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Clinical Characteristics of Mesial Temporal Lobe Epilepsy With Hippocampal Sclerosis and Temporal Lobe Epilepsies Due to Other Etiologies

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Objectives: This study compared the clinical characteristics of patients with mesial temporal lobe epilepsy with hippocampal sclerosis (mTLE-HS) to patients with temporal lobe epilepsy (TLE) due to other etiologies. **Methods:** In this prospective study, all patients with a clinical diagnosis of TLE were recruited at "Sanus" outpatient neurological clinic from June 2016 to June 2017. We took note if patients had mesial temporal sclerosis (MTS) (if they had clear signs of MTS and/or atrophy in their MRI) or any other MRI abnormality. **Results:** A total of 88 patients (36 patients with mTLE-HS and 52 patients with TLE due to other etiologies) were included in this study. High frequency of seizure ($p<0.05$), oroalimentary automatism ($p<0.05$), postictal nose wiping ($p<0.001$), and absence of psychomotor automatism ($p<0.05$) were commonly seen in patients with mTLE-HS, while vertiginous auras ($p<0.05$) was more frequently seen in those with TLE due to other etiologies. **Conclusion:** Clinical characteristics of patients with mTLE-HS were high frequency of seizure, oroalimentary automatism, postictal nose wiping, and absence of psychomotor automatism, while vertiginous auras was more frequent in those with TLE due to other etiologies.

Keywords: Epilepsy, Temporal Lobe, Hippocampus, Sclerosis, Automatism

Introduction

About two-thirds of all adult epilepsy patients experience focal epilepsy, and temporal lobe epilepsy (TLE) is the most common type of focal epilepsy [1-2]. Although epileptic focus originates from the temporal lobe and particularly the hippocampus in most cases of TLE, virtually all patients develop complex partial seizures with or without secondary generalization, and as many as 30% to 40% of TLE patients continue to have seizures despite receiving appropriate medical management [3-4]. Medical management using anti-epileptic drugs (AEDs) is considered first-line treatment, but up to one third of epilepsy patients have unsatisfactory treatment outcomes. The International League Against Epilepsy (ILAE) defines drug resistant epilepsy as a

"failure of adequate trials of two tolerated and appropriated chosen and used AEDs schedules to achieve sustained seizure freedom" [5]. Drug resistant TLE often requires surgical treatment along with lifelong AED therapy and is associated with greater co-morbidities and functional disabilities [6-7].

Widely accepted in developed countries, non-pharmacologic therapies include epilepsy surgery and neuromodulatory treatments, which are effective and may be helpful to consider early in the disease course. The surgical treatment has become increasingly more valuable and is now accepted for the management of drug resistant focal epilepsy due to major advances in pre-surgical investigation methods and surgical techniques [5]. With the advancement of understanding of the pathology of TLE, improved imaging techniques (functional magnetic resonance imaging (MRI), SPECT, and co-registration with other modalities), and a better understanding of neurophysiology based on the subdural and depth electrodes, surgery has become a safe option with better outcomes. Tailored or selective resections have been developed in an attempt to adapt the classic anterior temporal lobectomy (ATL) to individual patients. More recently, gamma knife surgery has been advocated as a possible surgical option, especially for MRI-negative epilepsy. However, most patients with TLE are currently treated with an ATL or selective anterior hippocampal ectomy [8].

Careful study of seizure semiology remains invaluable in addressing the search for the seizure onset zone [9]. Seizure auras occur in many TLE patients and often exhibit features that are relatively specific for TLE, but automatisms often have lateralizing significance. TLE is categorized into mesial TLE and (neocortical) lateral TLE [1, 3, 9]. Mesial TLE (mTLE) is the term used to describe seizure onset from mainly the hippocampal formation, especially in the case of hippocampal sclerosis (HS), and other seizure onset zones from temporal limbic structures. Neocortical TLE (nTLE) is the term used to describe temporal lateral or basal seizure onset zones, in the absence of any pathology of mesial temporal structures. Recently, mTLE-HS has been established as a syndrome with progressive HS, genetic predisposition, and the variability of past history (febrile seizures, trauma, hypoxia, and intracranial infection) [8].

As noted in previous studies, semiological features of mTLE consists of typical auras, such as rising epigastric sensations, déjà vu, affective phenomena (fear or sadness), or experiential phenomena followed by unilateral motor signs (ipsilateral contraction of face or mouth and/or head deviation) and bilateral motor phenomena in the face or axial muscles. Behavioral arrest and oral automatisms are common, and bi-temporal spread indicates alterations in consciousness, amnesia, autonomic phenomena, and prominent motor automatisms (tonic and dystonic posturing). As noted in the literature, semiological features of nTLE consist of auditory, vestibular and complex visual hallucinations, aphasia, and focal sensory-motor phenomena [10].

There have been many studies using videotape and computer technology to capture seizures and their associated EEG telemetry, which have been carefully reviewed to provide detailed descriptions of the features of temporal lobe seizures [7]. Some initial ictal symptoms can be reproduced with focal cortical stimulation to identify the corresponding symptomatogenic zone, but unfortunately, not all ictal symptoms can be reproduced. The tools available for localization of the epileptogenic zone are limited, and therefore, clinicians must try to deduce the epileptogenic zone using seizure semiology. Seizure semiology is a simple and cost effective tool that allows for the localization of the symptomatogenic zone, which overlaps or is in close proximity of the epileptogenic zone [11].

It is important to recognize localization of their seizure focus to distinguish nTLE from mTLE because it determines whether patients are considered nonsurgical candidates or are recommend undergoing extensive surgeries [9]. mTLE-HS is one of the most common types of epilepsy referred for surgical treatment. It is often refractory to AED but responds favorably to surgery, however surgical outcome may be worse with longer durations of epilepsy or increasing age, which suggests that mTLE-HS is a progressive disorder [1, 4, 12]. Lately, studies have described that patients with mTLE-HS and intractable seizures often experience progressive behavioral changes, including increasing memory deficits over time [12]. Therefore, to most plan the most optimal treatment strategy, this syndrome must be detected early and distinguished from other TLE syndromes.

The objective of our study was to compare the clinical characteristics of patients with mTLE-HS with those who had TLE due to other etiologies, in order to identify potentially differentiating clinical characteristics in seizure between these two groups of patient. The main difference of our study from other similar studies is the use of simple, cost effective tool such

a precise, short questionnaire to distinguish mTLE with HS from TLE due to other etiologies.

Materials and Methods

1. Study population

Our study, conducted in Ulaanbaatar, Mongolia, included 88 patients with TLE (38 male and 50 female), aged 15-65 years. All patients received health services from the neurological outpatient clinic of Sanus Hospital from June 2016 to June 2017.

2. Data collection

Diagnosis of TLE was made in 88 patients by neurologist researchers on the basis of the patient's history, anamnestic data, and clinical observations, and results of the EEG and MRI tests. All patients underwent an extensive investigation, which included a clinical history, comprehensive neurologic examination, interictal EEG, and routine visual 1.5 Tesla MRI analysis (which included T1 and T2 sequences in axial and coronal planes). We also took note if patients had mesial temporal sclerosis (MTS) (if they had clear signs of MTS and/or atrophy in their MRI) or any other MRI abnormality.

The questionnaire used in this study was developed by the authors of this study based on the "General diagnostic approach to the patient with epileptic seizure", which is included epileptic seizure history (aura, clinical seizure, postictal symptom, pattern of occurrence and precipitating factor, frequency, age at onset, progression of symptom, response to AED), past medical history (possible causative factors, other predisposing factors), family history, psychosocial history [13]. Other questions to distinguish TLE seizure onset zone localization, lateralization were performed after reading several studies of TLE: left or right handed, time from first seizure to second, duration of epilepsy, awareness during the aura, type of aura, progression and type of automatisms, duration of single seizure, type of postictal automatisms, presense of status epilepticus or serial seizure, presence of memory impairment, depression [8]. Age, gender, age at seizure onset (i.e., the first a febrile seizure), left or right handed, duration of latent period and epilepsy, average seizure frequency per month during the previous year, seizure type(s), initial precipitating factor (including birth complications, history of febrile seizure, CNS infection, significant head trauma, positive family history of epilepsy), EEG findings, and MRI findings of all patients were registered routinely. Responses to AED and number of AED were analyzed. The interictal EEG studies were always performed using routine sleep EEG, with >30-minute recordings using international standard "10-20."

The clinical diagnosis of TLE was based on the ILAE criteria: (1) seizure semiology consistent with TLE, with abdominal, epigastric, psychic, or autonomic auras, followed by behavioral arrest, progressive alteration of consciousness, oroalimentary, and manual automatisms; (2) mesial and/or anterior temporal interictal spikes from EEG; and (3) increased T2 signal and/or atrophy in hippocampal formation identified by MRI [14].

We only included nonsurgical patients with active epilepsy (experienced seizure in last 2 months) and excluded breastfeeding and pregnant women. Additional exclusion criteria in this study were a known history of alcoholism, addictions, or psychiatric co-morbidity that prevented either a neuropsychiatric interview or neuroimaging. We also excluded patients with any of the following: (1) medication history of psychoactive or central nervous system depressant drugs; (2) abnormal liver or renal functions (based on basic and complete blood cell results). These exclusion criteria were added to avoid the confounding effects of medication and physical disorders on memory.

After screening, 88 patients fulfilled the inclusion criteria and agreed to participate in the study. According to the seizure frequency, patients with ≤2 seizures per month were classified as Group 1, and patients with >2 per month were classified as Group 2, based on a widely used grouping among the epileptologists [14, 15].

When appropriate, the following data on patients were carefully taken from a pre-developed questionnaire answered by the caregiver: initial loss of contact and aura at the onset of seizure; aura feature; signs of lateralization, common type and duration of seizure; postictal symptom and amnesia of the ictal phase; occurrence of status epilepticus or serials of seizure; complaints of patients; triggers; and progression of seizure. Aura features included epigastric sensation; emotional (e.g. fear) or other psychic (e.g. de ja vu) auras and autonomic symptoms (tachycardia), pseudo-vertiginous sensation; gustatory, auditory, visual hallucinations at seizure onset. The following signs of lateralization of seizure were checked: auras progression towards a motionless stare; oroalimentary automatisms (e.g. lip smacking, chewing); verbal automatisms; and progressive clouding of consciousness, hand automatisms,

dystonic posturing; responsiveness of the patient in conjunction with automatisms. Postictal symptom and amnesia included occurrence of the transient postictal disorientation, postictal aphasia, or postictal nose wiping.

Duration of TLE was calculated by subtracting the date of the first seizure from the date of the last seizure. Seizure types were classified as simple partial, complex partial, and secondary generalized seizure in accordance with semiology and international classifications of epileptic seizures [13].

3. Statistical analyses

STATA ® software 12.0 (Stata Corp, LP, College Station, TX, USA) was used for statistical analysis. For descriptive statistics, the recorded data was statistically analyzed for percentages, means, and standard deviations of all variables. Then, we compared groups of patients using Chi-square test for categorical data. Findings were considered significant at $p < 0.05$.

4. Ethical statement

Ethical approval was obtained from the Ethical Committee of the School of Medicine, Mongolian National University of Medical Sciences. Each patient signed a written consent form before participating in the study. The investigator maintained confidentiality of research data.

Results

1. Demographic data

Of the 88 patients included in the study, 38 (43%) were men and 50 (57%) were women; 80 (91%) were right handed; and 36 were diagnosed with mTLE-HS and 52 patients were diagnosed with TLE due to other etiologies (Table 1). The mean age of participants at study entry was 35±2.5 years. Of all participants, 30 (34%) were highly educated, 18 (20.5%) were employed, and 49 (55.7%) were married.

2. Clinical characteristics

The following were not significantly different between the patients with mTLE-HS and the patients with TLE due to other etiologies: frequency of seizure types (i.e., simple partial, complex partial, and SGS), age at onset of seizure, time from first to second seizure, duration of epilepsy, mean duration of seizure, occurrence of status epilepticus, and triggers of seizure. However, frequency of seizure, specific types of auras, and automarism were significantly different between these two groups, though most auras were reported by both groups (Table 1, 2, 3).

Initial precipitating factors for patients with mTLE-HS versus TLE due to other etiologies were reported to be as follows: unknown 10 versus 21 ($p>0.05$), family history of epilepsy in 6 versus 5 ($p>0.05$), febrile seizure in 3 versus 4 ($p>0.05$), stroke at age <4 years 2 versus 0 ($p>0.05$), birth complications in 4 versus 4 ($p>0.05$), significant head trauma in 12 versus 16 ($p>0.05$), central nervous system infection in 2 versus 3 ($p>0.05$), other factors in 3 versus 4 ($p>0.05$).

Right sided, left sided, or bilateral focal epilepti-form discharges (i.e, temporal seizures, spikes, or sharp waves) were observed in all patients. Focal polymorphic delta activity or temporal intermittent rhythmic delta activity (TIRDA) was seen more among patients with mTLE-HS ($p>0.05$).

In patients with TLE due to other etiologies, MRIs showed hippocampal remnant cyst in 9 patients (17.3%), non-specific white matter MRI abnormalities in 18 patients (34.6%), cavernoma in 5 patients (9.6%), and sequels of head injury and other etiologies in 20 patients (38.5%).

In our study, there was no statistically significant difference on response to AED between patients with mTLE-HS and patients with TLE due to other etiologies. However, a majority of patients reported improper use of drugs (i.e, did not take appropriate drug, follow dose schedules, combinations, or duration, or discontinued because of fear of toxic effect).

Table 1. Demographic data and frequency of seizures

Variable (n%)	mTLE-HS[a] (n=36)	Other TLE (n=52)	Total (n=88)	p-value
Sex (Male/Female)	16/12	22/28	38/50	NS[b]
Group 1: ≤2 seizures per month	3 (8.3%)	22 (42.3%)	25 (28.4%)	p<0.05
Group 2: >2 seizures per month	33 (91.7%)	30 (57.7%)	63 (71.6%)	p<0.05

mTLE-HS[a], mesial temporal epilepsy with hippocampal sclerosis; NS[b], non significant;p>0.05

Table 2. Types of aura in patients with mTLE-HS compared with patients with TLE due to other etiologies

History of aura (n%)	mTLE-HS[a] (n=36)	other TLE (n=52)	Total (n=88)	p-value
Epigastric aura	24 (66.6%)	32 (61.5%)	66 (75%)	NS[b]
Vertiginous aura	19 (52.7%)	38 (73%)	57 (64.7%)	p<0.05
Autonomic aura	16 (44.4%)	27 (52%)	43 (48.8%)	NS
Affective aura	25 (69.4%)	27(52%)	52 (57%)	NS
Mnemonic aura (De javi)	23 (63.8%)	33 (63.4%)	56 (63.6%)	NS
Gustatory aura	17 (47.2%)	10 (19.2%)	27(30.6%)	NS
Auditory aura	14 (39%)	18 (34.6%)	32 (36.3%)	NS

mTLE-HS[a], mesial temporal epilepsy with hippocampal sclerosis; NS[b], non significant; p>0.05

Table 3. Automatisms of the patients with mTLE-HS compared with patients with TLE due to other etiologies

Type of automatism (n%)	mTLE-HS[a] (n=36)	other TLE (n=52)	Total (n=88)	p-value
Oroalimentary	27 (75%)	29 (55.7%)	56(63.6%)	p<0.05
Unilateral hand	20 (55.5%)	22 (42.3%)	42 (47.7%)	NS[b]
Postictal nose wiping	19 (52.7%)	8 (15.3%)	27 (30.6%)	p<0.001
Version automatism	26 (72.2%)	30 (57.6%)	56 (63.6%)	NS

mTLE-HS[a], mesial temporal epilepsy with hippocampal sclerosis; NS[b], non significant; p>0.05

Discussion

In countries where temporal lobe surgery is available for the treatment of epilepsy, mTLE-HS is a common type of epilepsy to be referred for surgical treatment due to its medical refractoriness and positive responsiveness to surgery [16]. It has been suggested that early surgical intervention after seizure onset is an important precondition for achieving seizure-free status after surgery [17]. Therefore, early detection of this syndrome has important practical implications on planning an optimal treatment strategy for patients, particularly those with drug resistant seizures.

In the current study, we observed the following more frequently among patients with mTLE-HS: high frequency of seizure (p<0.05), oroalimentary automatism (p<0.05), postictal nose wiping (p<0.001), and absence of psychomotor automatism (p<0.05); we observed vertiginous auras (p<0.05) more frequently among patients with TLE due to other etiologies.

Previous studies, which have been dominantly represented by patients presenting with HS on MRIs, have observed variable ages at onset [18]. In our study, age at onset was 17 in group 1 and 23 in the group 2. Age at onset may be a clinical variable used to distinguish mTLE-HS from TLE due to other etiologies and thus should be further explored in future studies.

Several studies have shown a significant relationship between a high frequency of seizures and MTS [6]. In our study, high frequency of seizures was statistically significant among patients with mTLE-HS compared to patients with TLE due to other etiologies. In a similar study that also grouped patients according to frequency of seizures, they found that diffuse subtle gray matter atrophy is strikingly more evident among patients with TLE-HS and with frequent seizures [15]. A study among TLE patients without psychiatric co-morbidities used similar criteria of TLE and grouping of patients according to frequency of seizures to study serum biomarkers, cognitive performance, and gray matter atrophy. They found that serum biomarkers were predictive of high frequencies of seizures among those with TLE. Furthermore, they found that HSP70 may be considered a stress biomarker among TLE patients, inversely correlated with memory scores and hippocampal volume [14].

An important finding from our study is that oroalimentary automatism (p<0.05) and postictal nose wiping (p<0.001) are found more frequently among patients with mTLE-HE compared to patients with TLE due to other etiologies. Similarly, a study found that automatisms occur in almost two thirds of CPSs of mesial temporal lobe onset and often involve the hands

(fumbling, picking, fidgeting) or mouth (chewing, lip smacking, swallowing) [12]. Postictal nose rubbing or wiping is also usually associated with an ipsilateral focus [13]. However, it is rare to find studies analyzing the quantities of these automatisms.

In previous studies and our study, no significant differences could be demonstrated in the comparison of symptoms consisting of auras (psychic, autonomic, abdominal, visual, somatosensory or gustatory, auditory, olfactory, and vertigo) or generalized tonic clonic seizures occurrence [16]. However, several studies, including ours, have shown a significant relationship between a vertiginous aura and lateral temporal epilepsy [13].

In one study, the authors examined the relationship between presence of different types of auras and post–surgical outcomes in 157 patients with drug resistant mTLE-HS (unilateral). The occurrence of multiple auras was not associated with any post-surgical outcomes (p=0.7), but the presence of extra temporal auras (somatosensory, visual, and dysphasic) was significantly higher in patients with poor outcomes [19]. Future studies investigating the difference between the presence of mesial temporal auras (e.g. psyhic symptoms cognitive and affective, autonomic such as epigastric sensation, olfactory and gustatory auras) versus the presence of lateral temporal auras (e.g. vertiginous and auditory) will help in the prediction of surgery outcomes in patients with mTLE-HS.

Among those with HS, non-invasive preoperative work-ups have been found to be useful in enabling doctors to obtain additional prognostic information to counsel patients who need to make a decision to undergo epilepsy surgery. A history of complex febrile seizures, the ability to react before the onset of complex partial seizure, the duration of mTLE of less than 10 years, ipsilateral interictal and ictal EEG findings, and the absence of a psychiatric diagnosis are all predictors of favorable outcome when MRI shows unilateral HS [8]. Thus, our future studies need to emphasize those findings that help select good candidates for resection for mTLE.

Literature as noted that epilepsy syndromes are complex neuropsychiatric disorders that cannot be defined by simply seizure types and aetiology; TLE impacts the neuronal networks that affect emotional states, perception, and communication. The study of cognitive in TLE, particularly memory impairment, is a crucial for researchers and implicative for future study [8]. Current study of the relationships between seizure semiology, EEG, MRI findings, and memory features among TLE patients is ongoing.

Limitations of our study should be noted. First, this was a clinic-based series and may not represent the full spectrum of TLEs. Second, we may have missed cases with subtle seizure and ictal events, due to the lack of video EEG facilities. Thirdly, because the majority of our patients improperly use of AED, it was difficult conclude AED effectiveness among the participants and more complicated to check drug resistance of epilepsy.

The foundation for making a correct diagnosis, when evaluating a patient with seizure, is having a standardized approach, particularly with regard to taking a detailed clinical history. One may find important clues in the clinical history (e.g. frequency of seizure, detailed seizure description, automatism, aura) to make a syndromic diagnosis, which forms the basis for an appropriate management plan.

In conclusion, clinical characteristics of patients with mTLE-HS were high frequency of seizure, oroalimentary automatism, postictal nose wiping and absence of psychomotor automatism, while vertiginous auras was more frequent in those who had TLE due to other etiologies.

Conflict of Interest

The authors state no conflict of interest.

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