Epilepsy & Behavior 83 (2018) 181–185

Contents lists available at ScienceDirect

Epilepsy & Behavior

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

Genetic polymorphisms of the 5HT receptors are not related with depression in temporal lobe epilepsy caused by hippocampal sclerosis☆

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ARTICLE INFO

Article history:
Received 13 January 2018
Revised 13 March 2018
Accepted 26 March 2018
Available online xxxx

Keywords:
Temporal lobe epilepsy
Hippocampal sclerosis
Serotonin receptor
Genetic polymorphisms

ABSTRACT

Background: Temporal lobe epilepsy caused by hippocampal sclerosis (TLE-HS) is the most frequent form of drug-resistant epilepsy in adults. Mood disorders are the most frequent psychiatric comorbidities observed in these patients. Common pathophysiological mechanisms of epilepsy and psychiatric comorbidities include abnormalities in the serotonin pathway. The primary goal of this study was to determine the possible association between polymorphisms of genes encoding the serotonin receptors 5HT1A (rs6295), 5HT1B (rs6296), and 5HT2C (rs6318) and the presence of mood disorders in patients with TLE-HS. Our secondary goal was to evaluate the possible association between these variants and susceptibility to develop seizures in TLE-HS.
Methods: We assessed 119 patients with TLE-HS, with and without psychiatric comorbidities; 146 patients with major depressive disorder; and 113 healthy volunteers. Individuals were genotyped for the rs6295, rs6296, and rs6318 polymorphisms.
Results: No difference was observed between the group with TLE-HS, healthy controls, and the group with major depressive disorder without epilepsy regarding the polymorphisms that were evaluated. There was no correlation between rs6318, rs6295, rs6296, and epilepsy-related factors and history of psychiatric comorbidities.
Conclusions: Our work suggests that the studied polymorphisms were not related to the presence of TLE, psychiatric comorbidities in TLE, and epilepsy-related factors.

1. Introduction

Temporal lobe epilepsy caused by hippocampal sclerosis (TLE-HS) is the most frequent form of drug-resistant epilepsy in adults. Mood disorders, particularly major depressive disorder (MDD), are the most frequent psychiatric comorbidities observed in these patients and may have a distinct clinical profile [1].

Common pathophysiological mechanisms of epilepsy and psychiatric comorbidities include abnormalities in the serotonin (5HT) pathway. Clinical and experimental studies have shown that 5HT levels may modulate the susceptibility to the occurrence of seizures [2] and are related to the presence of depressive symptoms in patients with TLE [3].

Brain 5HT availability depends on various factors, including genetics. The 5HT pathway has a complex neural communication system mediated by at least 14 subtypes of pre- and postsynaptic receptors [4]. The gene encoding 5HT1A receptor contains a single nucleotide polymorphism (SNP) in the promoter region (C-1019G — rs6295), which appears to regulate its expression [5]. The region encoding the 5HT1B gene contains a silent SNP (G861C — rs6296). The gene encoding the 5HT2C receptor has a functional SNP in the coding region (G68C — rs6318), which results in the substitution of a cysteine for serine at position 23 (Cys23Ser) [6].

Abbreviations: IBGE, Brazilian Institute of Geography and Statistics; ILAE, International League Against Epilepsy; MRI, magnetic resonance imaging; MDD, major depressive disorder; DSM-IV-TR, Multiaxial Diagnostic and Statistical Manual; PCR, polynucleotide chain reaction; PET, positron emission tomography; 5HT, serotonin; SNP, single nucleotide polymorphism; TLE-HS, temporal lobe epilepsy caused by hippocampal sclerosis; SCID-I, The Structured Clinical Interview for DSM-IV Axis I Disorders; USP, University of Sao Paulo; CNS, central nervous system; DNA, deoxyribonucleic acid.

☆ Declarations of interest: None.

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https://doi.org/10.1016/j.yebeh.2018.03.032
1525-5050/

To date, there are few studies on the association of polymorphisms in the 5HT pathway and TLE. However, these studies differ in several aspects, from objective to patients' selection [7–17], and only two considered psychiatric comorbidities [7,12]. To the best of our knowledge, there are no studies specifically designed for patients with TLE-HS and depression. In this context, our primary goal was to determine the possible association between polymorphisms of genes encoding the 5HT receptors 5HT1A (rs6295), 5HT1B (rs6296), and 5HT2C (rs6318) and the presence of mood disorders in patients with TLE-HS. The occurrence of these variants in patients with TLE-HS and depression, but not in patients with MDD without epilepsy, may partially explain the distinct clinical features of depression in TLE. Our secondary goal was to evaluate the possible association between some of these genetic variants and susceptibility to develop seizures in TLE-HS.

2. Methods

2.1. Participants

Patients with TLE-HS and MDD who participated in this study were assessed in the Outpatient Epilepsy Clinic and Mood Disorders Unit of Clinics Hospital, Faculty of Medicine, University of Sao Paulo (USP), and Goiania Neurological Institute, Brazil. Before taking part in this study, all patients and controls signed an informed consent form approved by the Clinics Hospital at University of Sao Paulo and Federal University of Goias Ethics Committee (number 17030713.2.1001.0068). This work follows the guidelines of the Declaration of Helsinki.

2.1.1. Patients with TLE-HS

2.1.1.1. Clinical profile of patients with TLE-HS. We included patients with TLE-HS with and without psychiatric comorbidities. Patients underwent a clinical evaluation and were interviewed with a standard questionnaire. For this study, we included patients diagnosed with TLE-HS, classified according to the criteria of the International League Against Epilepsy [18,19]. Therefore, all patients had a radiological diagnosis (magnetic resonance imaging — MRI) compatible with HS and with clinical and neurophysiological data that corroborated temporal lobe seizures following the ILAE criteria.

Patients with a clear TLE-HS were assessed by a psychiatrist using the Multiaxial Diagnostic and Statistical Manual — DSM-IV-TR [20]. The multi-axis system involves an evaluation of different axes through a clinical interview guided by DSM-IV using Axis I held by SCID-I/P (The Structured Clinical Interview for DSM-IV Axis I Disorders) [21]. The SCID provides the previous and current diagnosis of mental disorders. We excluded patients with other epileptic syndromes, dual pathology, or absence of a lesion in MRI.

Based on these criteria, we included 119 patients with TLE-HS. Fifty-one patients (42.8%) were male with a mean age of 38.6 yrs. (SD = 13.8 yrs.; min/max: 9–70 yrs.). The ethnicity of each participant was inferred from self-reported data about their ancestry utilizing Brazilian Institute of Geography and Statistics classification [22]. According to this criterion, the ethnic distribution was 87 (73.1%) Caucasians, 17 (14.3%) multiracial-Brazilians (a range of African ancestry), and 15 (12.6%) Afro-Brazilians.

2.1.1.2. Epilepsy profile of patients with TLE-HS. The mean age of first seizure in this group was 11.3 yrs. (SD = 10.6; min/max: 0.1–52 yrs.), with mean epilepsy duration of 25.9 yrs. (SD = 13.0; min/max: 3–62 yrs.). Forty-three patients (36.1%) had right, 62 (52.1%) left, and 14 (11.8%) bilateral TLE-HS. Twenty-seven (22.7%) patients were in monotherapy and 92 (77.3%) in polytherapy. The presence of focal to bilateral tonic–clonic seizures was observed in 84 (70.5%) patients. Status epilepticus occurred in 24 (20.1%) patients, and febrile seizures occurred in 29 (24.3%). Fifty-five (46.2%) patients had a family history of epilepsy, and 42 (35.3%) patients had a family history of psychiatric comorbidities.

2.1.1.3. Psychiatric profile of patients with TLE-HS. Psychiatric comorbidities were diagnosed in 95 patients (79.8%), and MDD, alone or in association with other psychiatric comorbidities, was the most frequently documented (56 [58.9%] of all patients; Table 1).

2.1.2. Patients with major depressive disorder without epilepsy

We included patients diagnosed with MDD without epilepsy and psychotic features, classified according to the criteria of DSM-IV-TR [20], based on clinical assessment and confirmed by SCID-I/P [21].

Based on these criteria, we included 146 patients with MDD. Forty-nine patients (33.6%) were male with a mean age of 47.0 yrs. (SD = 13.0; min/max: 18–76 yrs.). The ethnic distribution was 115 (78.7%) Caucasians, 18 (12.3%) multiracial-Brazilians, 6 (4.1%) Afro-Brazilians, and 7 (4.9%) with East Asian ancestry, according to IBGE criteria [22].

2.1.3. Healthy controls

We evaluated healthy volunteers, recruited from the general population, with no personal or family history of epilepsy or psychiatric comorbidities. First, controls underwent a neurological interview followed by a physical and neurological examination to exclude probable central nervous system (CNS) disorders not diagnosed or referred to by the subjects. Then, they were interviewed using the SCID-I/P [21]. We excluded volunteers if they presented a lifetime history of any psychiatric conditions.

Based on these criteria, we included 113 healthy volunteers. Fifty-six subjects (49.5%) were male with a mean age of 32.4 yrs. (SD = 11.0; min/max: 17–64 yrs.). The ethnic distribution was 68 (60.2%) Caucasians, 24 (19.5%) multiracial-Brazilians, 17 (15.0%) Afro-Brazilians, and 4 (5.3%) with East Asian ancestry.

2.2. Genotyping — biochemistry analysis

Deoxyribonucleic acid (DNA) was extracted from peripheral leukocytes by the salting-out method [23]. Individuals were genotyped for the polymorphisms of the gene encoding the receptors of 5HT1A, 5HT1B, and 5HT2C — rs6295, rs6296, and rs6318.

The three SNPs were genotyped by real-time polynucleotide chain reaction (PCR) with TaqMan allele-specific assays. Amplification reactions were as follows: GoTaq Probe qPCR Master Mix (Promega®) 1×/μL, TaqMan® SNP genotyping assay (Life Technologies®) 1×/μL, genomic DNA 10 ng/μL, ultrapure water to complete 7 μL volume.

Allelic discrimination was evaluated in a Line Gene 9600 (BIOER Technology CO.) comparing amplification curves and fluorescence levels before and after amplification (45 cycles of 15 s at 95 °C and 1 min at 60 °C).

2.3. Statistical analysis

Categorical variables were compared between groups by the Fisher's exact test, whereas numerical variables were compared by

Table 1
Psychiatric comorbidities in patients with TLE-HS.

	N
MDD	46/95 (48.4%)
MDD and ictal/interictal psychosis	6/95 (6.3%)
MDD and dissociative disorder	3/95 (3.2%)
MDD and anxiety disorder	1/95 (1.0%)
Ictal/interictal psychosis	15/95 (15.8%)
Dissociative disorder	2/95 (2.1%)
Anxiety disorder	9/95 (9.5%)
Other	13/95 (13.1%)

MDD — major depressive disorder.
TLE-HS — temporal lobe epilepsy caused by hippocampal sclerosis.