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Drug-responsive versus drug-refractory mesial temporal lobe epilepsy: a single-center prospective outcome study

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ABSTRACT

Objectives: To evaluate clinical, electrophysiological, and neuroradiological factors which correlate with the prognosis in patients with mesial temporal lobe epilepsy (MTLE).

Methods: This was a single-center prospective outcome study in patients with MTLE. The patients' family history, clinical characteristics, neurophysiological data (electroencephalography – EEG), neuroimaging, antiepileptic therapy, and outcome were collected and analyzed. The population was divided into four groups depending on the frequency of the seizures when they attended their last follow up. All variables and outcome measures were compared between the four groups.

Results: In total 83 consecutive patients were included within the four groups. Group 1 (seizure-free) consisted of 7 patients, (9%), Group 2 (rare seizures) consisted of 15 patients (18%), Group 3 (often seizures) consisted of 30 patients (36%), and Group 4 (very often seizures) consisted of 31 patients (37%). The groups did not differ significantly in demographic characteristics. There was a strong positive correlation between resistance to therapy and sleep activation on EEG ($p = 0.005$), occurrence of focal to bilateral seizures ($p = 0.007$), automatisms ($p = 0.004$), and the number of previously used antiepileptic drugs (AEDs) ($p = 0.002$). There was no association between febrile convulsions (FC), hippocampal sclerosis (HS), and the outcome that was found.

Conclusion: MTLE is a heterogeneous syndrome. Establishing the factors responsible for, and associated with, drug resistance is important for optimal management and treatment, as early identification of drug resistance should then ensure a timely referral for surgical treatment is made. This prospective study shows that sleep activation on EEG, ictal automatisms, occurrence of focal to bilateral tonic-clonic seizures, and increased number of tried AEDs are negative prognostic factors.

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Mesial temporal lobe epilepsy; prognostic factors; outcome; resistance; responsiveness

Introduction

Temporal lobe epilepsy (TLE) is the most common form of adult localization-related epilepsy [1] and mesial temporal lobe epilepsy (MTLE) is the most frequent type in adults [2]. Hippocampal sclerosis (HS) has long been identified as the principal pathologic substrate of MTLE, following definitions that were introduced in the 1985 International Classification [3,4].

Seizures are typically characterized by autonomic and/or psychic subjective symptoms (most commonly described as a 'sensation of something arising from the stomach'), alteration of consciousness and staring. They might also include dystonic postures, gestural or oral-alimentary automatisms and a prolonged postictal reorientation [5]. Auras (focal seizures with retained awareness) can be isolated or can be followed by staring and unresponsiveness (focal seizures without awareness), or evolve into bilateral tonic-clonic seizures (bilTCS). The clinical history of MTLE can sometimes present as an early initial event, such as febrile convulsions (FC), CNS infections or head injury then followed by a latent period, before chronic epilepsy finally develops [6]. However, there is a major gap in our knowledge regarding the causal relationship between FC, HS, and MTLE. There is a hypothesis suggesting that subtle hippocampal malformation can be a cause for FC [7]. Controversially, previous reports indicate that even simple FC can produce subtle long-term changes in neuronal connections – such as altered synaptic function [8]. A fundamental question in this is whether FC is developed on a background of a preexisting network derangement, or if FC is a causative factor for the development of MTLE [9].

Seizures are often resistant to AED [2], although clinical phenotypes with long seizure-free periods on AED have been in the literature [10,11]. In focal epilepsies, and particularly in MTLE, it is very important that AED resistance is identified as early as possible, because surgical intervention is effective in eliminating ensuing seizures in a high percentage of these patients [12,13]. Although MTLE-HS is the most common abnormality identified, its role in the development of drug-resistant epilepsy remains unclear [14].

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To date, many studies on MTLE have been orchestrated by groups with a special interest in surgical treatment, and therefore the most current information available is concerning patients with refractory MTLE. In some of these cases, risk factors for epilepsy, such as FC (especially complex FC and febrile status epilepticus) and cerebral infections, can be identified, as well as MRI evidence of HS which is the most frequent cause [6]. Conversely, little attention has been paid to milder forms of MTLE – despite the fact that this form of epilepsy was first documented almost half a century ago [15]. Some physicians suggest that such patients often remain undiagnosed, since many lack major seizures, experiencing only transient focal seizures that are either overlooked or are not investigated further [16].

The purpose of this prospective study is to research clinical, EEG, and neuroimaging features in relation to AED resistance in a substantial group of patients with MTLE medically treated at a tertiary epilepsy center.

Material and methods

We evaluated patients with MTLE diagnosed and medically treated at the Department of Clinical Neurophysiology and Epilepsies, of Guy's and St. Thomas' NHS Foundation Trust, London, UK, who were actively followed up at the outpatient epilepsy clinic from September 2013 to December 2014.

The inclusion criteria included: 1. Typical clinical description of mesial temporal lobe syndrome in accordance with the classification criteria listed in the International Classification of Epileptic Syndromes [6,17]; 2. Supportive EEG and/or MRI evidence of interictal or ictal epileptiform activity or focal slowing over the temporal or frontotemporal regions and atrophy and increased hippocampal signal (suggestive of HS) respectively; 3. The availability of all pertinent initial and follow-up clinical evaluation sheets, including both physical and neurological examinations, as well as all EEG recordings and brain MRI scans over the duration of the study.

All patients were clinically evaluated at least twice for the duration of the study. For the analysis, we considered the seizure frequency and antiepileptic medication at the second visit, which took place after at least 1 year of follow-up.

Patients with MTLE of other etiologies (tumors, vascular or cortical malformations) were not considered. Patients with other progressive neurological comorbidities possible causative for epilepsy were excluded.

All patients who met the inclusion criteria and had at least 1 year of follow-up visits, on record in the Department of Clinical Neurophysiology and Epilepsies at St. Thomas' Hospital, London, UK, were invited for a re-evaluation visit where the context of the study was explained, and informed consent was obtained. Data were collected in accordance with the principles of the Declaration of Helsinki.

Data from each patient were tabulated for analysis, including full details of all seizure types (auras or focal seizures with retained awareness, focal seizures without awareness and focal to bilTCS), their respective age at onset (excluding FC), clinical ictal manifestations (such as quality of auras, ictal automatisms or dystonic postures) and postictal phenomena, frequency and the time between onset of focal seizures and the first focal to bilTCS. We also included the response to AED at the last follow up, the total AED used, the brain MRI and the interictal and ictal EEG findings. We finally considered gender, dominance, family history of epilepsy and/or of FC, personal antecedents such as severe birth asphyxia, FC, severe head injury, viral encephalitis, bacterial meningitis or cerebral abscess, as well as neurological and psychiatric comorbidities. In patients with normal MRI, but still high clinical suspicion of (mainly AED-resistant) MTLE, an interictal positron emission tomography (PET scan) was performed irrespective of EEG findings. The duration of epilepsy was defined as the interval between the age of onset of habitual seizures and the time of the last follow up.

Video EEGs performed using an XLtek Natus system with the electrodes positioned according to the International 10–20 system were recorded both whilst awake and whilst asleep, with the latter obtained after partial sleep deprivation [18]. In the current series, all patients had at least two outpatient EEGs, of which at least one was recorded during sleep.

Epileptiform discharges (spike-wave and sharp waves) were classified according to their topography (temporal, temporal 'plus' and extratemporal), laterality (unilateral or bilateral), and their activation during sleep. Activation was deemed present when epileptiform discharges occurred only during sleep or occurred more than twice as frequently as when being aware. Temporal intermittent rhythmic delta activity (TIRDA) was considered epileptiform, while polymorphic delta/theta activity over the temporal lobes was noted as focal background abnormality, relevant to the localization of the epileptogenic focus [19]. The latter was further classified as mildly abnormal when it consisted of mainly theta activities and was present for less than 30% of the recording time and heavily abnormal when it contained mainly delta activities and was present for >30% of the recording time.

Standard T3 MRI was performed in all patients according to the epilepsy protocol and included T1- and T2-weighted series, as well as FLAIR images. All scans were reviewed by an expert neuroradiologist.

All clinical, neuroradiological, and EEG data were anonymized and stored in a password-protected, hospital-based electronic database.

We focused on AED schedules with an extensive evaluation of therapeutic response over time. The long-term seizure control of each patient was assessed from the seizure onset period and depending on the frequency of seizures, patients were divided into four groups. The first group included patients who were seizure-free (SF) at the time of evaluation. Seizure freedom was defined as a period without seizures for a minimum of 1 year [17,20]. Group 2 (rare seizures) included patients with only auras or up to three focal seizures with impaired awareness per year. Patients with more than three focal seizures with impaired awareness per year but less than eight per month were regarded as having frequent seizures (Group 3). Finally, patients with ≥2 seizures per week were considered as having seizures very often (Group 4).

Statistical analysis: Data are presented as means with SD and medians or percentages unless otherwise specified. We have used statistical tests including contingency tables, chi-square independency tests (using frequency variable as

nominal), chi-square linear trend test (using frequency variable as ordinal), and contingency measures – Kendall correlation coefficient in order to check positive/negative correlation between variables. Regarding age and duration (as quantitative variables) ANOVA was performed. We compared the four groups for each of the clinical parameters described above. The statistical significance level was defined as 5%.

Results

One hundred and three (103) consecutive patients that met the inclusion criteria were initially considered for this study. During the follow-up period, two of the patients died (from causes non-related to epilepsy), eleven failed to attend evaluation visits and seven were dropped out for other reasons (missing values, etc.), leaving 83 patients for analysis (47 women and 36 men). The age at the time of evaluation ranged between 20 and 78 years old (mean: 43.6 ± 13.6 years, median: 43) and the mean duration of the disease was 10.5 ± 13.2 years (median: 11.5, range 1–57 years). Seven patients (9%) were seizure-free, 15 (18%) had rare seizures, while 30 (36%) and 31 (37%) patients had often and very often seizures, respectively.

Over the course of their epilepsy our patients were treated with 15 different AED, of which; carbamazepine, lamotrigine, levetiracetam, oxcarbazepine and valproate acid were used most frequently (in decreasing order of frequency). The number of previously tried AED was significantly lower in the seizure-free patients (p = 0.002). Regarding the AED regime at last follow-up, six of the seizure-free patients were on monotherapy and only one patient was on dual therapy. In Group 2 seven patients (46.6%) were on monotherapy, seven were (46.6%) on dual therapy and one patient (6.6%) was on three AEDs. Finally, in Groups 3 and 4, the majority of the patients were receiving either dual-therapy or triple-therapy.

The demographic, clinical features, the neuroradiological and EEG findings for the four groups of patients are presented in Tables 1, 2, and 3. Of the clinical variables, only the occurrence of automatisms during focal seizures with impaired awareness and of focal to bilTCS were significantly associated with resistance to treatment with AED (p = 0.004 and p = 0.007, respectively, Table 2). We also found a strong association between activation of epileptiform discharges during sleep and poor response to AED treatment (p = 0.005), but not with the occurrence of epileptiform activity per se (Table 3).

Psychiatric comorbidities (mainly depression) were more frequent in groups 3 and 4 (with often and very often seizures) than in groups 1 and 2 (seizure-free and infrequent seizures), but the difference did not reach statistical significance (p = 0.101). Gender, age of seizure onset, duration of the epilepsy, history of FC, perinatal hypoxia and other antecedents for epilepsy, family history and MRI evidence of mesial temporal sclerosis had no effect on the response to AED treatment.

Discussion

To the best of our knowledge, this is the first single-center prospective outcome study of patients with MTLE treated exclusively with AEDs, aiming to assess the evolution of the disease over time and investigate possible predictors of resistance to AED treatment that can complement official criteria and guidelines [20].

The Task Force of the ILAE Commission on Therapeutic Strategies defined drug-resistant epilepsy as 'failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapy or in combination) to achieve sustained seizure freedom'. It has been proposed that the length of time for the latter is defined by the 'rule of 3', i.e. at least three times the longest inter-seizure interval, or longer than 12 months, whichever is longer [20]. The aim is to prove 'lack of efficacy' for the trialed AED through an 'informative' trial, although this is not always possible in daily clinical practice where not all patients are managed by expert epileptologists. For example, a primary antiseizure drug for focal seizures, such as carbamazepine, can be prematurely (and possibly erroneously) sidelined as either ineffective (for instance due to unsuspected problematic compliance) in which case lack of efficacy for only one more AED is enough to falsely characterize a focal epilepsy as drug resistant, or as poorly tolerated (because or rapid

Table 2. Clinical features and neuroradiological findings.

	Group 1 (SF)	Group 2 (Rare)	Group 3 (Often)	Group 4 (Very often)	P-value
Aura	3	10	22	21	0.559
Ictal Automatisms	1	6	19	22	**0.004**
Hallucinations	2	3	9	15	0.074
Focal to Bil[1]	5	14	28	27	**0.007**
Febrile convulsions	0	0	1	2	0.228
Perinatal event	1	1	1	1	0.232
Family History	2	0	1	2	0.286
Psychiatric No	7	13	20	21	0.101
Comorbidities Yes	0	2	10	10	
Hippocampal sclerosis (MRI)	3	3	10	12	0.445
Abnormal PET-Scan	2	0	4	7	0.743

[1]There is a statistical analysis between the frequency (never, rare, several times, and always) of focal to bilateral seizures among four groups.

Table 1. Demographic features.

Characteristics	Group 1 (SF)	Group 2 (Rare)	Group 3 (Often)	Group 4 (Very often)	P-value
No Patients	7	15	30	31	
Mean Age ± SD (Median) (range)	41 ± 6.5 (39) (31–52)	44 ±13.2 (43) (26–78)	44 ± 14.7 (42) (22–78)	44 ± 13.1 (46) (22–72)	0.960
Gender: Female	3	9	20	15	0.790
Male	4	6	10	16	
Mean Duration of disease ± SD (Median) (range)	15 ± 13.2 (9) (3–27)	14 ± 13.8 (10) (2–54)	15 ± 12.7 (12) (1–53)	15 ± 14.2 (12) (1–57)	0.303

Table 3. Neurophysiological data.

EEG characteristics		Group 1 (Seizure freedom)	Group 2 (Rare)	Group 3 (Often)	Group 4 (Very often)	P-value
Focal	Heavy abnormal	0	3 (20%)	5 (16.6%)	4 (13%)	0.575
Background	Mild abnormal	3 (43%)	4 (27%)	11 (36.6%)	6 (19%)	
	Normal	4 (57%)	8 (53%)	14 (46.6%)	21 (68%)	
Epileptiform	Yes	5 (71%)	10 (67%)	26 (87%)	23 (74%)	0.686
Discharges	No	2 (29%)	5 (33%)	4 (13%)	8 (26%)	
Laterality	Yes	4 (57%)	4 (27%)	15 (50%)	12 (39%)	0.660
(Bilateral)	No	3 (43%)	11 (73%)	15 (50%)	19 (61%)	
Sleep activation	Yes	3 (42%)	10 (67%)	22 (73%)	24 (77%)	**0.005**
	No	4 (58%)	5 (33%)	8 (27%)	7 (23%)	

escalation to high dose or when the conventional formulation is used instead or the slow release). Undiagnosed sleep disorder (such as severe obstructive sleep apnea – OSA) is another possibility; of an 'ineffective' AED may become effective when severe OSA is diagnosed and corrected [21]. Given the good results of resective epilepsy surgery in MTLE [13,22] early sound identification of drug resistance by combined treatment and other clinical and imaging/EEG criteria is particularly important for these patients.

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, HS, and female gender are found to be prognostic factors in a variety of studies on MTLE [23–26].

We found that the occurrence of focal to bilTCS, ictal automatisms during focal seizures with impaired awareness, and activation of interictal epileptiform discharges during sleep are strong predictors of resistance to treatment with antiepileptic drugs.

An interesting finding was that the presence of focal to bilateral tonic-clonic seizures influences outcome, which is different from what was published previously [23,26]. Growing evidence has demonstrated that pathophysiological underpinnings of seizure generation may involve both aberrant structural integrity in certain brain regions and abnormal connections between these areas, resulting in large-scale network instability [27]. Previous reports on MTLE have demonstrated patterns of increased connectivity related to the epileptogenic zone, coupled with decreased connectivity in widespread distal networks. Connectivity patterns appear to be related to the duration and severity of the disease, suggesting progressive connectivity reorganization in the setting of recurrent seizures over time. There are some studies supporting the 'network inhibition hypothesis' of neocortical deactivation during focal seizures with impaired awareness, and it is possible that recurrent network inhibition during seizures leads to long-term connectivity reorganization [28–30]. Epileptic activity may remain localized to a small area in part due to 'surround inhibition' and other less clear mechanisms. Otherwise, the epileptic focus propagates to cortico-cortical networks and multiple brain circuits to reach larger cortex areas and subcortical structures. Spread occurs when the focal seizure is adequately intense and when the surrounding activity is less inhibitory [31]. An emerging target for epilepsy researchers is to elucidate patterns of network connectivity that facilitates spread of the seizure, as it is well documented that seizure propagation correlates with favorable (i.e. seizure-free) vs. unfavorable (i.e. seizure persistent) epilepsy surgery outcomes [32]. It is possible our results reflect the worst prognosis of patients with focal to bilTCS seizures in the context of facilitated noncontiguous, disorganized seizure propagation patterns.

We also observed the impact of ictal automatisms during seizures on the severity of the disease. Oroalimentary automatisms (OAAs) refer to involuntary stereotypical appearances of chewing, lip-smacking, or swallowing, usually involving the mouth, tongue, and the throat during seizures. OAAs occur most frequently in temporal lobe epilepsy, especially originating from the mesial temporal lobe [33,34]. Previously published data reported that OAAs could be induced by stimulating the frontoopercular cortex that was distant from the seizure-onset zone (SOZ) [35]. This could be interpreted as the operculum was the symptomatogenic zone of OAAs. In operculoinsular epilepsy, the opercular cortex is often involved and even acts as the SOZ; OAAs are not commonly seen [36]. Other investigators suggest synchronized spread of rhythmical activity from mediobasal temporal regions to the insulaopercular regions [37]. Wang et al., in the latest relative study [38], proposes that unilateral functional connection from the hippocampus to the rolandic operculum, during seizure onset, is the basis for the generation of OAAs in MTLE. However, the specific symptomatogenic zone of OOAs and the functional connections with mesial temporal lobe structures have not been fully elucidated. Despite the various interpretations of findings, it is clear that the presence of ictal automatisms implies a focal excitation spreading to encompass broad regions of cortex and providing multiple distinct channels for interregional communication and worst outcome. This is also confirmed in our results.

Another major factor related to a poor outcome which has emerged from our study is activation of epileptiform discharges during sleep on EEG results. It is well known that sleep physiology has revealed neuronal networks governing wake/sleep alterations and cyclic changes during night sleep. Nowadays, we appreciate the association between the sleep/wake circuitry and its multifold relationship with the different epileptic networks [39]. In the microstructure of sleep, certain dynamic key points have shown to be associated with epileptic activation identified within the system of cyclic alternating pattern (CAP) correlating with reactive slow wave events. 'Focal' epilepsies are also not strictly localized to

a geometrical 'focus' but can involve wider, and sometimes even bilateral (e.g. temporal and occipital epilepsies), regional circuitries [40–42]. Sleep seizures are more frequent in NREM sleep, and focal to bilateral TC seizures tend to be more prominent in sleep. Discharges in sleep appear in higher rate and in a more explicit form compared to the findings when awake. NREM sleep is associated with an increase of spiking rate, extension of electrical field, and the rate of bilateral independent discharges, while in REM sleep a restriction of the electrical field was observed [43–45]. Within NREM sleep, the activation of temporal spiking was found to be the highest in stages 3–4, increasing as patients move to deeper stages of NREM sleep [43]. In addition, a previously published review suggests the theory of bidirectional interaction of hippocampus and neocortex: from the neocortex into the hippocampus during an awake state and in the opposite direction during sleep [46]. In conclusion, it is possible the increased rate of spike-wave discharges and the extended electrical field noticed in our drug-resistant groups reflect a more severe derangement of cerebral network, leading to a poor prognosis.

Interestingly, contrary to previous reports, no association of interictal epileptiform discharges was recorded in our study [25]. There is the concern that EEG data does not serve for prognosis due to the methodological limitations of the studies, namely discrepancies in EEG recording, the use of different criteria to define EEG abnormalities and the differing interpretations of the tracing. However, in our study, all EEG data were collected from our EEG laboratory, following the same protocol, and has been reviewed by an expert epileptologist.

The patients in our study were using a diverse range of antiepileptic drugs and a good seizure outcome was related to low numbers of previously tried AEDs, finding concordant with some earlier reports in MTLE [26,47].

A slight prevalence of psychiatric comorbidities (mainly depression) of epilepsy in group 3 and group 4 was evident, even if not statistically significant. This result could have a dual interpretation. Previous reports have recorded that people experiencing frequent seizures have a poor quality of personal, professional, and social life, which could explain the associated mood disorders [48]. However, several studies have demonstrated that psychiatric comorbidities (especially depression and anxiety disorders) are associated not only with an increased risk of developing epilepsy [49] but also of having treatment-resistant epilepsy [50]. The existence of common pathogenic mechanisms in primary psychiatric disorders and epilepsy has been postulated as one of the leading hypothesis to explain their close and very complex correlation [51].

We did not find a higher frequency of FC in the medical history of DR patients than in the SF patients. Personal history of febrile seizures was rather uncommon in our series (3.5%) and not related to seizure outcome. This is a rather controversial issue in the literature. Hitiris et al. [52] observed that FC were associated with drug-resistance in a general population of 780 newly diagnosed epileptic patients. The percentage of patients with FC rose to 67% in a study on patients with MTLE [6]. Another study recorded a more frequent personal history of FC in patients with MTLE-HS than in patients without MTLE-HS [25]. The association between FC and MT-HS seems to be well documented in clinical [53] and surgical [9] reports. Other investigators observed that the amygdala and hippocampus were smaller in patients with antecedents of prolonged FC compared with patients without [54]. This suggests that MT-HS could be the consequence of prolonged FC over the period of infancy or that hippocampal structures could be sensitized to generate prolonged seizures by the action of some prenatal or perinatal insults. Nevertheless, other authors disagree on the role played by FC in the etiopathogenesis of MT-HS. A prospective study reporting on patients who were followed up for 12 years found that the development of MT-HS is not common in children with a history of simple or prolonged FC [55]. Children who underwent an MRI study 48 h after a prolonged febrile convulsion had hippocampal abnormalities consistent with hippocampal edema [56]. However, follow-up MRI revealed only an asymmetry between the hippocampal structures persisted without MR signs of sclerosis, suggesting that the hippocampal injury related to FC, may include a spectrum of alterations from subtle neuronal injury to sclerosis, perhaps depending on a selective vulnerability in some patients [56]. This vulnerability could be associated with a genetic predisposition as the involvement of c-aminobutyric acid (GABA) B receptor 1 polymorphism [57]. Nevertheless, the role played by febrile convulsions in the etiopathogenesis and prognosis of MTLE is yet to be clarified.

The role of hippocampal sclerosis (HS) in drug resistance and whether MTLE with HS is a condition with a unique biological background is another area of controversy. Some reports identified phenotypic characteristics that distinguish MTLE-HS from other types of TLE [58]. Many reports emphasize the role of MT-HS as the main factor responsible for poor outcome in MTLE [25,52], either alone or associated with dual pathology [59]. However, a substantial number of patients with HS have also been found to have a good prognosis [11,14]. Furthermore, hippocampal volume reduction is not correlated with the frequency of seizures [60]. Similarly, our results did not establish the presence of HS as a prognostic factor in MTLE. Unlike other previous reports on this subject, our study is more representative of the general population of MTLE patients observed, because the selection was based solely on seizure semiology and not on presurgical evaluation of intractable epilepsy.

We did not find any differences between SF and non-seizure-free patients regarding general population characteristics such as gender and duration of the epilepsy.

In conclusion, our study, which seems to be more illustrative of the general population of MTLE patients observed in a single center, has demonstrated that MTLE is a heterogeneous syndrome. Different phenotypes are part of the spectrum of clinical manifestations. Our study on a substantial and heterogeneous population with either responsive or intractable MTLE identified the occurrence of focal to bilateral tonic-clonic seizures, ictal automatisms, persistent sleep activation on EEG, and the number of tried AEDs as negative prognostic factors, neglecting HS on MRI and FC.

There are two main limitations in our study: The first is that only a small percentage of our patients (9%) were seizure-free at the end of the follow-up period, which is less than what has been reported in the literature [10,15,25]. This difference may

partly reflect the general practitioners' tendency to refer more severe epilepsies to our tertiary epilepsy center, while milder epilepsies are being managed at the primary care level, and also the new and newly diagnosed focal epilepsies who present to our Accident and Emergency (and subsequently to our first seizure clinic) with the first-ever focal to bilTCS [61]. Of note, an additional 18% of our patients had only occasional (up to 3) focal seizures with or without awareness during the last year of follow up, most of whom were reluctant to accept modification of their AED treatment or dose increases to eliminate their seizures for fear of losing seizure control or of side effects.

The second limitation is the duration of the study. In addition, the identification of epilepsy connectivity networks is still unclear; therefore our results need to be interpreted with caution particularly in regards to pathophysiological mechanisms.

Establishing the factors associated with drug responsiveness or resistance is important for therapeutic purposes, as individuals with pharmacologically intractable epilepsy face challenges in everyday activities due to the anticipation and consequences of their unpredictable seizures. Further research combining multiple imaging and neurophysiological modalities is needed to fully characterize the network alterations that produce differential patterns of seizure propagation and, by extension, differential epilepsy outcomes. Such research has the potential to transform the management of patients with intractable MTLE syndrome.

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Declaration of interest

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