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Pharmacoresistance with newer anti-epileptic drugs in mesial temporal lobe epilepsy with hippocampal sclerosis

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ABSTRACT

This study aims to evaluate the overall prognosis, prognostic factors, and efficacy of treatment in patients with mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) who have access to third generation anti-epileptic drugs but not to epilepsy surgery. Eighty-five MTLE-HS patients were retrospectively placed into a seizure-free (seizure-free for > 1 year) or drug-resistant group, and the two groups were compared on the basis of age, sex, age at onset of seizures, duration of epilepsy, side of lesion, handedness, EEG findings, history of CNS infection, history of febrile convulsions, history of head trauma, history of cognitive impairment, family history of seizures, number of current anti-epileptic drugs (AEDs), total number of AED trials, and presence of individual AEDs. Only 24.7% of MTLE-HS patients had achieved seizure freedom for > 1 year. Poor prognosis and drug-resistance were associated with younger age at onset of seizures ($p = 0.002$), longer duration of epilepsy ($p = 0.018$), greater number of current AEDs ($p < 0.001$), and greater total number of AED trials ($p < 0.001$). In addition, regimens with newer AEDs had no greater efficacy than regimens with older AEDs. Most medically managed MTLE-HS patients do not achieve seizure freedom despite multiple AED trials, and treatment with third generation AEDs should not preclude evaluation for epilepsy surgery.

1. Introduction

Mesial temporal lobe epilepsy (MTLE) is the most prevalent form of focal epilepsy worldwide. In cases of MTLE refractory to medical therapy, the most commonly encountered pathology is hippocampal sclerosis (MTLE-HS) (Kim et al., 1999). The definitive treatment for refractory MTLE-HS is surgical, with approximately 70–80% of patients achieving seizure freedom post-operatively (Kim et al., 1999; Malmgren and Thom, 2012). Patients may be managed medically if not surgical candidates due to extrahippocampal pathology or if surgery is not an option due to financial constraints (Kurita et al., 2016).

Several studies have examined the prognostic factors associated with the success of medical therapy in MTLE-HS, finding that such treatment results in complete remission in only 5–42% of patients, a percentage much lower than that for other forms of epilepsy (Giussani et al., 2016; Kim et al., 1999; Kumlien et al., 2002; Kurita et al., 2016; Kuzmanovski et al., 2016; Semah et al., 2002; Stephen et al., 2001). Additionally, patients with MTLE-HS may remit and later relapse despite a period of seemingly adequate seizure control (Coan et al., 2015). Negative prognostic factors include earlier age at onset of epilepsy, bilateral or left-sided lesions, head injury at a young age, EEG abnormalities, and a large number of previously tried anti-epileptic drugs (AEDs) (Gomez-Ibañez et al., 2013; Sànchez et al.,2014). Studies are mixed regarding the role of gender in determining prognosis (Kuzmanovski et al., 2016; Varoglu et al., 2009). Though some evidence suggests that adjunctive lacosamide specifically may have good success in treating MTLE-HS (Borzì et al., 2016), no significant evidence has yet emerged suggesting an increased relative effectiveness of third generation AEDs compared to first and second generation AEDs in achieving seizure freedom.

This retrospective, cross-sectional study was conducted on a population of MTLE-HS patients who lack access to health insurance, and thus surgical intervention, giving the unique opportunity to evaluate the efficacy of newer anti-epileptic drugs.

2. Materials and methods

This cross-sectional study was approved by the Baylor College of Medicine Institutional Review Board (H-32620) as well as the Harris Health System Institutional Review Board (16-03-1365). In this

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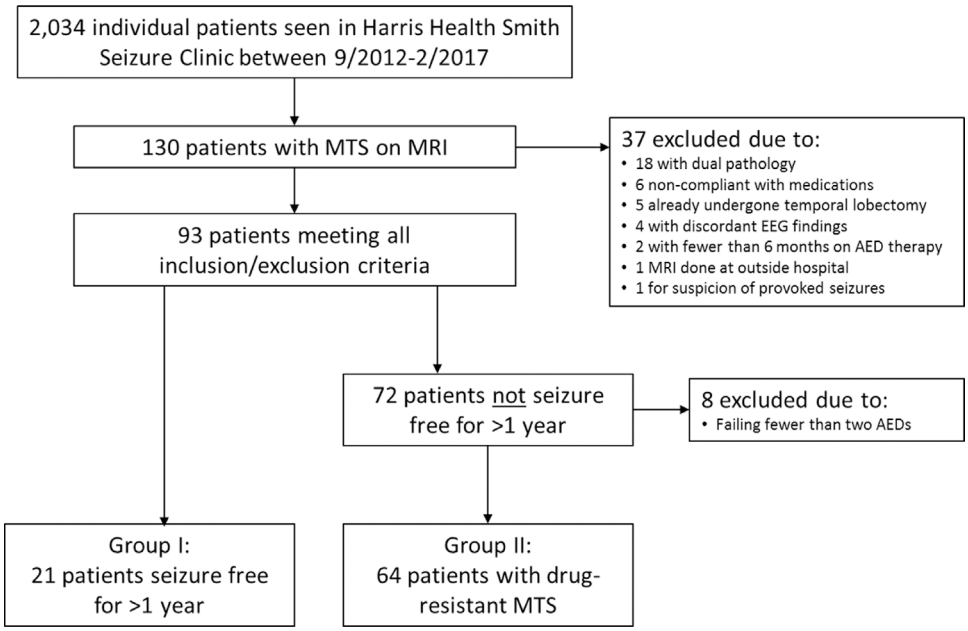

Fig. 1. Flowchart of inclusion and exclusion criteria. MTS, mesial temporal sclerosis. MRI, magnetic resonance imaging. EEG, electroencephalogram. AEDs, anti-epileptic drugs.

retrospective study, we reviewed all patients with a diagnosis of MTLE-HS treated in the Smith Neurology Clinic of the Harris Health System in Houston, Texas, USA, between September 2012 and February 2017. This clinic is staffed by medicine, psychiatry, and neurology residents who use a standard template for evaluating patients, overseen by board-certified neurology faculty at Baylor College of Medicine. One hundred and thirty patients with evidence of hippocampal sclerosis on MRI (hippocampal atrophy or structural alteration on T1-weighted images and/or hyperintensity on T2-weighted or FLAIR imaging) were marked for further review. All MR imaging was performed on a 1.5-T scanner and all studies were reviewed and interpreted by a board-certified neuroradiologist. Patients were excluded for the following reasons: patient-reported or laboratory-based evidence of persistent non-compliance, MRI evidence of a potential seizure focus outside the hippocampus (such as encephalomalacia, tumors, and cortical dysplasia), EEG results inconsistent with ipsilateral temporal lobe epilepsy, history of epilepsy surgery, not having undergone at least one six-month trial of anticonvulsant therapy, MRI performed only at an outside hospital, and suspicion of provoked seizures (Fig. 1). Six months was deemed an appropriate minimum length of therapy to assess a change in seizure frequency since seizures frequently occurred less than three times per month. This was also a standard time for a follow up appointment for patients and, therefore, for many of our patients, the minimum length of any AED trial. EEGs were interpreted by neurologists at Baylor College of Medicine with board certification in clinical neurophysiology and/or epilepsy. Additionally, patients who were not seizure-free for > 1 year were excluded if they had failed fewer than two AED trials – i.e., had only tried one AED, or were on one AED and had failed a previous AED trial due to side effects. These criteria were devised to isolate a group of patients that would be candidates for surgery under different economic circumstances.

Patients were placed into one of two groups, group I or group II, based on presence of seizure and aura within the twelve months prior to the most recent clinic visit. Group I, the seizure-free group, exhibited a total absence of seizure activity or only auras. Group II, the drug-resistant group, displayed focal dyscognitive (previously “complex partial”) or generalized seizures within the last year. Patients with seizures only within the setting of a brief, well-defined period of noncompliance were placed in Group I. Other clinical and demographic factors were also recorded, including age, sex, age at onset of seizures, duration of epilepsy, side of lesion, handedness, EEG findings, history of CNS infection, history of febrile convulsions, history of head trauma, history of cognitive impairment, family history of seizures, number of current AEDs, total number of AED trials, and presence of individual AEDs. Age referred to the patient age at last clinic visit, and age at onset referred to the age at which typical seizures began. A patient was considered to have a history of cognitive impairment if provider notes recorded a history of developmental delay or mental retardation for the patient. Absence of documentation for history of febrile convulsions, CNS infection, head trauma, cognitive impairment, and family history of seizures was considered to be a negative history. Older AEDs were defined as those approved by the United States Food and Drug Administration (FDA) before 1990, including phenytoin, carbamazepine, valproate, phenobarbital, and primidone, while the newer AEDs were defined as those FDA approved after 1990, including levetiracetam, lamotrigine, zonisamide, topiramate, oxcarbazepine, lacosamide, gabapentin, and clobazam.

Demographic and clinical factors were compared between groups I and II using an unpaired *t*-test or the Mann-Whitney *U* test (depending on normality of distributions) for numerical variables and the Fisher’s Exact *t*-test or chi-squared test for categorical variables. For the unpaired *t*-tests, Welch’s correction was added if the standard deviations were not equal. Normality for the numerical variables was determined by the D’Agostino-Pearson omnibus normality test. For the categorical variables, Fisher’s Exact *t*-test was performed whenever possible. The chi-squared test was performed if there were three or more categories. Linear regression analysis was performed to evaluate the correlation between duration of epilepsy and all other numerical variables. Statistical analyses were performed using GraphPad Prism version 7.02 for Windows, GraphPad Software, La Jolla California USA, www.graphpad.com. *p*-values less than 0.05 were considered significant.

Additionally, percent success rates were calculated for individual AEDs. A successful trial was defined as the presence of an AED on the current regimen of a seizure-free (Group I) patient. An unsuccessful trial was defined as the presence of an AED in the current regimen of a drug-resistant (Group II) patient, or past usage of the AED by any patient that was terminated due to ineffectiveness or unknown reasons (but not due intolerable side effects). Percent success rate for an AED was defined as the number of successful trials divided by the number of total trials multiplied by 100.