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On the prognostic value of ictal EEG patterns in temporal lobe epilepsy surgery: A cohort study

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ABSTRACT

Purpose: To investigate the prognostic value of ictal scalp EEG patterns in drug-resistant temporal lobe epilepsy associated with hippocampal sclerosis (MTLE-HS) prior to undergoing temporal lobectomy.
Methods: Scalp EEGs of the first seizure recorded during presurgical long-term video-EEG monitoring of 284 patients were reviewed. Patients were divided according to seizure laterality as either unilateral, when the EEG was restricted to one cerebral hemisphere for the entire seizure, or bilateral, when there was involvement of both hemispheres during the seizure. In patients with unilateral hippocampal sclerosis (HS), seizures were subdivided according to the side of initial ictal activity in relation to the side of the HS, as concordant, non-lateralising or contralateral. Postsurgical seizure outcome, according to Engel's classification, was verified at 1, 2, and 5 years after surgery.
Results: There was no significant association between ictal EEG characteristics and postsurgical seizure outcome. An Engel I seizure outcome was observed in 87.1% of the patients with unilateral ictal EEGs and in 79.6% of those with bilateral ictal EEGs ($p = 0.092$).
Conclusion: Analysis of the localisation, morphology, and lateralisation of ictal EEG patterns did not provide prognostic information regarding seizure-free status in patients with MTLE-HS undergoing temporal lobectomy.

1. Introduction

Mesial temporal lobe epilepsy associated with hippocampal sclerosis (MTLE-HS) is the most frequent epilepsy syndrome in patients with drug-resistant focal seizures. A meta-analysis assessing the effectiveness of anteromesial temporal lobe resection in MTLE-HS patients identified one Class I and 24 Class IV studies indicating that the benefits of surgery are greater than treatment with antiepileptic drugs (AEDs) alone and that the risks associated with these interventions are at least comparable.[1] However, long-term outcome studies have shown that approximately one third of patients experience persistent seizures after temporal resection.[2] In addition, up to 75% of all MTLE-HS patients who stop taking AEDs following successful surgery will experience a recurrence of seizures.[3] Therefore, questions emerge of how to better predict postsurgical seizure outcome in MTLE-HS patients and how to identify surgical candidates who are at a greater risk of seizure recurrence after surgery.

Previous studies of mesial temporal lobe epilepsy have shown that worse seizure outcome after temporal resection is associated with the absence of histopathological evidence of hippocampal sclerosis,[4] incomplete resection,[5] history of secondary generalised seizures,[6] and MRI evidence of epileptogenic lesions other than hippocampal atrophy.[7] The presence of interictal scalp EEG spikes that are lateralised to the side of hippocampal atrophy is associated with good postsurgical outcome.[4,8] Few studies have specifically addressed the prognostic value of ictal EEG patterns; however, the frequency and morphology of EEG presentation have been reported as potential prognostic markers in a mixed sample that included patients without HS.[9] Previous studies analysing scalp EEG have failed to find evidence of prognostic information[10]; however, sample sizes in these studies are generally small. Therefore, it remains uncertain whether detailed analysis of ictal scalp EEG morphology and propagation patterns may identify patients who would have good postsurgical outcomes after temporal lobectomy for MTLE. To address this question, we designed this study to consider a larger sample of patients who

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have a post temporal lobectomy status and a specific pathological substrate.

2. Patients and methods

2.1. Patients and inclusion/exclusion criteria

This is a retrospective cohort study that was conducted at the Epilepsy Surgery Center of the Ribeirão Preto Medical School University Hospital, São Paulo, Brazil, between February 2009 and July 2011.

The Epilepsy Surgery Center database was searched for patients fulfilling the following inclusion criteria: (a) anteromesial temporal lobectomies performed from 1994 to 2004; (b) pathologically proven hippocampal sclerosis; (c) video-EEG (scalp or invasive) consistent with seizures originating in the temporal lobe (complex partial seizures, anterior temporal interictal sharp waves or spikes and ictal patterns at temporal chains on longitudinal montages)[11,12]; (d) MRI evidence of exclusive hippocampal atrophy on T1-weighted sequences and increased signal intensity indicative of hippocampal sclerosis on T2-weighted sequences; and (e) at least 1-year follow-up.

We excluded patients satisfying any of the following criteria: (a) less than 18 years old; (b) abnormalities on neurological exam as a result of cerebral injury; (c) predominant extratemporal or generalised interictal discharges; (d) dual pathology; and (e) IQ < 60.

Ictal EEGs were reviewed by the principal investigator (BZM) and were randomly checked in part by a senior neurophysiologist (TRV). The postsurgical seizure outcomes were annotated at the pre-defined endpoints of 1, 2, and 5 years after surgery.

2.2. Data collection

Scalp ictal EEGs were obtained using the Vangard proprietary software (Cleveland Clinic, Cleveland, OH, USA). The international 10–20 system modified for temporal lobe epilepsy monitoring (10–10 system), including sphenoidal electrodes, was used. A 200 Hz sampling rate, 0.1 s time constant and 60 Hz notch filter were applied. Epochs of 10 s each were analysed. All subjects were scanned with 1.5-T MRI equipment (Siemens Magneton Vision, Erlangen, Germany). Surgery was not performed in patients exhibiting evidence of independent bilateral seizure onset zones from intracranial temporal electrodes (depth or subdural).

2.3. Variables

2.3.1. Analysis of ictal scalp EEG

The analysis of ictal scalp EEGs was performed in three steps. First, seizure logs were used to locate the first epileptic seizure recorded for each patient. Only the first recorded seizure was considered to be representative of ictal EEG patterns for analysis.

Second, we considered both the pattern at onset (PAO) and the late significant patterns (LSP) of each EEG according to protocols published elsewhere.[13] The PAO was defined as the first sustained (at least 3 s in duration) evidence of electroencephalographic seizure that was clearly distinct from background EEG activity and associated with clinical events (e.g., partial complex seizure). EEG activity morphology (whether repetitive discharge or sinusoidal), location (left or right temporal, left or right hemispheric, predominantly left or right bilateral, non-lateralising and secondary generalised) and frequency (delta, theta, alpha or beta) were registered. Over the course of seizure evolution, changes in any aspect of the above-mentioned EEG characteristics were considered as a new ictal pattern; new patterns were registered as LSP and numbered to indicate their sequential evolution.

Finally, the ictal scalp EEGs during PAO and LSP were classified as unilateral or bilateral using the following previously established definitions[13]:

(1) Unilateral: when the PAO and all LSP remained restricted to one cerebral hemisphere throughout the seizure, they could be:
  (a) left temporal or right temporal, if the amplitude ratio of the temporal versus the parasagittal chain was >2:1, and the ratio between left/right EEG amplitudes was >2:1; and
  (b) left hemispheric or right hemispheric, if the ictal EEG involved both the left or right temporal and parasagittal chains, but the amplitude ratio of the temporal versus the parasagittal chain was <2:1 and the ratio between the left and right EEG amplitudes was >2:1.
(2) Bilateral: when the PAO or any of the LSP showed relatively symmetric involvement of both hemispheres throughout the seizure, they could be:
  (a) non-lateralising, if the ratio between the left and right EEG amplitudes in both bipolar and referential montages were <2:1;
  (b) switch of lateralisation, when the dominant EEG ictal discharge changed from one hemisphere to the other; or
  (c) in the presence of secondary generalisation.

Patients were grouped according to localisation of their ictal EEGs as either unilateral or bilateral according to the above-mentioned criteria. In patients with unilateral HS we performed a subgroup analysis and classified patients according to the relationship between the localisation of the PAO without considering the hemisphere of propagation and the side of HS on MRI as (i) concordant: when the side of the unilateral ictal PAO on EEG coincided with the side of HS; (ii) nonlateralising: when there was no lateralisation of the ictal PAO on EEG, regardless of the side of HS; or (iii) discordant: when the side of the unilateral ictal PAO on EEG was contralateral to the side of the HS. Patients with bilateral hippocampal sclerosis were excluded from this analysis.

The delayed focal pattern, a condition in which nonlateralising PAOs later became restricted to one temporal region,[11] was considered as a bilateral ictal pattern in the analysis. For the second allocation analysis, the delayed focal pattern was considered to be lateralising in patients with unilateral HS.

All ictal EEG data were reviewed by the principal investigator (BZM). To assess interrater reliability, 10% of the sample was randomly selected for a blind review by a senior neurophysiologist (TRV). Both observers independently reviewed the data and their conclusions were compared. A fair to good correlation was obtained ($k = 0.5$, $p = 0.001$); this correlation was similar to previously published studies of interrater reliability in complex partial seizures.[14]

2.3.2. Seizure outcome

All patients had at least 1 year of postsurgical follow-up; 97.8% of the sample had 2 years of follow-up, and 90.8% had 5 years of follow-up. The postsurgical seizure outcome was assessed at the 1-, 2-, and 5-year follow-up and patients were classified in two subgroups: seizure-free (Engel Class I) and not seizure-free (Engel Classes II, III, and IV).[15] All patients' medical charts were reviewed by the principal investigator (BZM).

2.3.3. Statistical analysis

Statistical analysis was performed using PAWS Statistics 18 (SPSS Inc., Chicago, IL, USA). To evaluate potential associations between categorical variables, we used chi-square and Fisher's exact tests. The *t*-test was applied for parametric continuous variables. The Kaplan–Meier survival estimate was used to assess postsurgical seizure outcome. To calculate the sample size, we

performed a pilot study analysing the results of 94 patients. A 13% difference was observed in the seizure-free outcome rate favouring unilateral versus bilateral ictal patterns. Power analysis concluded that 140 patients would be necessary per group to detect an absolute difference of 13% using a power of 0.8 and a 0.05 alpha-level.

3. Results

Patient selection followed the diagram presented in Fig. 1. The clinical characteristics of the final cohort are shown in Table 1.

3.1. Preoperative clinical characteristics

The sample included 149 (52.4%) females, and the age at surgery ranged from 18 to 69 years (mean 36.4 ± 9.2 years). Mean epilepsy duration was 25.6 ± 9.9 years. Risk factors for epilepsy were observed in 141 (49.6%) patients; these included febrile seizures (61.7%), neurocysticercosis (17.7%), head trauma (7.8%), birth complications (7.8%), and meningitis (5%). The most common AED used was carbamazepine (53.3%), followed by phenytoin (28.4%) and phenobarbital (13%). The greatest seizure frequency was weekly (54.8%). Interictal EEG discharges were recorded in 95.5% of the patients. In 79.2% of these patients, discharges were unilateral (≥90% on one side); 59.8% occurred in the left temporal region, and 40.2% in the right temporal region. The only significant association found was between bilateral temporal interictal discharges and the presence of a bilateral ictal EEG pattern. Upon inspection of MRI data, we found HS in the left hemisphere in 53.2% of patients, on the right in 40.5% of patients, and bilateral in 6.3% of patients.

3.2. Ictal EEG and postoperative seizure outcome

A total of 284 seizures were assessed. According to the criteria defined above, 132 (46.5%) patients were classified as exhibiting a unilateral EEG pattern and 152 (53.5%) patients exhibited a bilateral EEG pattern. As shown in Table 2, no relationship was found between the EEG ictal pattern (unilateral or bilateral) and the likelihood of being seizure-free after temporal lobectomy, regardless of the amount of time past since surgery. Of 132 patients who exhibited a unilateral EEG pattern, 115 (87.1%) were seizure-free at the time of last follow-up. Of 152 patients who exhibited a bilateral EEG ictal pattern, 121 (79.6%) were seizure-free at last follow-up ($p = 0.092$; chi-squared test).

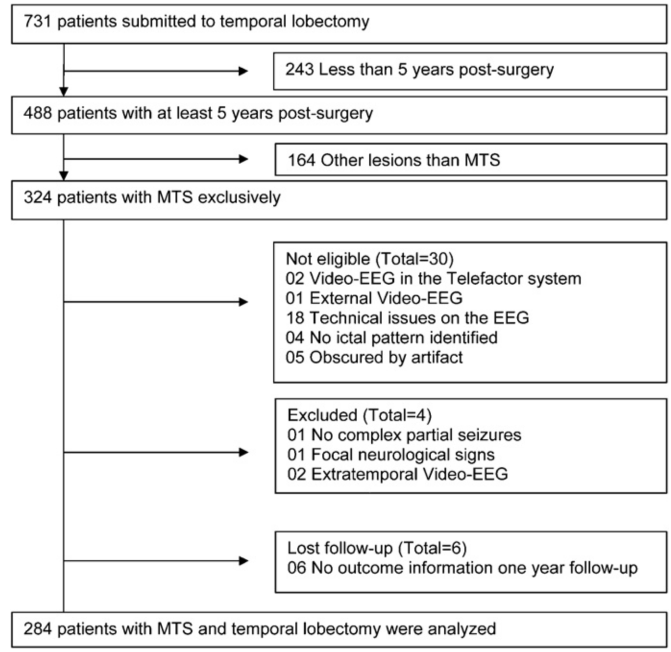

Fig. 1. Flowchart showing the inclusion criteria. MTS, mesial temporal sclerosis.

The pattern at onset (PAO) was separately analysed in a population with unilateral hippocampal sclerosis ($n = 266$), regardless of the laterality of ictal patterns or development into late significant patterns (LSP). This analysis was performed to approximate clinical findings because the side of ictal pattern initiation is relevant to surgical decisions and the majority of MTLE patients have unilateral HS. We compared the likelihood of good postsurgical outcome in patients whose pattern at onset (PAO) was concordant to the side of HS ($n = 192$; 72.2%) to those whose PAO was non-lateralising ($n = 53$; 19.9%) or discordant to the side of HS ($n = 21$; 7.9%) There was no difference in the frequency of seizure-free status between these three groups ($p = 0.506$; Fisher's exact test). Longer seizure duration was associated with worst seizure outcomes after surgery ($p = 0.018$, Student's t-test). Other variables were not associated with seizure outcome.

In the subgroup of patients submitted to invasive investigations, seizure-freedom was achieved in 18 patients (69.2%). When

Table 1
Clinical characteristics of the overall cohort and divided by ictal EEG status (unilateral vs bilateral).

	Overall group ($n = 284$)	Unilateral group ($n = 132$)	Bilateral group ($n = 152$)	p-Value
Female, *N* (%)	149 (52.4)	69 (46.3)	80 (53.7)	0.952
Mean age of epilepsy onset, years (range)	11 (±7.8)	11.6 (±7.3)	11.1 (±8.2)	0.658
Mean age at surgery, years (range)	36.4 (±9.2)	37.8 (±9.1)	35.9 (±10.1)	0.093
Mean epilepsy duration at surgery, years (range)	25 (±9.9)	26.2 (±9.3)	25.1 (±10.5)	0.358
Risk factor present, *N* (%)	141 (49.6)	67 (47.5)	74 (53.5)	0.727
Mean seizure frequency pre-op, *N* (%)				
Monthly	39 (13.8)	20 (15.2)	24 (15.8)	
Weekly	156 (54.7)	89 (67.4)	98 (64.5)	0.487
Daily	53 (18.7)	23 (17.4)	30 (19.7)	
Bilateral interictal EEG, *N* (%)	56 (19.8)	19 (14.4)	37 (24.3)	0.038
Side of hippocampal sclerosis on MRI, *N* (%)				
Left	151 (53.2)	67 (50.8)	84 (55.3)	
Right	115 (40.5)	54 (40.9)	61 (40.1)	0.401
Bilateral	18 (6.3)	11 (8.3)	7 (4.6)	
Side of surgery, *N* (%)				
Left	161 (56.7)	72 (54.5)	89 (58.6)	0.497
Right	123 (43.3)	60 (45.5)	63 (41.4)	
Seizure outcome, *N* (%)				
Engel I	236 (83.1)	115 (87.1)	121 (79.6)	0.092
Engel II, III, IV	48 (16.9)	17 (12.9)	31 (20.4)	

Table 2
Univariate analysis of predictors for seizure outcome.

	Seizure outcome		p-Value
	Engel I (N = 236)	Engel II, III, IV (N = 48)	
Female, N (%)[a]	125 (83.9)	24 (16.1)	0.708
Epilepsy duration, years (range)[b]	25.6 (10)	25.2 (10.2)	0.961
Risk factors present, N (%)[a]	119 (84.4)	22 (15.6)	0.562
Mean age of epilepsy onset, years (range)[b]	11.5 (7.9)	10.6 (7.7)	0.463
Mean age at surgery, years (range)[b]	37 (9.4)	35.9 (11.3)	0.464
Daily seizures, N (%)	44 (18.6)	9 (18.8)	0.279
Submitted to invasive monitoring, N (%)[a]			
Yes	18 (69.2)	8 (30.8)	0.048
No	218 (84.5)	40 (15.5)	
Side of MTS at MRI, N (%)[c]			
Unilateral	222 (94.1)	44 (91.7)	0.747
Bilateral	14 (5.9)	4 (8.3)	
Side of surgery, N (%)[a]			
Left	130 (55.1)	31 (64.6)	0.265
Right	106 (44.9)	17 (35.4)	
Interictal EEG, N (%)[a]			
Unilateral	189 (80.1)	39 (81.3)	1.000
Bilateral	47 (19.9)	9 (18.8)	
EEG pattern at onset (PAO) concordance with unilateral MTS, N (%)[a]			
Concordant	160 (83.3)	32 (16.7)	
Non-lateralising	46 (86.8)	6 (13.2)	0.506
Discordant	16 (76.2)	5 (23.8)	
Ictal status overall, N (%)[a]			
Unilateral	115 (87.1)	17 (12.9)	0.092
Bilateral	121 (79.6)	31 (20.4)	

MTS, mesial temporal sclerosis.
[a] Chi-square test.
[b] t-test.
[c] Fisher's exact test.

compared to patients who were not subjected to invasive investigations, there was a significant association between invasive monitoring and worse seizure outcomes (84.5% vs 69.2%; $p = 0.048$, chi-squared test).

3.3. Preoperative ictal EEG and interictal EEG

Ninety-five percent of our patients demonstrated interictal epileptiform discharges. Of these patients, 98.1% demonstrated discharges that were restricted to temporal electrodes; discharges were unilateral in 79.2% of all instances (spike index ≥90% on either side). There was a significant association between the presence of bilateral interictal temporal epileptiform discharges and bilateral ictal EEG. Of all patients demonstrating bilateral temporal discharges, 37 (66.1%) had a bilateral EEG ictal pattern, while 19 (33.9%) had a unilateral EEG pattern. Interictal epileptiform discharges were localised to the ipsilateral side of the ictal EEG and MRI in 207 patients (207/214; 97.2%; $p < 0.001$; Fisher's exact test).

3.4. Invasive investigations

In 26 patients (9.2%) in whom the ictal EEG was non-lateralising, bilateral, or contralateral to the side of HS, an invasive study was conducted to clarify the epileptogenic zone (foramen ovale, depth or subdural electrodes). Investigations were performed according to our centre's previously published protocols.[16,17] In this group, five patients (19.2%) were submitted to invasive monitoring by depth or subdural electrodes and 21 patients (80.8%) were monitored via foramen ovale electrodes. There was a significant association between the scalp EEG ictal onset zones contralateral to HS on MRI and performance of invasive monitoring ($p < 0.001$; chi-squared test).

4. Discussion

In a cohort of 284 patients with MTLE-HS who underwent temporal lobectomy, we evaluated the pre-surgical scalp ictal EEG patterns regarding duration, frequency, and propagation to the contralateral side and their relationship to postsurgical seizure outcomes. We hypothesised that distinct ictal EEG and seizure spread patterns would predict seizure outcome after surgery. We also explored the idea that involvement of both sides may potentially indicate increased epileptogenicity of the side contralateral to temporal lobectomy. However, analysis of these scalp ictal EEG characteristics did not correlated with postsurgical seizure outcome; this finding does not support our hypothesis. For example, the total Engel I outcome frequency at last follow-up was 87.1% for the group with unilateral ictal EEG pattern; in the bilateral ictal EEG pattern group, this value was 79.6%. This small (7.5%) difference in outcomes was proved to be non-significant ($p = 0.092$, chi-squared test; Fig. 2). Moreover, similar postsurgical seizure-free outcomes were found in unilateral HS patients with concordant pattern at onset (PAO) (83.3%) when compared to those with non-lateralising (86.8%) or discordant (76.2%) PAOs, regardless of the seizure pattern evolution.

Of the 74 patients with non-lateralising or discordant ictal EEG patterns, 21 underwent invasive studies because they exhibited discordant EEG patterns. Most patients with non-lateralising EEG patterns were submitted to temporal resection without invasive study because data yielded by other diagnostic assessments confirmed the side of hippocampal atrophy. The other diagnostic measures included procedures such as ictal semiology, interictal EEG, and ictal SPECT. Five patients with non-lateralising EEG patterns were submitted to invasive monitoring because other diagnostic data did not indicate clear seizure lateralisation. Because we did not analyse all seizures recorded from each patient considered for epilepsy surgery, our results cannot be applied to all patients with MTLE-HS being considered for surgery. Only patients who were actually submitted to temporal lobectomy were analysed; this study can only provide prognostic information for this group.

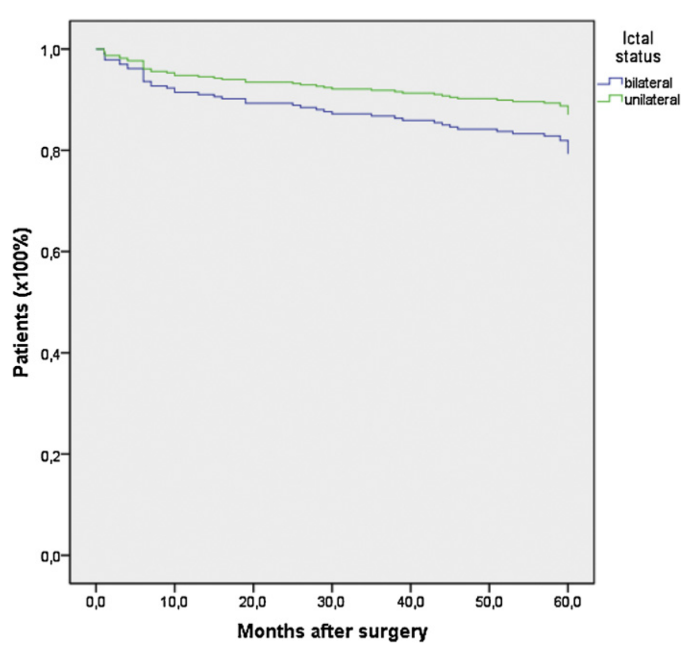

Fig. 2. Kaplan–Meier estimate of Engel I outcome in unilateral and bilateral ictal EEG status; $p = 0.099$.

Contrary to our findings, a previous study evaluating TLE patients via depth electrodes reported that propagation time to the contralateral hippocampal formation was related to seizure outcome. Interhemispheric propagation times of <0.5 s were associated with worse postsurgical seizure outcomes.[18] However, this study was performed in the 1980s, and included patients with refractory complex partial seizures who were operated on before the MRI era. Therefore, the cohort likely included a heterogeneous group of patients, including both those with and without HS. Indeed, another study by these authors showed that HS was associated with longer propagation intervals[19]; this observation raises the question whether the lesion itself, rather than propagation time, was responsible for better outcomes.[2,4] Our study was performed in a highly homogeneous group of patients exhibiting the constellation of MTLE associated with HS; this may underlie the lack of an association in the present study.

Few studies have evaluated scalp EEG ictal patterns and postsurgery seizure outcome in temporal lobe epilepsy.[9,10,13,20,21] Seizure-free outcomes are associated with unilateral EEG ictal patterns in cases demonstrating unilateral interictal temporal discharges.[10,13,20] We were not able to confirm these findings. However, we did observe that bilateral interictal discharges were correlated with bilateral ictal patterns. Moreover, unilateral interictal discharges that were localised to the side of HS were not associated with a better postsurgical seizure outcomes in our cohort.

An emerging opinion is that HS is not a homogeneous disease. The subdivision of HS according to the type of cell loss experienced and its semi-quantitative measurement may indicate different insult patterns and thus, different outcomes after surgery.[22] In the present study, such an analysis could not be performed; no clinicopathological correlation can be made.

We chose to analyse only the first recorded seizure because, similar to other centres, most patients with TLE are instructed to reduce their epilepsy drug dosages for long-term video-EEG monitoring. Antiepileptic drug tapering may lead to various neurological symptoms, including iatrogenic secondarily generalised seizures, even in patients who habitually have complex partial seizures only. Therefore, the first seizure should be the one which closely resembles the usual clinical condition experienced by the patient. We believe that our sample size was large enough to be confident to assume that the ictal EEG pattern is not an appropriate prognostic instrument.

In our group of MTLE-HS patient who underwent temporal lobectomy, scalp ictal EEG patterns could not predict outcomes when ictal patterns involved both hemispheres, compared to patterns restricted to only one hemisphere. This may indicate that in MTLE-HS, the propagation of ictal activity to the contralateral hemisphere could be a normal pattern of seizure propagation in an epileptogenic focus localised in the hippocampal formation. Our study supports the notion that seizure propagation to the contralateral side in MTLE-HS does not appear to imply more widely spread epileptogenesis.

Conflict of interest

None of the authors has any conflict of interest to disclose.

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