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Importance of neuropsychological and clinical features to predict seizure control in medically treated patients with mesial temporal epilepsy and hippocampal sclerosis

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ABSTRACT

Objective: It is not yet understood why seizures in certain patients with mesial temporal lobe epilepsy and hippocampal sclerosis (MTLE-HS) develop resistance to antiepileptic drugs (AEDs) while others achieve good seizure control with this treatment. We analyzed clinical and neuropsychological features associated with seizure control in patients with MTLE-HS who had not undergone resective surgery.
Methods: We enrolled 40 patients with medically treated MTLE-HS and retrospectively collected the following data from prospective databases: sex, febrile seizures, central nervous system infection, history of head trauma, cognitive impairment, psychiatric disturbances, history of status epilepticus, age at onset of epilepsy, aura, seizure type and frequency, electroencephalography abnormalities, HS side, AEDs, global cognitive status, and neuropsychological functions such as cognitive processing speed, attention and executive functions, verbal and visual memory, language, and visuospatial ability. These factors were compared between patients who achieved seizure control (no seizures or a >50% reduction in seizure frequency) with AED treatment and those who continued with poor seizure control (increase or no change in frequency or <50% reduction) after starting treatment.
Results: The factors associated with poor seizure control in the multivariate analysis were >2 seizures per month before treatment (odds ratio [OR] 3.2, 95% confidence interval [CI] 1.2–4.8, p = 0.04), moderate or severe cognitive impairment (OR 2.1, 95% CI 1.8–7.6, p = 0.02), and impairment of >2 neuropsychological functions (OR 2.88, 95% CI 2–6.6, p = 0.04). No associations were observed between poor seizure control and specific neuropsychological function impairment.
Conclusions: Poor seizure control in MTLE-HS is associated with moderate–severe cognitive impairment but not with a specific profile of impairment. Recognizing poor prognostic features such as a high frequency of monthly seizures prior to starting AED treatment could help to identify patients with medically intractable MTLE-HS who may be good candidates for early epilepsy surgery.

1. Introduction

Mesial temporal lobe epilepsy (MTLE) is the most prevalent form of partial epilepsy and resistance to antiepileptic drugs (AEDs) is common when hippocampal sclerosis (HS) is present [1–4]. Resective surgery is the cornerstone of MTLE-HS treatment [5], but not all patients are considered optimal candidates, as they may have bilateral lesions (detected in the presurgical evaluation), or comorbidities that preclude surgery. Other reasons for not performing surgery include the risk of post-surgery memory loss and patient refusal. Patients whose seizures respond well to AEDs are also not usually referred for resective surgery. It is not yet understood why certain patients with MTLE-HS have intractable seizures while seizures in others respond well to medical treatment. Most studies of prognosis in MTLE to date have analyzed patients who have undergone resective surgery or patients without neuroimaging evidence of HS [6–10], and very few studies have focused on patients treated exclusively with AEDs. Several poor prognostic factors have been reported in patients with MTLE-HS treated exclusively with AEDs. They include female sex, a history of febrile convulsions, age of traumatic brain injury, presence of cognitive impairment, early onset of epilepsy, duration of epilepsy, number of seizures per month before treatment, interictal epileptiform activity on electroencephalography (EEG), dual pathology, and response to the first AED [11–14]. The analysis of clinical, radiological, and EEG features of MTLE-HS has provided insights into the risk of developing drug-resistant epilepsy and highlighted the importance of recognizing predictors of medically intractable MTLE to ensure timely evaluation for surgery.

It is well known that in addition to seizures, patients with MTLE-HS may manifest neuropsychological deficits [15,16]. Cognitive dysfunction

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is frequently observed in patients with epilepsy and represents an important challenge in the management of patients with this disorder. In this respect, the relative contribution of AEDs is of relevance. The fact that a considerable number of patients require AED therapy for many years, or perhaps even a lifetime, emphasizes the need to focus on the long-term adverse effects of these drugs on cognition. There seems to be agreement that polytherapy and high-dose treatment can produce cognitive adverse effects and when high dosages or adjunctive polytherapy is needed, the balance between benefits and disadvantages may be negatively biased against drug treatment. Thus, drug treatment requires careful balancing in the attempt to reach maximal seizure control while avoiding neurotoxic adverse effects. Nevertheless, cognitive function in individuals with epilepsy may also be influenced by several factors, of which AEDs constitute only one of many putative causes [17,18].

The lateralization of cognitive function is also well-established. For example, left HS in a right-handed patient usually produces verbal memory impairment, while right HS typically produces visual memory impairment [19,20]. However, little research has been done on the association between seizure control and neuropsychological features in patients with MTLE-HS.

The aim of this study was to investigate factors associated with AED response in patients with MTLE-HS treated exclusively with AEDs by comparing clinical and neuropsychological characteristics in patients with good and poor seizure control while taking AED therapy.

2. Methods

We included patients evaluated at the Epilepsy Unit of Hospital Universitari Germans Trias i Pujol in Barcelona, Spain between 2008 and 2016. Diagnosis was based on semiology and evaluation by a neurologist who specialized in epilepsy. Patients with semiologic features of MTLE and magnetic resonance imaging (MRI) evidence of HS and treated only with AEDs were included. We excluded patients in whom presurgical evaluation detected generalized or multiregional epilepsy or epilepsy involving other lobes. Patients who had undergone a temporal lobe resection were also excluded.

Magnetic resonance images were obtained on a 1.5 or 3.0T system. The MRI protocol for patients with epilepsy at our hospital includes coronal 3D T1-weighted gradient-echo images acquired parallel to the brainstem, fluid-attenuated inversion recovery (FLAIR), T2-W turbo spin-echo, and T1-W inversion recovery images obtained perpendicular to the hippocampus, in addition to routine brain imaging. Hippocampal sclerosis was diagnosed if a visual analysis of the brain MRI scans showed atrophy, loss of internal structures, and an increased signal in T2-W images of the hippocampus or a decreased signal in T1-W images.

Patients were divided in two groups: those who achieved good control of seizures with AEDs and those who did not. Good seizure control was defined as an absence of seizures or a reduction in seizure frequency of at least 50% after starting AED treatment, while poor seizure control was defined as no change in seizure frequency, an increase in frequency, or a reduction of less than 50%.

Clinical, EEG, and MRI findings were obtained from the Epilepsy Unit outpatient database. Although the study was retrospective, some variables were recorded prospectively and systematically according to an established protocol prior to AED treatment and were therefore considered prognostic indicators. These variables were sex, a history of febrile seizures or head trauma, central nervous system (CNS) infection, cognitive impairment, psychiatric disturbances, a history of status epilepticus, age at onset of epilepsy (defined as age at onset of habitual seizures, excluding febrile seizures), duration of epilepsy before treatment, presence of aura, and type and frequency of seizures. Neuroimaging, EEG, and neuropsychological variables were not considered prognostic variables as the corresponding studies were performed at different times depending on the clinical needs of the patients.

Global cognitive status was assessed by a neuropsychologist blinded to the clinical data. This evaluation included assessment of global cognitive impairment (absent/mild versus moderate/severe). Mild global cognitive impairment was defined when the results of cognitive tests of one or more specific neuropsychological functions were one standard deviation below the mean; moderate global cognitive impairment was defined when the results of cognitive tests of one, two or three specific neuropsychological functions were two standard deviations below the mean or when there was one specific neuropsychological function with three standard deviations below the mean; severe cognitive impairment was defined when the results of cognitive tests of more than three specific neuropsychological functions were two standard deviations or when there were two or more specific neuropsychological functions with three standard deviations below the mean. The evaluation of cognitive status also included the evaluation of specific neuropsychological functions, such as cognitive processing speed, frontal functions such as attention and executive functions, verbal memory, visual memory, language, and visuospatial ability. These functions were rated as normal, mildly impaired, moderately impaired or severely impaired by an expert neuropsychologist based on the results of cognitive tests from a full neuropsychological battery. A mildly impaired function was defined when the result of cognitive testing was one standard deviation below the mean, moderately impaired when the result of cognitive tests was two standard deviations below the mean, and severely impaired when the result of cognitive tests was three standard deviations below the mean according to age and education corrected norms.

Speed was evaluated with the Trail Making Test part A (TMT-A); attention and executive functions were evaluated with the Digit Span subtest of the Wechsler Adult Intelligence Scale-III (WAIS-III) and the Trail Making Test part B (TMT-B); phonemic verbal fluency and verbal memory were evaluated with the Rey Auditory Verbal Learning Test (RAVLT) and the Logical Memory I and II tests from the Wechsler Memory Scale-III (WMS-III); visual memory was evaluated with the Rey Complex Figure (RCF) and the Visual Reproduction I and II and Faces subtests of the WMS-III; language was evaluated with the Boston Naming Test (BNT) and semantic verbal fluency tasks; and visuospatial ability was evaluated with the Block Design subtest of the WAIS-III and copy of the RCF.

All clinical and neuropsychological variables were compared statistically between patients who achieved good seizure control with AEDs and those who did not. Descriptive statistics (mean, standard deviation [SD] and frequency tables) were used to analyze the main variables. We investigated the discriminatory ability of seizure frequency to differentiate between patients with good and poor seizure control. This ability was quantified by calculating the c static analogous to the area under a receiver-operating characteristic curve (AUC), which estimated the probability of a model assigning a higher risk of poor seizure control to patients with a higher frequency of monthly seizures before AED treatment. Youden's index was calculated to identify the cutoff point that optimized sensitivity and specificity for the prediction of outcomes. The chi-square test was used to compare categorical variables and the *t* test was used to compare continuous variables. Multiple regression analysis with the entry method was used to assess the independent effects of each variable. Data were collected and analyzed using SPSS version 18.0. In all cases, statistical significance was established at $p < 0.05$. The study was approved by the local ethical committee. All patients signed the informed consent.

3. Results

3.1. Patients

In total, 950 patients were seen at the Epilepsy Unit of Hospital Universitari Germans Trias i Pujol between January 2008 and April 2016. Of these, 268 (28%) had temporal lobe epilepsy and 66 had HS. Of the 66 patients with MTLE-HS, 14 underwent resective surgery and