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Psychotic disorders in Argentine patients with refractory temporal lobe epilepsy: A case–control study

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ABSTRACT

The issue of psychotic disorders in epilepsy has given rise to great controversy among professionals; however, there are not many studies in this area and the physiopathological mechanisms remain unknown. The aim of this study was to describe the spectrum of psychotic disorders in an Argentine population with refractory temporal lobe epilepsy (RTLE) and to determine the risk factors associated with psychotic disorders. Clinical variables of the epileptic syndrome were compared among a selected population with RTLE with and without psychotic disorders (DSM-IV/Ictal Classification of psychoses). Logistic regression was performed. Sixty-three patients with psychotic disorders (Psychotic Group, PG) and 60 controls (Control Group, CG) were included. The most frequent psychotic disorders were brief psychotic episodes (35%) (DSM-IV) and interictal psychosis (50%) (Ictal Classification). Risk factors for psychotic disorders were bilateral hippocampal sclerosis, history of status epilepticus, and duration of epilepsy greater than 20 years.

1. Introduction

The issue of psychotic disorders in epilepsy has given rise to great controversy among professionals [1–6]. Epidemiological studies conducted on patients with epilepsy from general medical attention centers reported a prevalence of psychosis ranging from 0.7% to 7%; however, those performed in neurology and/or epilepsy centers reported a prevalence of psychosis ranging from 8% to 40% [1,3–6].

The individual's risk of developing psychosis could be related to the epileptic syndrome, as well as to the patient's response to treatment [3,5,7–9]. Refractory temporal lobe epilepsy (RTLE) has been associated with a high incidence of psychotic disorders [3,7,8,10]; however, the physiopathological mechanisms among these patients remain unknown. Some authors have postulated that homeostatic mechanisms in response to seizures (inhibitory processes), including electrophysiological and neuroplastic changes in specific neurochemical systems of limbic areas, promote the development of psychotic symptoms (hallucinations and delusion) in vulnerable patients [8,11–14].

Risk factors reported for developing psychoses in epilepsy include a higher frequency of seizures, early epilepsy onset with a longer duration of seizures, and presence of multiple lesions [2,15–17]. Other risk factors reported include localization of the epileptogenic zone within the temporal lobe and left-sided focus [18–20], disorders of cortical development [21,22], hippocampal sclerosis [23], and factors associated with antiepileptic treatment, such as polytherapy and the use of new-generation antiepileptic drugs [5,24,25]. More recently, the presence of bilateral independent ictal foci was associated wth postictal psychoses [26–28].

At present, the use of contemporary psychiatric nosography as DSM-IV, in conjunction with Ictal Classification, which enables consideration of the temporal relationship between the onset of psychosis and epileptic seizures, is recommended [29–33]. According to Ictal Classification, postictal, interictal, and bimodal psychoses are considered separate syndromes; however, they have a number of similarities, and progression from postictal to interictal psychosis has been described [34–36]. Furthermore a unifying hypothesis suggesting the same pathomechanisms are involved has been proposed [14]. In a previous study conducted at our epilepsy center, we reported a similar profile in patients with partial epilepsy of different origins (temporal, frontal, and parietal) with postictal, interictal, and bimodal psychoses [37]. The aims of this study were to determine the spectrum of psychotic disorders using DSM-IV criteria and Ictal Classification, and to analyze the risk factors associated with psychotic disorders in a selected population with RTLE.

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2. Methods

2.1. Population

This investigation was performed at the Epilepsy Center of Ramos Mejía Hospital (ECRMH). All patients selected and admitted to this study were evaluated by the same group of professionals to confirm the epileptogenic zone and determine eventual inclusion in the epilepsy surgical program. The study was conducted with the approval of the ethics committee of Ramos Mejía Hospital in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki, and all the subjects submitted informed consent [38,39].

2.2. Patient selection

During December 2001–December 2007, 2800 patients were admitted to ECRMH. Over the same period, 403 patients (14.4%) with refractory epilepsy were admitted to the surgical assessment protocol. In this study, 123 selected patients were included according to the following criteria:

1. Male or female aged 18–60
2. Clinical diagnosis of temporal lobe epilepsy (TLE)
3. Complementary studies (video/EEG monitoring, interictal EEG, and MRI), confirming the temporal localization of the epileptogenic zone
4. Pharmacological treatment-refractory epilepsy (Patients having at least one seizure per month during the last 2 years with the appropriate treatment were considered to have refractory epilepsy.)

Exclusion criteria were:

1. Failure to complete all diagnostic steps
2. Partial epilepsy of extratemporal origin
3. Other types of epilepsy
4. Other neurological diseases associated with epilepsy
5. History of mental retardation (attending a special school) and/or IQ < 70 according to the Wechsler Adult Intelligence Scale [40]
6. Comorbid psychogenic nonepileptic seizures confirmed during video/EEG monitoring and/or other current psychiatric disorder codified in DSM-IV [41,42]

2.3. Diagnosis of temporal lobe epilepsy

All patients included in this study underwent a complete clinical and neurological assessment, according to a standardized clinical history (epidemiological surveillance program, VIGIA) [38,39]. Clinical history data were gathered retrospectively by anamnesis. Every patient underwent a systematic study on seizure semiology and epileptic aura. In this protocol, four major types of epileptic auras were distinguished according to current classifications of epileptic auras: autonomic aura, psychic aura, special sensory aura, and somatosensory aura [43,44].

Additional studies confirming the temporal origin of epilepsy were interictal EEG, video/EEG monitoring, and MRI, with a temporal lobe epilepsy protocol. The sequences used were the following:

- Sagittal plane T1-weighted image for the purpose of detecting the hippocampus in the parasagittal slices
- Inversion–recovery (IR) pulse sequence, fluid-attenuated IR (FLAIR), and three-dimensional gradient echo sequence (volumetric), perpendicular to the long axis of the hippocampus
- T2-weighted axial sequence parallel to the long axis of the hippocampus

2.4. Psychiatric diagnosis: diagnoses of psychoses

The psychiatric semiology of the witnessed examination was supplemented with structural interviews from DSM-IV (Structured Clinical Interview for DSM Disorders [SCID]-I and -II). Psychiatric assessment was performed by a specialist trained in psychiatry. For the present study we used the clinical version translated into Spanish and validated for Spanish-speaking populations [45,46]. All patients with psychotic symptoms (Module B of SCID-I) were grouped according to DSM-IV diagnostic criteria. Patients with psychotic disorders codified in Axis I of DSM-IV (Module C of SCID-I) were distinguished regardless of the diagnostic digression as "psychotic disorder due to a medical condition" (e.g., schizophreniform disorder in Axis I and temporal lobe epilepsy in Axis III [medical condition]) [47]. These patients with clear psychotic episodes in Module C were grouped depending on Ictal Classification, which takes into account the temporal relationship between the ictal episode and the onset of psychosis. Three main subtypes of psychoses were distinguished: postictal psychosis (PIP), a psychotic episode preceded at least 24 h by one or more seizures with a lucid interval; interictal psychosis (IIP); and psychotic disorder in the absence of a clear temporal relationship between onset of psychotic symptoms and epileptic seizures. Patients who met the criteria for both types of psychoses occurring in different episodes were considered a third subgroup, bimodal psychosis (BP) [12,30,33–36].

Patients who had mild psychotic symptoms with no criteria for Axis I psychotic disorder, but who had criteria for a Cluster A personality disorder (schizoid, paranoid, and schizotypal) were also analyzed (DSM-IV). In these cases it was not possible to determine the moment of onset of psychotic symptomatology; neither was it possible to determine Ictal Classification.

2.5. Selection of cases and controls

Two main groups with RTLE were included: the Psychosis Group (PG, cases), and the Control Group (CG, controls). Patients included in the PG had current and/or past Module B symptoms (psychotic symptoms) codified in SCID-I (psychotic disorder in Axis I) or in SCID-II (Cluster A in Axis II) of DSM-IV. The CG was composed of patients who did not have a current or past psychotic disorder or symptoms, nor other current psychiatric disorder according DSM-IV criteria.

Cases and controls were compared with respect to clinical variables. The following variables were analyzed: gender, age, schooling, employment, age at seizure onset, epilepsy duration, history of febrile seizures, presence of secondarily generalized seizures, pharmacological history, status epilepticus history, laterality of epilepsy according to electrophysiological results (video/EEG monitoring), and MRI results.

2.6. Data analysis

Student's t test was performed to compare the quantitative variables, and the χ^2 test or Fisher's exact test, to compare qualitative variables. Binary logistic regression was applied to qualitative variables, and the odds ratio (OR) and 95% confidence interval (95% CI) were determined. Quantitative variables such as age at epilepsy onset and time of evolution were converted into dichotomic qualitative variables to determine logistic regression. SPSS for Windows was used for statistical analysis.

3. Results

For this investigation 123 patients with RTLE were selected and consecutively included in this study. Sixty-three patients had cur-

rent and/or past Module B symptoms (psychotic symptoms) in SCID-I and were included in the PG. Sixty patients had no history of psychotic disorders and/or psychotic symptoms and were included in the CG.

In the PG, the most frequent subtypes of psychotic disorders according to DSM-IV are summarized in Fig. 1. The psychotic symptoms required the use of antipsychotic drugs in 45 patients (71%): risperidone (40%), haloperidol (21%), other antipsychotic drugs (10%).

Transient evolution with complete remission of psychotic symptomatology (<6 months of evolution with or without treatment) was determined in 67% of patients with episodes codified in Axis I ($n = 52$): brief psychotic episodes (<1 month, $n = 22$), schizophreniform disorder (<6 months, $n = 8$), and transient affective psychoses (<6 months, $n = 5$). Forty percent had recurrent episodes. The clinical semiology during psychotic episodes in the PG is summarized in Table 1.

Ictal Classification was also established in patients with episodes codified in Axis I ($n = 52$). The most frequent subtype was interictal psychosis (Fig. 2). In patients with postictal and bimodal psychoses ($n = 26$), postictal episodes were observed after generalized seizures in 10 patients (38%), seizure clusters in 7 patients (27%), status epilepticus in 3 patients (12%), and complex partial seizures similar to the usual ones in 6 patients (23%).

Time elapsed from onset of seizures to appearance of psychotic symptoms in Axis I was 20.8 ± 12.5 years, and age at onset of psychotic symptoms was 31.3 ± 10 years.

At least one of the acute psychotic episodes codified in Axis I was induced by antiepileptic drugs in six patients (12%) (topiramate in four and vigabatrin in two), and discontinuation of the drug resulted in complete remission of psychotic symptomatology. Psychotic episodes induced by antiepileptic drugs met criteria for schizophreniform disorder in five patients and schizoaffective disorder in one patient. All episodes had an interictal presentation; however, one patient had a history of PIP episodes, and this case was considered a bimodal psychosis. The semiology of psychotic disorders induced by antiepileptic drugs included: delusions (6, 100%), hallucinations (3, 50%), disorganized behavior (3, 50%), affective symptoms (4, 66%), disorganized speech (3, 50%), and negative symptoms (2, 33%).

All patients in the PG and CG had completed elementary school; 38 patients (63%) in the CG and 42 patients (67%) in the PG had completed high school. All patients included in both groups had received AED polytherapy (they had been treated with at least one new drug in conjunction with classic drugs, because of the refractoriness of the seizures).

Demographic and clinical variables on which the two groups were compared are summarized in Tables 2 and 3. No differences between the groups were found in the other clinical variables analyzed. The laterality of the epileptogenic focus was established in 103 patients, and there was no difference with respect to side of fo-

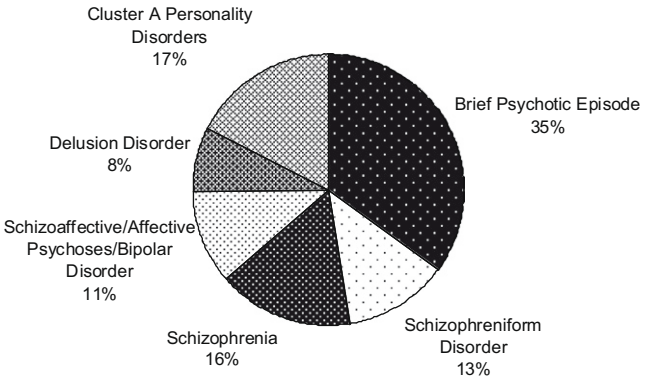

Fig. 1. Patients with psychotic symptoms (Module B of SCID I): DSM-IV diagnostic criteria codified in Axis I/II (SCID I and II) ($n = 63$).

Table 1
Clinical semiology in patients with psychotic symptoms codified in the SCID I (Module B) and in patients with psychotic disorders codified in Axis I and II (DSM-IV criteria) ($n = 63$).

Clinical semiology	Number (%) of patients
Delusions	53 (84%)
Hallucinations	46 (73%)
Disorganized behavior	42 (66%)
Affective symptoms	57 (90%)
Disorganized speech	13 (20%)
Negative symptoms	28 (44%)

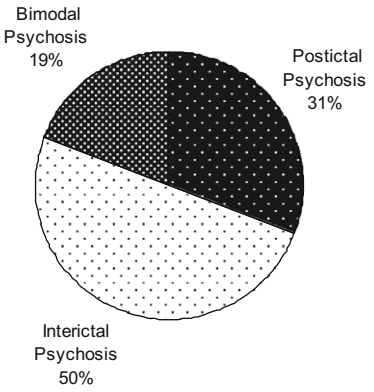

Fig. 2. Ictal Classification of psychosis in patients with psychotic disorders codified in Axis I of DSM-IV ($n = 52$).

Table 2
Clinical and demographic variables.

Clinical variable	Control group ($n = 60$)	Psychotic group ($n = 63$)	P (control group vs psychotic group)
Sex			
Female	29 (48%)	19 (30%)	0.039
Male	31 (52%)	44 (70%)	
Employment	22 (37%)	7 (11%)	0.001
Status epilepticus	1 (2%)	9 (14%)	0.017
Aura	55 (92%)	50 (79%)	0.054
Epilepsy duration >20 years	31 (51%)	45 (71%)	0.02
Epilepsy onset before age 15	34 (56%)	43 (68%)	0.18
Unilateral hippocampal sclerosis	30 (50%)	24 (38%)	0.34
Bilateral hippocampal sclerosis	0	11 (17%)	0.001
Plus hippocampal sclerosis	16 (27%)	13 (21%)	0.59

Table 3
Quantitative variables: age and duration of epilepsy.

Age	Control group (n = 60)	Psychotic group (n = 63)	95% confidence interval	P	Total (n = 123)
Current age	37.12 ± 9.9[a]	38.49 ± 12[a]	−2.5 to 5.3	0.49	37.8 ± 11[a]
Age at onset	14.63 ± 11.1	10.21 ± 8.25	−8.0 to 0.8	0.016	12.4 ± 10.28
Duration of epilepsy	22.48 ± 11.67	28.29 ± 14	1.1–10.4	0.014	25.5 ± 13.2

[a] Mean ± SD.

Table 4
Risk factors (logistic regression).

Variable	Odds ratio	95% confidence interval
Bilateral hippocampal sclerosis	13.8	1.73–113
Status epilepticus	9.5	1.1–79.9
Duration of epilepsy >20 years	2.4	1.11–5.1

cus between the groups. The outcome of logistic regression is summarized in Table 4.

4. Discussion

In this investigation we studied a population of patients with refractory epilepsy who were included in a study protocol to determine eligibility for surgery. A homogeneous sample with the same type of refractory epilepsy, temporal lobe epilepsy, was selected and included in this analysis to determine the spectrum of psychotic disorders in patients with RTLE and the risk factors related to the epileptic syndrome. Two additional diagnostic instruments were used to reach the diagnosis of psychosis, DSM-IV (SCID-I and -II) and Ictal Classification, following the advice of different contemporary authors [12,29–32]. The simultaneous use of both classifications enabled us to obtain additional and more complete information and, at the same time, to identify the clinical differences among the spectrum of psychotic disorders.

In this study, the spectrum of psychotic disorders in patients with RTLE was represented by different psychotic entities codified in DSM-IV [47]. Psychotic episodes exhibited a transient outcome, with total remission of acute symptomatology (postpsychosis functioning similar to the usual) with greater frequency. These findings match most descriptions, from those proposed by Falret, Griesinger, and Wernike to the current descriptions [3,48–50]. On the other hand, chronic psychotic disorders (>6 months of evolution) such as schizophrenia, chronic schizoaffective disorder, and delusion disorder were observed in a smaller proportion of patients. Antiepileptic treatment induced interictal psychoses in 12% of the PG. In these cases, the subtype "alternative psychosis" should be considered, as epileptic seizures were significantly reduced during drug treatment and during clinical psychoses [14]. In a subgroup of patients who had mild psychotic symptoms and met criteria for a Cluster A personality disorder (schizotypical/schizoid or paranoid), it was not possible to determine the moment of onset of psychotic symptomatology. However, they were included in the PG because these personality traits constitute the schizophrenia spectrum referred by contemporary psychiatry and are considered a premorbid condition for psychotic disorders in Axis I such as schizophrenia and other psychotic disorders [55–58].

After Ictal Classification, patients with postictal psychotic disorders exhibited a short evolution of less than a month, generally shorter than a week, and episodes were preceded by worsening of the epileptic seizures as described by contemporary authors [3,33,59]. On the other hand, interictal psychosis status varied and did not always progress to the chronic form initially described as *schizophrenia simil* [15]. In many patients, interictal psychotic episodes were of short duration (brief psychotic episodes, schizophreniform psychosis, and affective psychoses; >1 month, but <6 months). These conditions have previously been referred to as acute interictal psychoses [51], interictal dysphorias with psychotic symptoms [52], and interictal psychosis with better prognosis than schizophrenia [53]. However, a third group of patients had a history of postictal episodes prior to the development of chronic interictal psychosis (bimodal psychosis) [34,35,54].

According to this investigation, bilateral hippocampal sclerosis, a history of status epilepticus, and longer duration of epilepsy (>20 years) are risk factors associated with the spectrum of psychotic disorders. The presence of bilateral hippocampal sclerosis has been previously reported in patients with TLE [7]. Multiple brain lesions have been observed in patients with epilepsy and psychosis [60]. Other authors found a higher incidence of lesions caused by alterations in neurodevelopment, such as gangliogliomas, hamartomas, and dysplasias [21,22]. More recently, a higher bilateral frontotemporal anatomical compromise of the white matter detected through diffusion tensor imaging has been reported [61]. Apart from a greater structural brain compromise, independent bilateral electrical abnormalities were reported as a risk factor for the development of postsurgical psychosis among patients with TLE who had undergone surgery [17,62,63] and during presurgical assessment in patients with postictal psychosis [26–28].

A history of status epilepticus constitutes a risk factor for psychosis in this investigation. In only three cases, the status led to an immediate postictal psychosis. In most of the patients, the status formed part of the history of the current disease, and psychosis developed many years after the status. The relationship between status epilepticus and intensity of the epileptic syndrome is well known [64]. Status epilepticus has been considered a possible cause of postictal psychosis, whereas nonconvulsive status epilepticus has been associated with psychotic manifestations occurring during the status itself (ictal psychosis) [7,12]. Furthermore, status epilepticus is responsible for a number of neurochemical events and induces neuroplasticity and neurotoxicity in experimental models [13,65,66]. The appearance of alterations such as abnormal neuroplasticity and the development of aberrant synaptic connections in the affected structures by epileptic discharges have been related to cognitive and behavioral abnormalities in experimental models of epilepsy [65,66]. Furthermore it has been postulated that neurochemical changes affecting the dopaminergic system and other neurotransmitters would be partly responsible for acute and chronic psychotic manifestations [13,14].

A longer duration of epilepsy (>20 years) may increase the risk of developing psychoses among predisposed patients according to this study. However, it is worth mentioning that the distribution of data was quite broad and that this study had a retrospective design. Nevertheless, a longer duration of seizure exposure in critical stages of neurodevelopment has been described as a risk factor by different authors [17,23,32,35,67]. Furthermore, psychosis onset was late in life (mean: 30 ± 10 years), in agreement with a recent report that found that patients with epilepsy developed psychoses later than patients with schizophrenia [68].

When sex distribution was analyzed, there was a significant predominance of men in the PG. Recent investigations have reported a higher prevalence of schizophrenia, with a greater ten-

dency to have the most devastating effects of this disease, in the male population [69,70].

A significantly higher incidence of unemployment was observed in the PG. This variable enables us to appreciate the fact that psychiatric comorbidity, and especially psychotic disorders, is a serious condition and affects the patient's quality of life beyond the frequency of the seizures [8,71].

Pharmacological treatment of psychoses in patients with epilepsy requires the use of antipsychotic drugs. Additional psychotherapeutic treatment and psychosocial rehabilitation of the patient are also important, particularly in chronic psychoses [33,52]. Furthermore, the systematic study of psychotic disorders with appropriate implementation of treatment takes on added importance in patients with refractory TLE who are admitted to a surgical assessment protocol [29,31,72].

5. Conclusions

According to this investigation, psychotic disorders in patients with refractory temporal lobe epilepsy are transient with a good outcome in most cases. Bilateral hippocampal sclerosis, a history of status epilepticus, and longer duration of epilepsy have been identified as risk factors associated with the spectrum of psychotic disorders. All these factors implicate a worse outcome for the epilepsy and, simultaneously, higher exposure to seizures. These findings agree with current neurobiological theories that postulate that psychotic disorders in patients with epilepsy may be related to the physiopathology of the seizures and to the abnormal neuroplastic effects that are induced by epileptic seizures over time, among vulnerable patients.

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