and eighty-one consecutive people with refractory epilepsy who were proposed to presurgical evaluation were enrolled. Fifteen were secondarily excluded because of intellectual disability (Intelligence quotient < 70), 13 because they did not undergo surgery, 44 because of loss of follow-up, 1 because he has undergone VNS, and finally, 1 died and 1 refused to participate. Thus, a total of 106 individuals were included in the study.

2.2. Psychiatric evaluation

Psychiatric evaluations include a clinical psychiatric history (demographic data, previous psychiatric history, psychiatric medication, family history, use of substances as well as other relevant clinical data). The evaluation also included the following psychopathological tests:

2.2.1. The Hamilton Anxiety Rating Scale (HARS)

This rating scale was developed to measure the severity of anxiety symptoms consisting of 14 items and measures both phobic anxiety and somatic anxiety [24].

2.2.2. The Hamilton Depression Rating Scale (HDRS)

This is the most widely used rating scale used to access depression. The version used corresponds to the original 17-item version and has a particular focus on melancholic and physical symptoms [25].

2.2.3. Brief Psychiatric Rating Scale (BPRS)

This rating scale is one of the most widely used scales to measure psychotic symptoms and is based on the interview with the patient, his speech, and behavior.

2.2.4. Symptom Checklist-90 (SCL-90)

This multidimensional instrument is a 90-item self-report symptom inventory developed to measure psychological symptoms and psychological distress. There are three global indices for the SCL-90: the Global Severity Index (GSI), the Positive Symptom Distress Index, and the Positive Symptoms Total. The GSI is suggested to be the best single indicator of the current level of the disorder.

After this initial evaluation, people with refractory epilepsy presenting major psychiatric disorder or considered to have a higher risk of developing psychiatric disorder were referred to a psychiatric outpatient clinic of one of the investigators.

De novo major psychiatric disorders were classified according to the International Statistical Classification of Diseases and Related Health Problems (ICD-10) [26]. Lifetime prevalence of psychiatric syndromes was determined using information from patients and family members, accompanying the patient, at the presurgical evaluation moment.

2.3. Statistical analysis

The statistical analysis was performed using Stata software (version 14.2; StataCorp, Texas, USA). Descriptive statistics were used to report the analysis of data presented as mean $\pm$ standard deviation or number and proportions. Student's t-test and the Mann–Whitney U test were used for parametric and nonparametric data, respectively. As the population studied is an open cohort, person-time variables were taken into account in a time-to-event analysis. Potential risk factors were analyzed using the Cox proportional hazards model.

First, we performed univariate analysis including variables that were considered to have clinical relevance both for epilepsy and psychiatric disorders. These variables include sex, age at surgery, years of education, duration of epilepsy, and age at onset of epilepsy, analyzed as continuous variables. Employment and marital status, epileptogenic zone side (right, left, or bilateral cerebral hemispheres), epileptogenic zone topography (temporal, extratemporal, or multilobar) were considered as categorical variables. As Engel Classes (I, II, III, or IV) reflect progressive stages of prognosis with Class I meaning "Seizure-free or no more than a few early, nondisabling seizures; or seizures upon drug withdrawal only" and IV reflecting "No worthwhile improvement; some reduction, no reduction, or worsening are possible" [23], we treated these variables as continuous in order to increase the power of our analysis. Previous history of other mental disorders, family history of psychiatric disorders, epileptogenic zone concerning one (unilobar) *versus* more than one lobe (multilobar), and resective surgery *vs* ANT-DBS were analyzed as binary variables.

The outcome variable, *de novo* psychopathology, was coded as a binary variable (0 = no event; 1 = at least one event).

Variables achieving statistical significance as predictors of *de novo* psychopathology were included in a multivariate analysis.

The assessment of model assumptions was tested using Schoenfeld residuals test.

Measures of association were expressed as hazard ratios. A significant p value from the Cox proportional hazards model was set at ≤0.004, after a Bonferroni correction was made, considering the number of tests performed (14).

Ties were handled using the Efron method for ties.

3. Results

3.1. Demographic and clinical findings of the people with refractory epilepsy with and without de novo psychopathology (Table 1)

The study included 106 persons with refractory epilepsy. Ninety-two (88%) had a temporal epileptogenic zone, 57 (62%) had mesial sclerosis, and 34 (37%) with other pathologies; 1 had a parietal epileptogenic zone, 7 a frontal epileptogenic zone, and 5 had an epileptogenic zone affecting more than one brain lobe.

After surgery, the majority of people were considered to be Class Engel I (75%). No statistically significant differences were found, concerning these variables, between patients with and without follow-up.

Regarding lifetime psychiatric history, no statistical differences were found between patients submitted to resective surgery or ANT-DBS. In the first group, 62 patients had no previous psychiatric history, 36 had a history of depression, 6 had a history of an anxiety disorder, 3 had a history of a psychotic disorder, 6 had a history of alcohol or drug abuse, and the rest of the sample had other pathologies. In the second group, 3 had no previous diagnosis and 4 had a lifetime history of depression. At the presurgical evaluation, patients had a medium HARS score of 8.6 ± 6.9, a medium HDRS score of 8.3 ± 7.7, a medium BPRS of 27.4 ± 8.9, and the medium score of the GSI of SCL-90 of 0.9 ± 0.6. No statistical differences were found concerning surgical groups.

3.2. De novo major psychopathology

After surgery, 16 patients (15%) developed a major psychiatric syndrome that has never been reported before surgery. The incidence rate was 0.005 events per month. The mean time until the first psychiatric event was 13 months, and the median was 7 months (ranging from 1 to 36 months). Nine had a *de novo* depressive episode (F32) (8% of the sample), 6 had an acute and transient psychotic disorder (F23) (6%), 2 had a manic episode (F30) (2%), and 1 patient had a *de novo* anxiety disorder (F41) (1%). Four patients had 2 events during the follow-up period. Treatment and psychiatric follow-up were offered to all these patients and all improved with treatment.

3.3. Results from the Cox regression model

Multilobar epileptogenic zone, bilateral epileptogenic zone, ANT-DBS, and higher Engel Class were found to be significant predictors of *de novo* major psychopathology, after surgery, with hazard ratios of 13.24 (Confidence Interval (CI) 95%: 4.22–41.49; p < 0.001), 7.68 (CI 95%: 1.90–31.01; p = 0.004), 7.84 (CI 95%: 2.58–25.22; p < 0.001), and 2.18 (CI 95%: 1.36–3.49; p = 0.001), respectively.

On the multivariate model, laterality and Engel Class after surgery were not significant predictors. Using backward selection, only variables concerning unilobar *versus* multilobar epileptogenic zone and type of surgery were included in the final model with hazard ratios of 9 (CI 95%: 2.60–31.19; p = 0.001) and 6.81 (CI 95%: 1.95–23.78; p = 0.003), respectively.

Schoenfeld residuals test showed no statistically significant results allowing us to assume that there is no departure from the proportional hazards assumption.

Multicollinearity was not detected using the variance inflation factor test.

Kaplan–Meier curves showed a much shorter time to event for patients with multilobar compared with unilobar epileptogenic zone (Fig. 1) and for those submitted to ANT-DBS comparing with resective surgery (Fig. 2).

Table 1
Clinical characteristics and sociodemographical of the participants.

	Clinical and sociodemographical characteristics	
	Mean ± SD	Range
Age, years	37.6 ± 10.7	18–65
Sex/males, n (%)	40 (37.7)	
Education, years	10.2 ± 4.4	1–18
Active workers, n (%)	57 (58.8)	
Married, n (%)	49 (49)	
Age at onset, years	14.4 ± 10.1	1–58
Duration of epilepsy, years	23.2 ± 12.9	3–59
Temporal epileptogenic zone, n (%)	92 (87.6)	
Extratemporal epileptogenic zone, n (%)	8 (7.6)	
Multilobar epileptogenic zone, n (%)	5 (4.8)	
The side of the epileptogenic focus		
• Left	50 (47.2)	
• Right	52 (49.1)	
• Bilateral	4 (3.8)	
Number of antiepileptic drugs	2.3 ± 0.6	1–4
Type of surgery, n (%)		
• Resective surgery	99 (93.4)	
• Deep brain stimulation	7 (6.6)	

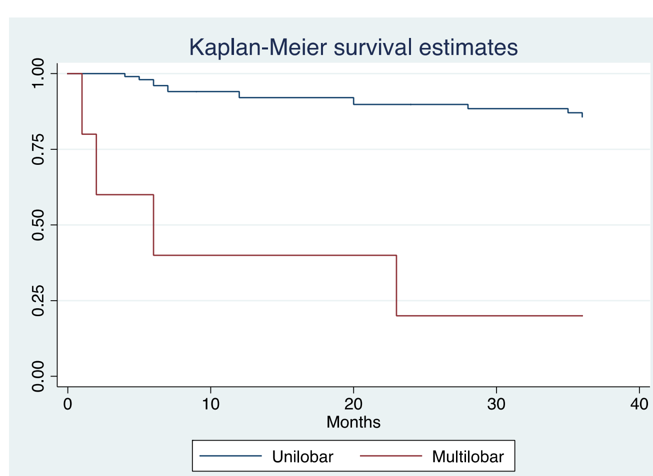

Fig. 1. Kaplan–Meier estimates of survival comparing multilobar with unilobar epileptogenic zone (p < 0.001).

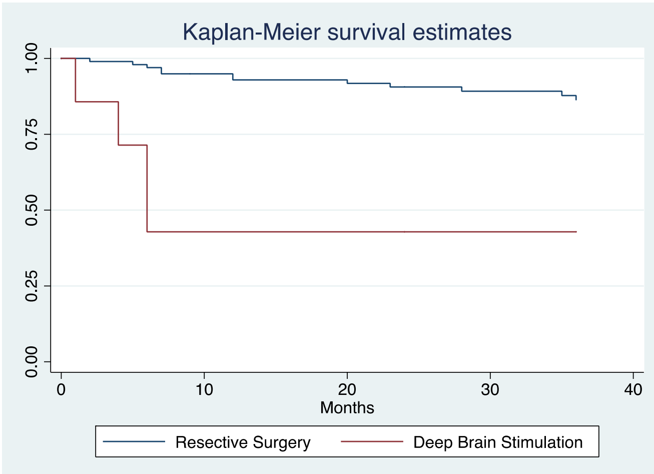

Fig. 2. Kaplan–Meier estimates of survival comparing resective surgery with DBS ($p < 0.001$).

4. Discussion

This cohort study was conducted in a reference center for refractory epilepsy using a sample of people who underwent surgery. Our aim was to identify clinically relevant risk factors for the development of major psychopathology that was not identified in these patients' life, before surgery.

Forty-two percent of the surgical candidates, of this sample, had a lifetime history of at least one psychiatric disorder. This high prevalence is in line with other studies using a sample of patients with refractory epilepsy [27,28].

After the surgical procedure, although the overall quality of life and psychiatric symptomatology improvement have been reported, for the majority of people with refractory epilepsy [29], a significant proportion of patients may develop serious psychiatric episodes [12]. In our sample, 15% of participants developed major psychiatric episodes that were never reported before surgery. However, these events were transient and responded to pharmacotherapeutic intervention. This incidence rate is higher than what would be expected in the general population in the same 3-year period [30,31] and appears to be surgery related as half of the patients with *de novo* psychopathology had the first event up to 7 months after surgery.

The main predictors of major psychiatric events were an epileptogenic zone affecting more than one lobe and being submitted to ANT-DBS. People with multilobar epileptogenic zone were 9 times more likely to develop new psychiatric events after surgery, and those submitted to DBS were almost 7 times more likely to develop these events.

A multilobar epileptogenic zone reflects a more widespread brain epileptogenicity. This finding is in line with previous studies, showing an association between a more general attainment of the brain such as bilateral functional and structural abnormalities, bilateral interictal discharges, and frontal hypometabolism after temporal lobe surgery and the emergence of new psychopathology after surgery [14,32,33].

Generalized epileptiform activity may disrupt important circuits involved in the control of mood and behavior, leaving patients more vulnerable to develop these disorders after a major neurosurgical procedure.

The second significant predictor was the type of intervention. Patients submitted to ANT-DBS have a higher hazard of developing psychiatric disorders after surgery. In previous literature, the stimulation of the ANT, in refractory epilepsy, has been associated with higher rates of self-reported depression [34]. A more recent study, with 22 patients submitted to ANT-DBS for the treatment of refractory epilepsy, showed that 2 patients, with a history of depression, developed depressive symptoms, and 2 others, with no history of psychosis, developed clear paranoid symptoms and anxiety [35].

Earlier studies concerning DBS use on Parkinson's disease and dystonia have found an association between this procedure and other serious psychiatric events such as hypomania/mania [36], psychotic disorders [37], and suicidal ideation/attempts [38]. There seems to be a different risk of developing mania or depression according to the location of the electrodes [39,40]. Older patients might also be particularly vulnerable to adverse psychiatric events [41].

Patients with refractory epilepsy submitted to this type of surgery may, likewise, be at a higher risk of the same psychiatric adverse events. This can be explained by the fact that although there are different targets, according to the disease that is intended to be treated, these structures participate in circuits that have implications for the control of mood and cognition.

This study has some limitations. It was an observational ambispective study with a retrospective component. There are some missing data and loss of follow-up. To account for this limitation, we used a survival analysis model. Secondly, as only annual evaluations were carried on, interevaluation disturbances may have been missed. Notwithstanding, psychiatrists involved were in constant communication with other members of the Epilepsy Surgery Group involved in the follow-up of participants, and, every time a psychiatric disturbance was identified, they were promptly referred to a psychiatric consultation. We did not control for the type of antiepileptic drugs or changes in dosages. Some antiepileptic drugs may have different effects on mood and behavior, however, as previously stated, for the majority of patients, no changes were made during the follow-up period. Moreover, we did not analyze each type of psychiatric episode separately. Although they have different clinical presentations, only major episodes and serious adverse psychiatric events were considered. The occurrence of any of these events is always an important factor that has a major impact on quality of life of people with epilepsy.

Another important limitation is related to the possibility that, during presurgical evaluation, patients and families underreport psychiatric symptoms because they may be considered it a “natural reaction” to epilepsy or because of their fear of not being qualified for surgery. This may lead to an overestimation of what could be considered *de novo* psychopathology. Furthermore, as the sample size is relatively small, there are only a few numbers of events limiting the statistical power and stability of our models.

Despite these constraints, our study allows the identification of clinical variables that could be associated with an increased risk for *de novo* psychiatric events and a shorter time-to-event after surgery. Moreover, it may suggest potential biological mechanisms involved in postsurgery psychiatric morbidity. New studies with larger number of patients submitted to DBS and resective surgery for epilepsy are required to confirm these results. Our study also reinforces the need for a comprehensive assessment of patients, the importance of adequate counseling presurgery, and psychiatric follow-up. We suggest that patients with a multilobar epileptogenic zone and those submitted to invasive procedures for the treatment of epilepsy-like refractory epilepsy, particularly DBS, should be submitted to more frequent psychiatric routine assessments after surgery.

In conclusion, our study identified two important factors that are highly associated with an increased risk of developing a serious psychiatric event after surgery, a wider epileptogenic zone, and thus, a more general involvement of the different areas and brain circuits and the neurosurgical procedure to which patients are submitted.

Conflict of interest

None.

Disclosures

The main author is responsible for data collection and integrity. This work has not been published or presented before.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author's contributions

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

Acknowledgments

We sincerely thank all patients for their participation in the study. We gratefully acknowledge Professor Ebrahim Barkoudah and Dr. Alexandre Campos for reviewing the manuscript. We also thank all members from Refractory Epilepsy Reference Centre and the Epilepsy Surgery Group, of our institution, for their contribution to patients' evaluation.

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