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Postoperative interictal spikes during sleep contralateral to the operated side is associated with unfavourable surgical outcome in patients with preoperative bitemporal spikes

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Summary Purpose: To correlate the persistence of contralateral spikes during sleep after unilateral surgery with seizure outcome in a temporal lobe epilepsy (TLE) population and to test the existing hypotheses about the origin of the contralateral spikes in temporal lobe epilepsy. **Methods:** In the 19 patients selected for this study unilateral temporal lobe surgery was performed. To investigate the course of bilateral interictal epileptiform discharges observed before surgery in awake or sleep over the temporal lobe contralateral to surgery, 24 h mobile 12 channel EEG recording was performed at minimum two, in average 4.6 (2–10) years after the surgery. **Results:** The association of postoperative contralateral spikes and non-seizure free outcome was highly significant. The existence of unilateral pathology before surgery was highly predictive for good outcome and disappearance of contralateral spikes. The association between good seizure outcome, disappearance of contralateral spikes and the existence of unilateral pathology before surgery was also significant. Our data partially satisfies the expectations of both the “seizure induced” and mirror type secondary epileptogenesis hypotheses concerning origin of contralateral spikes, but were not completely congruent with either of them. **Conclusions:** Unfavourable surgical outcome in a temporal lobe epilepsy group with preoperative independent bilateral interictal spikes was associated with the persistence of postoperative contralateral spikes and lack of unilateral pathology. Compared with seizure outcome the presence/absence and distribution of postoperative interictal spikes in NREM sleep not entirely fit to the predictions of existing secondary epileptogenesis hypotheses.

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Introduction

The predictive value of interictal epileptiform discharges in temporal lobe epilepsy (TLE) was studied in several works. The majority of the authors concluded that the presence of bilateral indepen-

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dent interictal epileptiform discharges is associated with unfavourable outcome in temporal lobe surgery compared to patients with pure unilateral discharges.^{1,2} On the other hand, surgical outcome with bilateral spikes was shown to be as good as 50–77% seizure freedom.^{3,4} The lateralising value of sleep recording is also stressed in recent studies.⁵ There are evidences that postoperative seizures originate from the ipsilateral in 70% and from the contralateral temporal lobe in 30%.⁶ The postoperative persistence of spikes on the operated side was studied and found to be associated with unfavourable surgical outcome.^{7,8} However, the relationship of persistent postsurgical spiking in sleep with seizure outcome was never tested in a population showing presurgically bilateral independent interictal discharges.

The origin of the contralateral spikes in TLE patients having unilateral seizure onset, associated with or without known pathology, is not yet clear. There are different interpretations. One of them is the secondary (mirror) epileptogenesis proposed most consistently by Morrell and co-workers.^{9–11} According to this concept, the contralateral spikes are induced by the bombardment of discharges originating from the primary focus and they reflect the development of a secondary epileptogenic focus issuing sooner or later not only interictal spikes, but seizures as well.

The mirror type secondary epileptogenesis (SE) of Morrell would predict independent, time related, contralateral epileptogenesis in some of those patients in whom the contralateral discharges do not disappear after the resection of the primary focus.⁹ Mirror type SE is clearly proved in experimental models.¹¹ However, in humans, the existence of mirror type SE in TLE is still controversial.^{12–14} The cases of Morrell¹⁰ were not video documented at that time and even the EEG proof of secondary contralateral seizures is questionable.¹⁵ To provide proofs in the human context is quite difficult since it needs long-term follow up studies with video-EEG evidences. Up to now only some cases¹⁶ provided arguments for the existence of independent mirror type SE in humans.

Another hypothesis attributes more important role to the seizure spread to the contralateral side in the development of contralateral spiking.¹⁷ According to this concept, contralateral spikes are not necessarily concomitant with the development of a seizure onset zone in the contralateral side. This concept is based on studies showing more frequent contralateral spikes among patients with contralateral seizure spread compared to those without^{18,19} and on the study of Janszky et al.¹⁷ in which they found more contralateral interictal

spikes after seizures spreading to the contralateral side compared to the postparoxysmal period of strictly unilateral seizures.

Therefore a study in which the late postoperative state is tested for the presence of contralateral discharges in sleep seemed to us interesting for two reasons. One is to correlate the disappearance or persistence of contralateral spikes with seizure outcome and second is to test the above-mentioned two hypotheses about the origin of the contralateral spikes in TLE.

Patients and methods

The 19 patients selected for this study underwent surgery between 1990 and 2000. A sleep record was performed in all of them during the presurgical monitoring. All had at minimum 2 years and in average 4.6 (2–10) years follow up. Unilateral temporal lobe surgery (standard or tailored resection) was performed on the basis of seizure semiology, high-resolution MRI studies and seizure detection by video-EEG monitoring. In certain patients registration with foramen ovale electrodes or ictal SPECT helped the surgical decision. All patients had unilateral temporal seizure onset zone, and some of them, unilateral pathology (Table 1). In most (15/19) patients, ictal EEG spread to the contralateral side during presurgical evaluation. All the patients had “lateralised seizure termination”,²⁰ no sustained seizure activity was observed on the contralateral side following ipsilateral termination of the ictal pattern. Before surgery independent bilateral anterior temporal epileptiform discharges were registered in wakefulness or sleep in all of them. The bilateral independent discharges were repeatedly observed in different unrelated records of the patients independently from the presence or absence of a previous seizure. Inclusion criteria for “bilateral independent discharges” were independent spiking over the side contralateral to surgical intervention in a rate not less than 2:10. To investigate interictal epileptiform discharges over the temporal lobe contralateral to surgery, 24 h portable 12 channel EEG recording was performed minimum two, in average 4.6 (2–10) years after surgery, covering both temporal regions by minimum three electrodes on each sides (F7-8, T3-4, T5-6). Results of sleep records were compared with the long-term results of the surgical intervention. Seizure outcome was measured in terms of the Engel categorization:²¹ “Seizure free” Engel class I, “improved” Engel class II and III, and not improved Engel IV. At the time of the postoperative EEG recording 13 (68.5%) of the patients were seizure

Table 1 Clinical data of patients

Patients	Age of onset (years)	Seizure type(s)	Side of operation	Aetiology	Seizure outcome	Psychopathology	
						Presurgical	Postsurgical
BI	24	CP	Left	Without known pathology	Engel I		
CM	24	CP, GM	Right	UHS	Engel II-III	+	+
DKA	12	CP	Right	UHS	Engel Ia		
GyM	33	CP, GM	Right	UHS	Engel II-III		
KZ	13	CP, GM	Left	UHS	Engel Ia		
KM	2.5	CP, GM	Right	UHS	Engel I		
KMn	23	CP, GM	Right	TU	Engel II-III		
KT	24	CP, GM	Right	UHS	Engel I		
LV	17	CP	Right	TU	Engel Ia		
MG	46	CP	Right	CAV	Engel Ia		
SG	9	CP, GM	Left	CAV	Engel I		
SL	22	CP, GM	Right	LES	Engel I		
SSZ	8	CP, GM	Left	UHS	Engel Ia		
SZI	9 months	CP	Right	TU	Engel I		
TZ	27	CP, GM	Left	TU	Engel IV	+	++
TL	8	CP, GM	Left	MR norm	Engel IV	+	++
VA	15	CP, GM	Left	MR norm	Engel IV	+	++
VKA	8	CP, GM	Left	HIMAL ^a	Engel Ia		
VI	12	CP, GM	Right	UHS	Engel Ia		

CP: complex partial; GM: generalized tonic-clonic; UHS: unilateral hippocampal sclerosis; HIMAL: hippocampal malrotation; TU: tumour; CAV: cavernoma; LES: posttraumatic lesion; +: psychiatric co-morbidity; ++: psychosis; MR norm: no MR abnormality.

^a Hippocampal malrotation is a minor developmental abnormality of the hippocampal formation, not necessarily associated with epilepsy.

free, three (15.75%) improved and three (15.75%) did not improve. Three of our patients showed single or repeated psychotic episodes not seen before surgery. The patient's data are shown in Table 1.

Results

From the 19 patients involved in the study both ipsi- and contralateral discharges disappeared in seven, only ipsilateral discharges were present in five, only contralateral in three and the independent bilateral spiking persisted in four. The correlation of seizure

outcome and the late postoperative discharge pattern during sleep is shown in Tables 2 and 3.

All 12 patients who had no contralateral discharges postoperatively became seizure free after surgery, among them seven patients belongs to Engel Ia group. Among those seven patients in whom contralateral discharges persisted, either as pure contralateral or as bilateral independent discharges, only one seizure free patient was found. Three of them showed improvement while three did not improve. From the improved group only one patient had postoperative seizure recording, which showed the same seizure onset as during

Table 2 Correlation between seizure outcome and postoperative spiking pattern

Postoperative spikes	Seizure free (Engel I)	Improved (Engel II-III)	Not improved (Engel IV)	Sum
No spike	7	—	—	7
Ipsilateral spikes	5	—	—	5
Contralateral spikes	1	2	—	3
Independent bilateral spikes	—	1	3	4
Sum	13	3	3	19

Table 3 Correlation between seizure outcome and persistence of contralateral spiking

	Seizure free	Not seizure free	Sum
Contralateral spikes disappeared	12	—	12
Persistence of contralateral spikes	1	6	7
Sum	13	6	19

Fisher’s exact test: $P < 0.0001$.

the presurgical workup. In the seizing group all the three not improved patients had persisting bilateral discharges. From the four patients who did not show contralateral seizure spread three belonged to the seizure and spike free group and one patient to the not improved group with persisting bilateral spikes (Fig. 1). The association of postoperative contralateral spikes with non-seizure free outcome was highly significant ($P < 0.0001$) measured by Fisher’s exact test.

Comparing the waking and the sleep record part of our 24 h records (Table 4), sleep records were more sensitive for revealing persisting contralateral spikes. From the six seizing patients, all active during sleep, only two showed contralateral spikes in wake state.

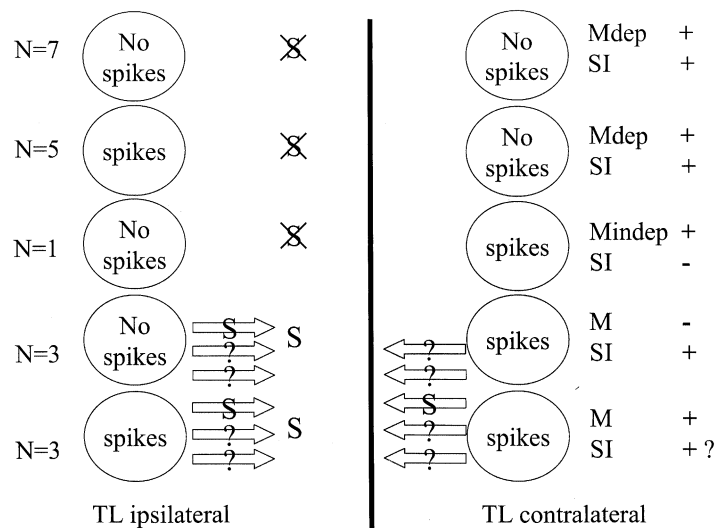
To look for the effect of other factors may influence seizure outcome and spike lateralisation, we analysed the relationship between aetiological

Table 4 Correlation between spiking in awake state versus in sleep and seizure outcome

	No contralateral spikes		Contralateral spikes	
	In awake state	In sleep	In awake state	In sleep
Seizure free	12	12	1	1
Not seizure free	4	—	2	6

factors, seizure outcome and the laterality pattern of spiking. Unilateral hippocampal sclerosis (UHS) was the most frequent pathology found in eight patients. Further eight patients had other unilateral pathology as alien tissue or different kind of lesions (see Table 1). Three patients were without any detectable pathology. From the 16 patients with unilateral pathology 11 remained seizure free and their contralateral spikes disappeared, while from the three patients without any detectable pathology only one was seizure and contralateral spike free, and in two the seizures and contralateral spikes persisted (Table 5). The association between good seizure outcome, disappearance of contralateral spikes and the existence of unilateral pathology before surgery was significant ($P < 0.05$) measured by Fisher’s exact test.

All three patients who did not improve and their bilateral independent spiking persisted had psychiatric complications. These patients had personality



S = seizure, TL = temporal lobe, arrows = indicates the possible or actual side of seizure start of seizures persisting after surgery M = Morell hypothesis fulfilled. Mdep = Morrell type dependent mirror-focus hypothesis fulfilled, Mindep = Morrell type independent mirror-focus hypothesis fulfilled, SI+ = seizure induced hypothesis fulfilled, SI- = seizure induced hypothesis not fulfilled

Figure 1 A schematic overview of the laterality pattern in spiking compared to the seizure status in our patients. Fitting to the predictions of the existing secondary epileptogenesis hypotheses is also indicated.

Table 5 Correlation between aetiology and postsurgical spiking pattern

	UHS + alien tissue or lesion	Without detectable pathology	Sum
No contralateral spikes and seizure free	11	1	12
Persistence of contralateral spikes and not seizure free	5	2	7
Sum	16	3	19

Fisher's exact test: $P < 0.05$.

disorders before, and recurrent psychotic bouts after surgery. Only one of the three (TL) has been re-evaluated by video-EEG up to now. The post-operative seizure detection showed seizures starting from both hemispheres with clearly different seizure semiology, while during the preoperative evaluation seizures were started strictly from the operated side (Fig. 1). Therefore in this case both the unimproved ipsilateral and the contralateral seizures contributed to the unfavourable postoperative state.

Discussion

Seizure outcome and contralateral pre- and post-operative spiking

Fifteen of our 19 patients had contralateral seizure spread and all of them had bilateral independent interictal spiking. Both phenomena had been connected with unfavourable seizure outcome.^{1,2,22} However, there are reports about 50–77% seizure free outcome.^{3,4} Our 78% seizure free rate is congruent with the results of Holmes et al.⁴

The main finding of our study is that the post-operative persistence of contralateral spiking in sleep was significantly associated with poor seizure outcome after surgical intervention in TLE patients with preoperatively independent bitemporal spikes. Conversely in those patients who became seizure free after the operation the bilateral spiking disappeared or in a smaller group only ipsilateral discharges persisted.

Our findings emphasize that contralateral spiking in patients without MRI lesion may indicate the involvement of the contralateral side in ictogenesis even among cases where presurgical evaluation showed ipsilateral seizure origin. In this constellation more prolonged video-monitoring is recommended to rule out the possibility of bilateral independent seizure origin and avoid the bias of the cluster effect.²³

The lateralising value of sleep recording was demonstrated in the work of Mallow.⁵ In this study the predicting value of sleep records forecasting the seizure outcome after 1 year of surgery was studied in a small sample. Bilateral discharges recorded in sleep were associated with unfavourable outcome compared with those in whom spiking were strictly unilateral. The laterality of spiking recorded at a latter time when seizure outcome could be measured more reasonably, was not studied hither to.

The association of the persistence of postoperative bilateral spiking and the most unfavourable seizure outcome needs further comments. This suggests that seizure persistence is most likely in patients whom both temporal lobes emanates interictal spikes long time after surgery and the pathological co-operation between the two temporal lobes could be assumed.

The involvement of both temporal lobes might play an important role underlying the co-morbidity in psychopathology as well. This was also demonstrated in other studies.²⁴ As it was shown all three patients who had bilateral spiking on the postoperative sleep EEG had both persisting seizures after surgery and psychotic episodes not seen before surgery. It is congruent with the findings pointing to correlation between persisting seizures and unfavourable psychiatric outcome.²⁵ In this regard it should be mentioned that all this three patients had severe personality disorders already before surgery and probably this contributed to the 'de novo' exploding psychotic behaviour episodes after surgery. However, the small number of patients limits considerably our conclusions.

On the other hand, taking into consideration the aetiological factors of our patients the question of bilateral involvement could be seen from another viewpoint. The presence of unilateral HS or other temporal pathology has a well-known effect both on the seizure outcome and on the laterality of discharges.^{1,2} In our material the distribution of the seizure free and not free patients according to the presence or absence unilateral pathology

was the same compared to the distribution of patients with persistence or lack of contralateral spiking. Therefore we can say that in the seizure and contralateral spike free patients the resected unilateral pathology is the underlying factor of the good prognosis and the epileptogenesis is essentially limited to one side, while in the group with persistent seizures the lack of underlying unilateral pathology determines the worse outcome and the bilaterality of the epileptogenic process. These conclusions are congruent with the reports of larger populations.^{26,27}

Secondary contralateral spike- and seizure genesis

In most (15/19) patients seizures spread to the contralateral side during presurgical evaluation. This seems to be congruent with the hypothesis originating the contralateral spiking from the contralateral seizure spread,¹⁷ however, it argues against the universal validity of this hypothesis. After surgery the contralateral spikes disappeared in those patients who became seizure free and persisted parallel with the unfavourable seizure outcome. The disappearance of the contralateral discharges after surgery shows that in 13 patients the resected side exerted influence on the contralateral side before surgery, and argues against the independent origin of their bilateral spiking.

Analysing our results in terms of the "seizure induced" hypothesis of Janszky et al.¹⁷ (contralateral spikes stem from contralateral seizure spread), both the situation when in the seizure free patients no spikes or only ipsilateral spikes persist is congruent with it, because in these cases after the excision of the inducing side the contralateral spikes disappeared. Thinking according to the Morrell-model, patients who became seizure free and their contralateral discharges disappeared may belong to the so called dependent contralateral (assumed mirror) focus group of Morrell in which contralateral discharges disappear after the excision of the primary focus.

In one patient without seizures and still existing contralateral discharges the Morrell hypothesis would be fulfilled only if we would suppose a stadium of evolution with independent contralateral spikes, but still without secondary seizures. This constellation is not congruent with the "seizure induced" hypothesis since the contralateral discharges persist in the absence of the inducing ipsilateral seizures.

In all the other constellations of the spike laterality pattern when seizures persist it is difficult to

judge the validity of either hypotheses without the knowledge from which temporal lobe the postoperative seizures come.

From the patients with continuing seizures in improved state having only contralateral spikes in one of them we have a postoperative seizure record during sleep from the original (operated) side. In this case the "seizure induced" hypothesis is valid, but the Morrell type secondary epileptogenesis would predict seizures from the contralateral side, which is not the case. Concerning the other two patients we do not know from which side the postoperative seizures come.

From the three patients with remaining bilateral spikes in one video-EEG recorded postoperatively both ipsi- and contralateral seizures, in two of them the postoperative seizure onset is unknown.

Therefore our data could be interpreted as they are in the majority of the investigated conditions not contradictory either to the "seizure induced" or to the Morrell hypothesis, but provide not complete proof of either of them.

In the Morrell model hexobarbital sleep test was developed to reveal the dependence or independence of the mirror focus.¹⁰ In the present work, natural sleep proved to be similarly useful, or at least more sensitive compared to the wake activity in this regard.

Taking into consideration other data, the disappearance of the contralateral hypometabolism after successful temporal lobe surgery^{28,29} is an argument in favour of the "seizure induced" hypothesis. The presence of a chemical transformation in the region of the contralateral spikes showed by MR spectroscopy³⁰ and the transformation in the protein structure showed by experimental works of Morrell³¹ on the other hand assumes more fundamental changes behind spiking of the contralateral side.

These data provide some evidence that essentially not the secondary epileptogenesis but the nature (and aetiology) of the primary epileptogenic lesion is what determines the uni- or bilaterality of the symptoms in TLE.

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