Original article

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Intracranial electrographic analysis of preictal spiking and ictal onset in uni- and bitemporal epilepsy

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ABSTRACT – *Aim*. Ictal onset patterns in bilateral mesial temporal lobe epilepsy have not been comprehensively studied. A retrospective review of intracranial electrographic data was undertaken to establish whether it is possible to distinguish between unilateral and bilateral mesial temporal lobe epilepsy based on ictal onset patterns, including periodic preictal spiking.

Methods. A total of 470 ictal onset patterns were analyzed by bitemporal extraoperative electrocorticography in 13 patients with medically intractable mesial temporal lobe epilepsy. Ictal onset patterns were categorized, by frequency, as type A (<12 Hz), type B (12-40 Hz) and type C (>40 Hz). Preictal rhythmic spiking, of at least five seconds duration, and time to contralateral propagation were also measured with each ictal event. We determined if the proportion of "ictal onset pattern frequencies" or "incidence of preictal spiking" differed between unilateral and bilateral mesial temporal lobe epilepsy.

Results. Seven patients with unilateral mesial temporal lobe epilepsy received surgery and achieved Engel class I outcomes, while the remaining six did not undergo resective surgery, due to the bilateral ictal onsets in extraoperative electrocorticography. The proportion of patients experiencing any preictal spikes was higher in unitemporal than in bitemporal cases (100% *vs* 50%; p=0.069). Of the 470 ictal onset patterns analyzed (174 unitemporal and 296 bitemporal), a significant greater percentage of preictal spikes was found in unilateral cases (78% unitemporal *vs* 14% bitemporal; p=0.002). Low-frequency patterns were more evident in bitemporal cases (45%) than in unitemporal (10%), although the difference was not statistically significant (p=0.129). No differences were detected between the unitemporal and bitemporal groups regarding age at onset or at presentation.

Conclusion. A greater proportion of preictal spiking, based on extraoperative electrocorticography, was present in unilateral, compared to bilateral, mesial temporal lobe epilepsy. Further studies are warranted to determine the causal significance of preictal spiking in mesial temporal lobe epilepsy.

Key words: mesial temporal lobe epilepsy, unilateral, bilateral, ictal onset pattern, extraoperative electrocorticography, preictal spike

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Mesial temporal lobe epilepsy (mTLE) is a surgically amenable condition (Spencer, 2002), but presurgical non-invasive diagnostic evaluation may be insufficient to lateralize the condition and necessitate extraoperative electrocorticography (eECoG). This may, in turn, confirm bitemporal epileptogenicity in some cases (So *et al.,* 1989a) despite a rather variable range of EEG features (Wasade *et al.,* 2013). Preictal spiking (*figure 1*) identified by eECoG is specific to mesial temporal sclerosis (MTS) (Perucca *et al.*, 2014) and favours a good outcome following anterior temporal resection (Schuh *et al.*, 2000). Pathology confirms neuronal loss in the CA1 subregion in these circumstances (King and Spencer, 1995). However, the electrographic features obtained by eECoG, particularly those of ictal onset that would distinguish unilateral from independent bilateral mTLE, have not been sufficiently characterized. This study reviews these features in two well-studied cohorts in order to establish the differences quantitatively.

Patients and methods

An archival review of patients investigated for TLE and requiring eECoG of both temporal lobes during a four-year period (2005-2008) identified 13 patients (male: female; 5:8). The mean age at presentation was 40.8±11.1 years (range: 19-57) (*table 1*) and that at onset of epilepsy was 9.0±9.1 years (range: 3 months-35 years). All patients underwent inpatient scalp EEG with video monitoring over a period of 8-17 days, MRI, an intracarotid amobarbital procedure (IAP), neuropsychological assessment, as well as ictal and interictal single-photon emission computed tomography (SPECT). Select patients underwent interictal positron emission tomography (PET) and magnetoencephalography (MEG). All patients were reviewed by an epilepsy board and a decision was rendered to proceed with eECOG of both temporal lobes.

Seven patients (Cases 1-7), who had unilateral temporal ictal onset patterns (IOPs) on scalp EEG monitoring with discordant non-electrographic data on presurgical testing, underwent temporal resection after confirmation of ictal pattern lateralization by eECoG. The mean age at epilepsy surgery was 38±11.6 years. Pathological investigation showed hippocampal sclerosis in four of the seven patients (Cases 1, 3, 5, and 6). Sufficient clinical follow-up of 5.4±0.8 years revealed Engel class IA in six patients (Cases 1-6) and class IC outcome in one patient (Case 7). One patient (Case 2) died with metastatic breast cancer four years following surgery, but had remained seizure-free from the time of surgery.

In the bitemporal group (Cases 8-13), all had evidence of independent bitemporal ictal and interictal patterns on scalp EEG monitoring and underwent eECoG to better define the predominant side of seizure origin (So *et al.*, 1989b). None of these patients proceeded to resective surgery.

Electrocorticography

The implantation of intracranial electrodes was performed by a single surgeon (KE). A near-symmetric distribution of subdural multicontact electrodes, numbering 16 to 62 contacts on each side, was possible in all cases with coverage of peri- and entorhinal areas in addition to the remaining surfaces of the temporal lobes. The recording lasted 8 to 17 days with tapering of antiepileptic medications, as required. Intracranial EEG was recorded with a sampling rate of 200 Hz. For the purposes of this study, the recordings were analyzed by two electroencephalographers (SG, VSW) using the Nihon Kohden system (HFF: 70 Hz; TC: 1 s; sens: 75 μV/mm), followed by a review by a third (DEB).

Analysis

Ictal onset patterns were identified by the presence of sustained, rhythmic, localized discharges and were further categorized by onset frequencies of less than 12 Hz (type A) (*figure 1*), 12-40 Hz (type B) (*figure 2*), and greater than 40 Hz (type C) (*figure 3*). Time to propagate to the contralateral mesial temporal lobe structures was noted in all cases.

Preictal epochs of 30 seconds were reviewed for all ictal patterns. Preictal spikes (*figure 3*) were characterized by the presence of rhythmic spikes or sharp-wave discharges, lasting at least five seconds, with a repetition rate of 1-2 Hz prior to seizure onset in the same location (Spencer and Spencer, 1994; King and Spencer, 1995). These were followed by IOPs (type A, B or C), as described above, that in turn further evolved in frequency and amplitude to constitute ictal patterns on eECoG.

Magnetic resonance imaging

Images were acquired with a General Electric 1.5 T Signa system (GE Medical Systems, Milwaukee, WI). All subjects underwent coronal T1-weighted MR study using a spoiled gradient-echo (SPGR) sequence with TR/TI/TE: 7.6/1.7/500 ms; flip angle: 20°; field of view (FOV): 200×200 mm^2; matrix size: 256×256; pixel size: 0.781×0.781 mm^2; slice thickness: 2.0 mm (voxel size: $0.781 \times 0.781 \times 2.0$ mm^3); number of slices: 124; bandwidth: 25 kHz; and scanning time: 5.75 minutes. Coronal FLAIR MR data sets were acquired with TR/TI/TE: 10002/2200/119 ms; flip angle: 90°; FOV: 200×200 mm^2; matrix size: 256×256; pixel size: 0.781×0.781 mm^2; slice thickness: 3.0 mm (voxel size: $0.781 \times 0.781 \times 3.0$ mm^3); minimum number of

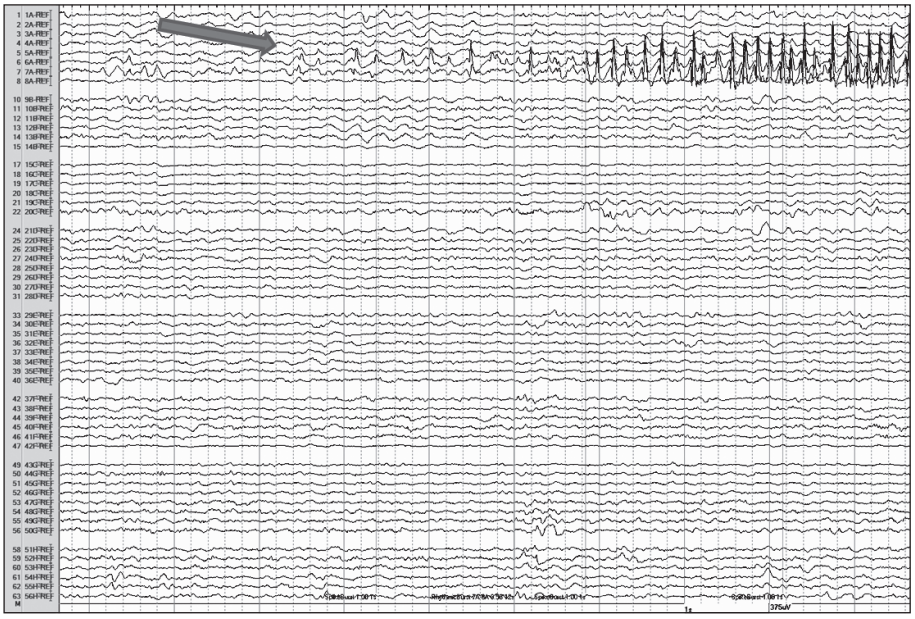

Figure 1. Recording from bilateral temporal subdural electrodes showing ictal onset pattern with frequency <12 Hz (type A) (shown with an arrow) in the left parahippocampal contacts.

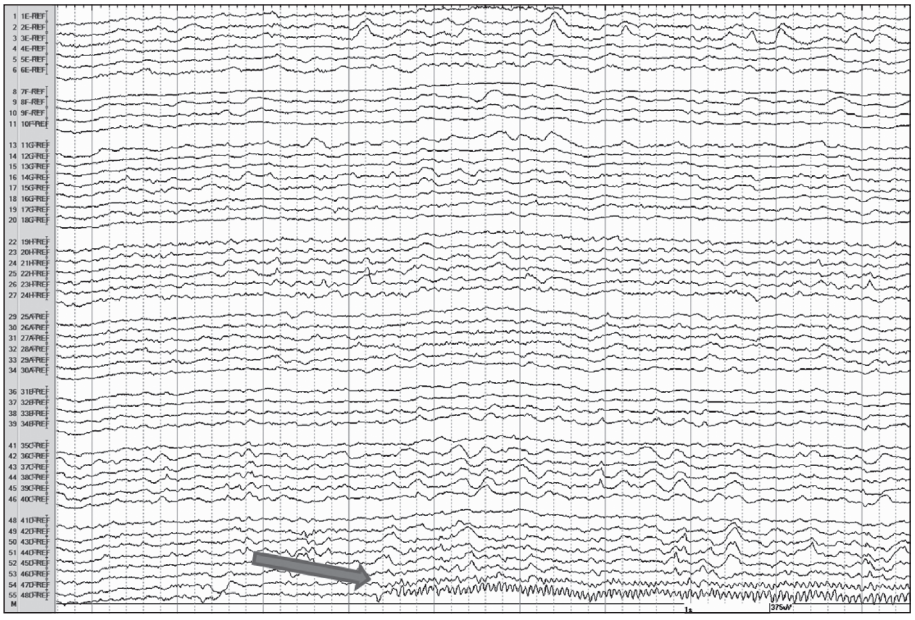

Figure 2. Recording from bilateral temporal subdural electrodes showing ictal onset pattern with frequency of 12-40 Hz (type B) (shown with an arrow) in the right parahippocampal contacts.

slices: 47; bandwidth: 20.8 kHz; and scanning time: 12 min. All MR images were re-examined (KE) to render a final impression of MTS according to the following criteria: (1) reduction of hippocampal volume and right-left asymmetry on T1-weighted coronal images, (2) increased T2-FLAIR MR signal intensity and, (3) loss of intrinsic hippocampal laminar structure.

Statistical analysis

The primary outcome measure was the proportion of patients with preictal spikes in each group. Fisher's exact test was used to assess the difference in this proportion between the unitemporal and bitemporal groups.

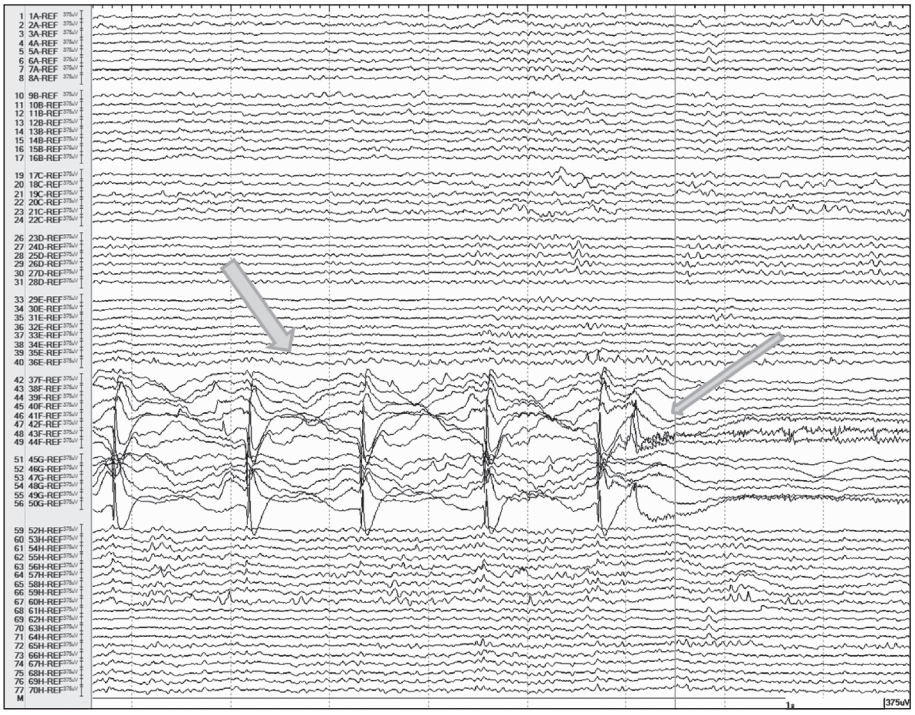

Figure 3. Recording from bilateral temporal subdural electrodes demonstrating preictal spiking (shown with a thick arrow) in the right parahippocampal contacts. Preictal spiking is characterized by rhythmic periodic spike discharges for at least five seconds, and ictal onset pattern with high-frequency (>40 Hz) activity (type C) (shown with a thin arrow) in the same location.

Secondary outcome measures included the proportions of preictal spikes and frequency patterns (<12 Hz: type A; 12-40 Hz: type B; >40 Hz: type C) among the IOPs. For each group, the proportion of preictal spikes was computed as the number of IOPs with preceding preictal spikes, divided by the total number of IOPs. Similar calculations were performed for each of the frequency patterns (type A, type B and type C). Because the number of IOPs varied by patient, from 3 to 114, Rao-Scott chi-square tests were performed to compare the rates between the two groups. This method takes into account the possible correlations among multiple observations within the same cluster (patient). Two sample t-tests were used to compare the age at epilepsy onset and age at presentation for the two groups. The null hypothesis of no difference between the unitemporal and bitemporal groups was assumed for the proposed outcomes. All testing was performed at the 0.05 level. Analyses were performed using SAS version 9.2.

Results

Unitemporal group

Of the seven patients who underwent resective surgery, all had Engel class IA outcomes with the exception of a single patient (Case 7) who acquired an Engel class IC outcome. All patients experienced at least one preictal spike. In the 174 unitemporal ictal patterns recorded, preictal spiking was noted in 78% (136/174 IOPs) of seizures. Four patients (Cases 1, 3, 5, and 6) had hippocampal sclerosis (HS) and showed a trend toward a slightly lower rate of preictal spikes when compared to those without this pathological feature (HS: 75% *vs* no HS: 85%; p=0.063). Ictal frequencies of 12-40 Hz (type B, 52%; 90/174 IOPs) were most often encountered followed by those with frequencies greater than 40 Hz (type C, 39%; 67/174 IOPs) and, finally, those with less than 12 Hz (type A, 10%; 17/174). Only one patient (Case 5) had seizures (10%, 6/60 IOPs) that propagated to the contralateral temporal lobe after 41 to 101 seconds, although there were no interictal epileptiform discharges or IOPs observed contralaterally. MTS on brain MRI was present in five of seven patients in this group who all had preictal spiking.

Bitemporal group

In the bitemporal group of six patients (Cases 8-13), half the patients experienced at least one preictal spike. Of the 296 ictal patterns (173 right; 123 left) studied, only 42 (14%) showed preictal spiking. The predominant onset frequency remained under 12 Hz (type A, 45%; 133/296 IOPs). The remaining were categorized as type B (40%; 119/296) or

Table 1. Summary of demographics and electro-diagnostic attributes in the study population. Age, age at epilepsy onset, and follow-up after surgery are presented in years. Time to propagate to contralateral temporal lobe is presented in seconds.

Case	Age	Sex	Age at Epilepsy onset	Brain MRI	Side/ ictal events	No. of IOPs with PS (type)	A		B		C		Propagation-time (no. of ictal events)	Patho-logy	Follow-up
							R	L	R	L	R	L			
1	57	M	7	R MTS	R/12	7(B)	1		11				NP	HS	5
					L/0	0							-		
2	50	F	6	NL	R/9	7(B), 1(A)	2		7				NP	ND	4
					L/0	-							-		
3	19	F	4.5	R MTS	R/10	9(C)					10		NP	HS	6
					L/0	0							-		
4	35	F	15	L MTS	R/40	34 (C)			2		38		NP	ND	6
					L/0	0							-		
5	50	F	0.25	L MTS	R/0	-							-		7
					L/60	32(B), 12(C)				41		19	41-101 (6)	HS	
6	42	M	5	L MTS	R/0	-							-		5
					L/37	16(B), 13(A)		14		23			10-75 (21)	HS	
7	48	M	35	NL	R/6	5(B)			6				24-46 (4)	ND	5
					L/0	-							-		
8	23	M	15	NL	R/12	0	2		10				NP		
					L/22	0		22					NP		
9	47	F	11	NL	R/15	0	15						10-22 (12)		
					L/22	0		22					NP		
10	39	F	10	NL	R/45	2(C)	1				44		20 (1)		
					L/30	0		28		2			20 (1)		
11	39	M	3	NL	R/19	2(A)	18		1				NP		
					L/14	0		13		1			7-45 (12)		
12	33	F	5	NL	R/2	0			2				NP		
					L/1	0				1			NP		
13	48	M	0.5	b/l MTS	R/80	31(B), 2(A)	12		68				80 (1)		
					L/34	5(B)			34				20-30 (2)		

M: males; F: females; IOP: ictal onset pattern; R: right temporal; L: left temporal; R MTS: right mesial temporal sclerosis; L MTS: left mesial temporal sclerosis; NL: normal MRI; NP: no propagation to contralateral temporal lobe; b/l MTS: bilateral mesial temporal sclerosis; HS: hippocampal sclerosis; ND: no diagnostic feature.
A: IOP with <12 Hz activity; B: IOP with 12-40 Hz activity; and C: IOP with >40 Hz activity.

type C (15%; 44/296) at ictal onset. Contralateral temporal lobe propagation occurred in 10% of ictal events (29/296) after a mean ictal duration of 26 seconds. Only three patients (Cases 10, 11, and 13) in the bitemporal group had preictal spiking on eECoG. Two of these (Cases 10 and 11) had apparently normal MRI and the other, bilateral MTS (Case 13).

Unitemporal group *vs* bitemporal group

A higher proportion of patients with preictal spiking was observed in the unilateral mTLE group than the bilateral mTLE group (100% *vs* 50%; p=0.069). The unilateral group had a significantly higher percentage of preictal spikes compared to the bilateral group (78% *vs* 14%; p=0.002). When considering the frequency distribution, the bilateral group had a higher percentage of low-frequency IOPs (<12 Hz, type A) compared to the unilateral group (10% *vs* 45%). A greater percentage of higher-frequency patterns (>12 Hz, types B and C) was observed in the unilateral group, compared to the bilateral group (90% *vs* 55%). Neither of these differences were significant (p=0.129, for both comparisons). No differences were detected between the unilateral and bilateral groups regarding age at onset (10.4±11.7 *vs* 7.4±5.5; p=581) or at presentation (43.0±12.6 *vs* 38.2±9.3; p=0.456).

Discussion

In this first study of preictal spiking using eECoG to compare unilateral and independent bilateral mTLE, there was a trend favouring greater preictal spiking in the unilateral case. Moreover, a higher-frequency pattern (*i.e.* ≥12 Hz) favoured unilateral over bilateral mTLE, however, the difference was not statistically significant. Neither the age at onset of the epilepsy nor the duration of the condition exerted any influence upon this attribute. The generation of this activity is a consequence of interaction among mesial temporal structures, specifically, the entorhinal cortex and hippocampus, where either might be the primary source (Spencer and Spencer, 1994; Bartolomei *et al.,* 2004; Bartolomei *et al.,* 2005). Synchronized discharges involving the entirety of the hippocampal-parahippocampal structure during ictogenesis appears to be a prerequisite for spread of epileptiform activity from the area (Shimizu *et al.,* 2006; Umeoka *et al.,* 2012). An increase in synchrony has been particularly noted at the onset of seizure activity in coherence studies (Duckrow & Spencer, 1992; Bartolomei *et al.,* 2004; Bartolomei *et al.,* 2008). This synchronous interaction of a variety of structures in the mesial temporal lobe is felt to comprise the epileptogenic zone (Bancaud *et al.,* 1965; Bancaud *et al.,* 1970; Bragin *et al.,* 2000; Bartolomei *et al.,* 2004) which may include the entorhinal cortex (Spencer and Spencer, 1994; Bartolomei *et al.*, 2005), the limbic portion of the temporal pole (Chabardès *et al.*, 1999), and the insula (Isnard *et al.*, 2000; Isnard *et al.*, 2004; Sudbury and Avoli, 2007), and be regarded as a network (Bragin *et al.,* 2000; Briellmann *et al.*, 2004).

There remains relatively little information regarding the preictal phenomenon. Prior to epileptic seizures, decrease in synchronization has been described (Mormanna *et al.*, 2003). Presumed pathophysiological mechanism for periodic preictal spiking embraces an understanding of enhanced excitation and inhibition leading to hypersynchronous neuronal discharges (Engel, 2013). Different IOPs are shared by biologically distinct epileptogenic lesions, except for periodic spiking that are specific to MTS and delta brush that are exclusive to focal cortical dysplasia (Perucca *et al.*, 2014). Our study demonstrates that preictal spiking is more common in unilateral mTLE and reveals that, in bilateral TLE, a relatively low percentage of preictal spiking and predominant low-frequency IOPs may be found.

An earlier study (Katz *et al.,* 1991) had identified that spiking did not differ among different epochs of 0-5 m, 5-10 m and 0-60 m prior to an ictal event, either for all channels or for those specifically showing the onset pattern, while another (Lange *et al.,* 1983) declared a reduction preceding onset, although the state of arousal had not been reported in the latter study. Preictal spiking in the immediate interval prior to ictal onset may have some bearing on the results of the current study compared to that of Katz *et al.* (1991), as some would argue that the immediate-early ictal period, rather than a preictal epoch, was assessed.

Surface placement of electrodes along the mesial polar, peri- and entorhinal cortices, and the remainder of the parahippocampal gyrus provides substantively greater surveillance of epileptogenicity along the mesiobasal temporal corridor than the point-selected targeting offered by depth stereoencephalography. Sampling bias is lessened by this approach, by including neo- and paleocortical areas, although certainly not eliminated. Hence, one is never assured that ictal onset has occurred in a given location or in a proximate, but anatomically distinct, area and with a direct influence upon the recording site. The paucity in detection of seizure onset in the parahippocampal gyrus may reflect such bias, particularly in cases where a single site is chosen arbitrarily as representative of the whole (Wennberg *et al.,* 2002). Any declaration that a particular site, such as the hippocampus, in the mesial temporal structure is the ictogenic site must remain speculative for the same reason. Mesial temporal ictogenesis is, in fact, a regional phenomenon more than a focal one, and a variety of electrographic patterns may

exist to mark the putative site (Quesney, 1986; So *et al*., 1989b; Spanedda *et al*., 1997). A low-amplitude rhythmic fast activity does, however, predominate in ictal expression (Babb *et al*., 1987; Engel, 1993; Wennberg *et al*., 2002), as it has in the current study.

The time duration for propagation of discharge to the contralateral temporal lobe, notably after 20 seconds or more, has been correlated with hippocampal sclerosis (Lieb and Babb, 1986), particularly with a reduced cell count in the CA1 subfield (Spencer *et al*., 1992). It has been regarded as a prognostic feature in establishing the unilaterality of mTLE and the success of subsequent surgery (Risinger and Gumnit, 1995). There is considerable variability in propagation time in the current study with durations of only 10 seconds, even in the presence of unilateral MTS and pathological confirmation of hippocampal sclerosis. Preictal spiking, particularly with that of higher frequency, lends support in favour of unilateral mTLE in the circumstance of prolonged propagation time and it may also support the notion of unilaterality even in the absence of a suitable propagation time period. The predominant conventional application of eECoG has involved recording of frequencies up to and including the gamma band (*i.e*. 40-100 Hz) with a sampling rate of 200 Hz (Jirsch *et al*., 2006). The current study addresses the matter of mTLE unilaterality using this standard method without pursuing high sampling rates (*i.e*. 1000-2000 Hz). The high-frequency oscillations (HFOs) provide discrete localization of a focal epileptogenicity, the complete resection of which, ostensibly, would offer a favourable outcome (Jiruska *et al*., 2008; Fujiwara *et al*., 2012). The distinction of a unilateral temporal lobe epileptogenicity in the form of preictal spiking may be gleaned from conventionally derived data and further technical sophistication may not be required unless there is a requirement to isolate a discrete area more often found in the extratemporal domain.

Greater understanding of the nature of neural connectivity and the extent of cellular pathology in bilateral mesial temporal epilepsy is generally a matter for post-mortem study. The advent of high-resolution MR imaging with diffusion tensor imaging (DTI) and functional studies will undoubtedly shed light on local neural network structure in this situation, but will never supplant the need for ultrastructural immunocytochemical assessment of the relationships with cellular phenotypes, in addition to their synaptic and electrotonic connectivity.

Our study analyzed only a small number of cases, although with a large number of ictal patterns. Because of this, the relationship between MTS, based on MRI, and preictal spiking was not analyzed. The contribution of other diagnostic evaluations was beyond the scope of this study.

Conclusion

Preictal spiking identified by well-distributed contact surveillance with eECoG of the mesial temporal structure, extending from the temporopolar region posteriorly along the parahippocampal gyrus, suggests a unilateral TLE. The low percentage of preictal spiking and the presence of predominant low-frequency patterns at ictal onset may raise suspicion of a bilateral mTLE. These findings may suggest differences reflected in network activity that is unique to the unilaterally epileptogenic mesial temporal lobe and distinct from that found in bilateral TLE. □

Supplementary Data.

Summary didactic slides are available on the www.epilepticdisorders.com website.

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TEST YOURSELF

(1) What are the indications for invasive monitoring with intracranial electrodes in people with drug-resistant mesial temporal lobe epilepsy (mTLE)?

(2) What are the characteristics of preictal spikes?

(3) How do preictal spikes and ictal onset patterns (IOPs) during intracranial EEG monitoring assist in the distinction between uni-temporal and bitemporal epilepsy?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".