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Factors predicting the outcome following medical treatment of mesial temporal epilepsy with hippocampal sclerosis

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ABSTRACT

Purpose: There is a lack of information from South America regarding factors that predict the clinical outcomes of patients treated medically for mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS). This study was conducted to determine which of these factors are the most important.
Methods: This study included 110 South American patients with MTLE-HS treated with antiepileptic drugs. The factors considered included age, gender, age of epilepsy onset, interval between the lesion and the first seizure, central nervous system infection, traumatic brain injury, perinatal asphyxia, febrile convulsion, history of status epilepticus, types of seizures, site of hippocampal sclerosis (HS), extrahippocampal pathology, and electroencephalogram (EEG) abnormalities. The patients were divided into two groups based on the response to treatment: Group I, seizure free for at least two years; and Group II, not seizure free.
Results: On the multivariate analysis, the factors associated with a poor prognosis in terms of seizure frequency and control following treatment included the presence of an early onset of seizure, more than 10 seizures per month before treatment, and EEG abnormalities.
Conclusion: The recognition of risk factors, such as early onset of seizures, more than 10 seizures per month before treatment, and EEG abnormalities, could lead to the identification of risk groups among patients with MTLE-HS and refractory epilepsy, possibly designating these individuals as candidates for early epilepsy surgery.

1. Introduction

Hippocampal sclerosis (HS) is the most common pathology in the brain of patients with drug-resistant mesial temporal lobe epilepsy (MTLE).[1–4] HS is present in 50–70% of cases in which a temporal lobectomy was performed for the treatment of refractory epilepsy.[5–7] Various studies have confirmed that MTLE-HS is a chronic disease characterised by prominent neuronal loss and fibrillary gliosis at the level of the hippocampal pyramidal cell layer, but the pathophysiological mechanisms of HS are not clear.[2,8,9]

Early surgery is typically recommended because uncontrolled epilepsy is associated with cognitive impairment, psychosocial dysfunction, and increased morbidity and mortality. It has been found that if refractoriness is detected early, aggressive drug therapy or early surgery can improve the responsiveness to treatment and minimise these adverse effects.[10,11]

Reports of seizure remission in patients with MTLE-HS range from 5%[12] to 42%.[3] An early onset of epilepsy, history of febrile convulsions, interictal epileptiform activity on electroencephalogram (EEG), duration of epilepsy, response to the first antiepileptic drug, number of seizures per month before treatment, presence of mental retardation, age of traumatic brain injury(TBI), dual pathology,[2] and female gender[13–16] are prognostic factors in MTLE-HS. The majority of research studies on the prognostic factors of medically treated MTLE-HS have been conducted in developed countries, but of the approximately 70 million people with epilepsy in the world, 80% (56 million) live in developing countries.[17] The purpose of this study was to identify the prognostic factors in patients with medically treated MTLE-HS in South America.

2. Methods

We conducted a prospective study of 110 patients who met the inclusion criteria described below and who were treated at the Department of Neurology, Institute of Neurosciences, in Guayaquil, Ecuador, between January 2008 and December 2010. This institute

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is a referral hospital for patients with epilepsy for the entire country and primarily serves a low-income population. The patients were diagnosed according to the criteria proposed by the International League Against Epilepsy (ILAE), which include seizure semiology, EEG, and magnetic resonance imaging (MRI) findings.[18] We only considered seizure semiology and MRI findings as the inclusion criteria. We did not consider EEG as an inclusion criterion because the standard 30-min EEG in patients with mesial temporal lobe epilepsy can be normal or indeterminate, which does not rule out the presence of MTLE-HS; ictal epileptiform activity is nearly all always detected using long-term EEG monitoring or repeated standard EEGs.[9] We conducted medical histories with an emphasis on seizure semiology. We conducted conventional EEGs using 18 digital channels for 30 min, following the international standards requiring the placement of 10–20 electrodes. The studies were conducted using an Intera1.5 Teslas MRI instrument (Philips Healthcare, Andover, MA, USA) in weighted sequences in T1, T2, FLAIR, and IR T1. The protocol comprised the following: (a) sagittal T1 SPIN-ECHO, with a field-of-view (FOV) of 22 cm, a thickness of 4.5 mm at 1 mm; intervals, TR 597 ms, TE 15 ms, 448 reconstruction matrix, yielding 22 sagittal slices; (b) axial T1 SPIN-ECO, with a FOV of 23 cm, a thickness of 4.5 mm at 1 mm intervals, TR 450 ms, TE 15 ms, 256 reconstruction matrix, yielding 22 axial slices parallel to the corpus callosum; (c) axial T2 TURBO SPIN-ECHO, FOV of 23 cm, a thickness of 4.5 mm at 1 mm intervals, TR 4882 ms, TE 110 ms, 448 reconstruction matrix, 90° angle, yielding 22 axial slices parallel to the corpus callosum; (d) coronal T2 TURBO SPIN-ECHO, FOV of 23 cm, thickness of 3.5 mm at 1 mm intervals, TR 2000 ms, TE 110 ms, 512 reconstruction matrix, 90° angle, yielding 22 coronal slices perpendicular to the hippocampal axis; (e) coronal T1-IR, focused on the hippocampus, with a FOV of 23 cm, thickness of 1.5 mm at 1.2 mm intervals, TR 3064, TE 15 and TI of 400, 576 reconstruction matrix, yielding 22 coronal slices perpendicular to the hippocampal axis; and (f) coronal FLAIR T2 TURBO SPIN-ECHO, focused on the hippocampus, with a 23 cm FOV, thickness of 1.5 mm at 1 mm intervals, TR 600, TE 120 of TI 2000, 576 reconstruction matrix, 100° angle, yielding 22 coronal slices perpendicular to the hippocampal axis.

The inclusion criteria for the study were the following: (1) clinical history and signs of epilepsy corresponding to MTLE, usually with auras that consisted of epigastric, autonomic, and/or psychic sensations followed by an arrest of motor activity, progressive loss of consciousness, and automatisms of the mouth and hands, with or without secondary generalisation; and (2) MRI findings: the presence of atrophy (coronal T1-IR) and/or increased hippocampal signal (coronal T2 and FLAIR) detected by visual analysis by 2 neuroradiologists). We analysed the following factors: age, gender, age at onset of epilepsy, history of febrile seizures, presence of TBI, infections of the central nervous system (CNS), perinatal injury, family history of epilepsy, interval between brain injury and onset of epilepsy, seizure frequency before the start of treatment with antiepileptic drugs, type of seizures, site of HS, extrahippocampal pathology, and alterations in the EEG.

We included patients who were at least five years old. The onset of epilepsy refers to the patient's age when the seizures started, excluding febrile seizures. The ability to distinguish between simple febrile seizures (generalised, shorter than 10 min, without recurrence within 24 h or during the duration of the febrile illness) and complex febrile seizures (present focal symptomatology, duration longer than 10 min, occurs two or more times within 24 h or during the duration of the febrile illness),[20] is problematic because of the amount of time that passes between the onset of a febrile seizure and the time at which the patient is first seen for their epileptic symptoms. The patients or their relatives are typically unable to remember the exact duration of the febrile seizure. Because of this difficulty, we did not differentiate between simple and complex febrile seizures. The identification of a patient as having a suspected CNS infection was primarily based on the history given by the patient or their relatives and the absence of other potential aetiological factors for their cases of epilepsy, e.g., history of significant head trauma, history of febrile convulsions, history of perinatal injury or non-febrile seizures preceding the suspected CNS infection.

One potential limitation of our study is that the primary criterion for the selection of a case of suspected CNS infection or perinatal asphyxia was the history provided by the patient or their relatives. It was not possible to obtain definitive confirmation of the precise nature of the reported event because it occurred many years before or was managed at another institution. Many of our native patients, particularly in rural areas, have home deliveries without medical assistance. TBI was considered when there was a loss of consciousness, post-traumatic amnesia, or focal neurological signs after a brain injury.[21] A family history of epilepsy was considered in patients who had relatives of at least first or second-degree co-sanguinity with epilepsy. The interval between the brain injury and the occurrence of the first seizure could not be determined for all the subjects. The interval was established for 94 patients (85.5%). These brain injuries included: febrile seizures, perinatal asphyxia, CNS infections, and TBI. We considered brain injuries that occurred before the age of five. Mathern GW et al. (1995), in a series of 20 patients, demonstrated that patients who suffered brain injuries before the age of five showed significant unilateral hippocampus atrophy versus those who did not.[22] The seizure frequency prior to the initiation of treatment was considered by calculating the median seizure frequency for the last three months. The seizure types included simple partial seizures, complex partial seizures, and secondarily generalised partial seizures. We included patients with unilateral or bilateral hippocampal sclerosis and those with additional extra-hippocampal pathology ("dual" pathology) according to the findings of the MRI. Abnormal electroencephalographic findings included temporal intermittent rhythmic delta activity (TIRDA) and/or interictal epileptiform activity (IEA) of either spike or sharp wave type in the temporal regions, with maximum electronegativity in the anterior temple (F7/F8).

Follow-up examinations were performed every two to three months. After two years of follow-up, the patients were divided on the basis of the outcomes after medical treatment into two groups. Group I was seizure free for at least two years, and Group II was not seizure free.[23] We compared the clinical, neurophysiological, and imaging factors across these two groups of patients using statistical methods. We made a note of any antiepileptic drugs used by the patients in both groups.

2.1. Statistical analysis

The statistical analyses were performed with SPSS software (IBM, Chicago, IL, USA).

The data are presented as the means, standard deviations, and percentages. The Kolmogorov–Smirnov test was used to determine the normality of the data distribution, and Levine's test was used to assess the homogeneity of variance. Analysis of variance (ANOVA) or the non-parametric Kruskal–Wallis test were used for continuous variables and normally distributed data. The Chi-squared test or Fisher's exact test (when the number of observations was too small) were used to compare the percentages. P values of <0.05 were considered statistically significant. For the multivariate analysis, we used the Logistic Regression Model with the Enter Method for variables selection, the Hosmer–Lemeshow test to determine the goodness of fit of the model (0.629) and the Wald