Epilepsy & Behavior 25 (2012) 593–597

Contents lists available at SciVerse ScienceDirect

Epilepsy & Behavior

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

Psychiatric comorbidity in refractory focal epilepsy: A study of 490 patients

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ARTICLE INFO

Article history:
Received 13 July 2012
Revised 24 August 2012
Accepted 17 September 2012
Available online 14 November 2012

Keywords:
Psychiatric comorbidities
Temporal lobe epilepsy
Frontal lobe epilepsy
Limbic system
Neocortical epilepsy

ABSTRACT

We studied the prevalence and associated factors of psychiatric comorbidities in 490 patients with refractory focal epilepsy. Of these, 198 (40.4%) patients had psychiatric comorbidity. An Axis I diagnosis was made in 154 patients (31.4%) and an Axis II diagnosis (personality disorder) in another 44 (8.97%) patients. After logistic regression, positive family history of psychiatric comorbidities (O.R. = 1.98; 95% CI = 1.10–3.58; $p = 0.023$), the presence of Axis II psychiatric comorbidities (O.R. = 3.25; 95% CI = 1.70–6.22; $p < 0.0001$), and the epileptogenic zone located in mesial temporal lobe structures (O.R. = 1.94; 95% CI = 1.25–3.03; $p = 0.003$) remained associated with Axis I psychiatric comorbidities. We concluded that a combination of clinical variables and selected structural abnormalities of the central nervous system contributes to the development of psychiatric comorbidities in patients with focal epilepsy.

1. Introduction

Epilepsy is a chronic brain disorder that affects approximately 50 million people worldwide. Patients with epilepsy have significant physical, social, neuropsychological, and psychiatric comorbidities that impact their health-related quality of life (HRQOL). Due to a combination of this high prevalence of comorbidities and the presence of long-term seizures, patients with refractory epilepsy experience even more deleterious effects on their individual health when compared to those with controlled seizures [1–7]. Population-based studies have shown that epilepsy is associated with an increased prevalence of mental health disorders when compared to the general population. In one study, the lifetime prevalence of suicidal ideation in people with epilepsy was almost double than that in individuals without epilepsy [6]. In another study, it was shown that up to 58% of patients with refractory epilepsy had a current or past history of psychiatric disorders [8]. These comorbidities are frequently associated with a significant decrease in HRQOL in such patients [9,10].

To reduce the burden of the disease, considerable efforts have been spent to develop effective and safe therapies to treat patients with epilepsy. With the increasing recognition that such comorbidities represent a significant challenge to achieve this goal, one of the top priorities in epilepsy research is to prevent, limit, and reverse the occurrence of comorbidities associated with the epilepsies, such as cognitive impairment and psychiatric disorders. Regarding the last ones, approaches to understand the natural history of psychiatric comorbidities associated with epilepsy constitute a reasonable first step to achieve the above-mentioned goal. Although the prevalence and characteristics of psychiatric disorders have been extensively studied in patients with temporal lobe epilepsy (TLE), supporting the view that TLE and psychiatric illness are closely related [1,6,11–17], the natural history of psychiatric comorbidities in extratemporal lobe epilepsy (ExTLE) is much less understood. More importantly, the identification of all factors that are independently associated with psychiatric comorbidities in epilepsy remains to be fully elucidated.

Here, we report a large series of 490 patients with refractory epilepsy as defined by the ILAE criteria [18], submitted to a comprehensive and multidisciplinary pre-surgical evaluation. Our goal was to identify the relationship between psychiatric comorbidities and location of the epileptogenic zone (EZ). In addition, we aimed to assess whether or not specific features of the epileptic syndrome, such as gender, etiology, age at seizure onset, seizure frequency, epilepsy duration, and seizure clinical characteristics, were factors associated with psychiatric comorbidities in some forms of refractory focal epilepsy.

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1525-5050/$ – see front matter © 2012 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.yebeh.2012.09.026

2. Methods

2.1. Subjects

We retrospectively reviewed clinical, neuroimaging, video-EEG monitoring, and psychiatric data of patients with refractory epilepsy evaluated at the CIREP (Center for Epilepsy Surgery), Ribeirão Preto School of Medicine, University of Sao Paulo, Brazil, from 1995 to 2005. Inclusion criteria were adult patients older than 18 years, with refractory epilepsy, and with well-defined focal epilepsy. During this period, five hundred and twenty-four patients fulfilled the inclusion criteria. From these, thirty-four patients were excluded because of incomplete data at the time of the study. The remaining four hundred and ninety patients were included in this study. The mean (± standard deviation) age at evaluation was 41 ± 9.9 years (range: 18 to 66 years), the mean age of epilepsy onset was 12.2 ± 8.6 years (range: 0 to 43 years), and the mean epilepsy duration was 29.12 ± 11.76 years (range: 1 to 58 years). Medically refractory epilepsy was defined according to the ILAE criteria [18]. Patients whose epileptogenic zone could not be determined during presurgical evaluation and those with incomplete clinical, electrophysiological, or neuroimaging data were excluded. This study was approved by the Ethics Committee of our institution and followed the ethical standards defined by the Declaration of Helsinki. All persons included in the study gave written informed consent prior to their inclusion in the study.

2.2. Clinical variables

Clinical variables were abstracted from the medical records. These included age at evaluation, age at seizure onset, epilepsy duration, seizure frequency per month, frequency of generalized tonic-clonic seizures per year, gender, family history of epilepsy, family history of psychiatric disease, years of education, intelligence quotient (IQ), and side of MRI lesion. Epilepsy duration was calculated as the interval (in years) from age at seizure onset to age at evaluation. During the neurological interview, patients and their family members were questioned about the presence of a family history of epilepsy in first- or second-degree relatives. During the psychiatric interview, a family history of psychiatric disorders was considered positive if a first- or second-degree relative had a confirmed diagnosis of a psychiatric disorder.

2.3. Psychiatric evaluation

All patients were submitted to an extensive, formal, and standardized psychiatric evaluation as part of the pre-surgical evaluation protocol. This evaluation was performed by psychiatrists dedicated to the assessment of patients with epilepsy in our center (J.H., R.G., and M.P.C). In these assessments, all patients were initially interviewed alone. Next, they were reevaluated when accompanied by a family member. During these evaluations, a complete family history of psychiatric disorders was recorded. Detailed Axis I and II diagnoses were made clinically during psychiatric evaluation based on the Diagnostic and Statistical Manual of Mental Disorders — Fourth Edition (DSM-IV and DSM-IV-RT). For the purpose of this study, a lifetime psychiatric diagnosis was used.

In addition, Axis I psychiatric comorbidities were grouped into mood disorders (depression, mania, hypomania, bipolar, and dysthymic disorder), anxiety disorders (generalized anxiety disorder, panic, obsessive–compulsive disorder, post-traumatic stress disorders), and psychosis (interictal and post-ictal). The personality disorders were classified according to the groups A, B, and C of personality disorders of the DSM-IV. The "epileptic personality condition" was classified within "other personality disorders". The presence of an Axis I diagnosis did not exclude the possibility of an overlapping personality disorder (Axis II). Because of the lack of psychiatric categories in the DSM-IV classification specifically applied to epilepsy, we additionally considered three specific psychiatric comorbidities frequently associated with epilepsy: interictal dysphoric disorder, postictal psychosis, and interictal psychosis. Interictal dysphoric disorder has been classified by Blumer et al. [19] as an intermittent course of depressive somatoform and affective symptoms. Depressive somatoform symptoms include depressive mood, anergia, pain, and insomnia. Affective symptoms include irritability, euphoric mood, fear, and anxiety [19,20]. The postictal psychosis group was defined according to Logsdail and Toone's criteria: a psychotic state characterized by hallucinations, delusions or disorders of thought, and eventually mood changes, occurring within 24 h to 7 days after the last epileptic seizure. During the psychotic state (ranging from a few days to 90 days), consciousness is often preserved [21]. The interictal psychosis group was defined as a prolonged psychotic state not temporally related to the epileptic seizures. Features include hallucinations, preoccupation with religious themes, and Schneider's first-rank symptoms, i.e., certain symptoms as being characteristic of schizophrenia and, therefore, exhibiting a "first-rank" status in the hierarchy of potentially diagnostic symptoms [22]. Ictal psychosis or psychosis associated with changes in AED regimen, status epilepticus, and delirium were not included.

2.4. Definition of the epileptogenic zone

The gold standard to determine the localization of the EZ was a combination of diagnostic tests. The standard presurgical evaluation included a detailed clinical interview and neurological examination, interictal and ictal scalp EEG-video recordings, structural high-resolution MRI, ictal and interictal SPECT, and neuropsychological and social assessments. If the standard protocol failed to localize the EZ unequivocally, patients were submitted to semi-invasive (foramen ovale) or invasive investigations with subdural grids and strips. Patients were then categorized according to the localization of the EZ as having mesial temporal lobe epilepsy (MTLE), neocortical temporal lobe epilepsy (NeoTLE), and extratemporal epilepsy (ExTLE).

2.5. Study design and statistical analysis

All data were analyzed with SPSS 15.0 for Windows (SPSS, Inc.). The chi-square test was used for categorical variables, and results are expressed as odds ratios (OR) and 95% confidence interval (95% CI). The Kolmogorov–Smirnov test was applied to test normality of the data. When variables presented a normal distribution, a parametric test such as the Student's *t*-test or analysis of variance (ANOVA) was used. When variables did not present a normal distribution, the non-parametric Mann–Whitney or Kruskal–Wallis test was used. Binary logistic regression was used to control for confounding variables for Axis I psychiatric comorbidities when $p \leq 0.10$. Additionally, we forced these same variables in a multinomial logistic regression model to study independent effects and their relationship with each and with Axis I psychiatric comorbidities (mood, anxiety, or psychotic disorders). Results were considered significant if $p < 0.05$.

3. Results

3.1. Clinical and demographic characteristics of study participants

The clinical and demographic characteristics of our series are presented in Table 1. Of the 490 patients included in the study, 328 (66%) had MTLE, 47 (10%) had NeoTLE, and 115 (24%) had ExTLE. The natural history of patients with refractory focal epilepsies differed depending on the location of the EZ. For example, patients with MTLE had a lower frequency of secondarily generalized tonic-clonic seizures ($p < 0.001$) and better seizure outcomes after surgery ($p < 0.001$) compared to patients with NeoTLE and ExTLE. In addition, patients with NeoTLE had a slightly higher IQ ($p = 0.006$) and a lower