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FULL-LENGTH ORIGINAL RESEARCH

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Unilateral temporal interictal epileptiform discharges correctly predict the epileptogenic zone in lesional temporal lobe epilepsy

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Summary

Objective: To evaluate the necessity of recording ictal electroencephalography (EEG) in patients with temporal lobe epilepsy (TLE) considered for resective surgery who have unilateral temporal interictal epileptiform discharges (IEDs) and concordant ipsitemporal magnetic resonance imaging (MRI) pathology. To calculate the necessary number of recorded EEG seizure patterns (ESPs) to achieve adequate lateralization probability.

Methods: In a retrospective analysis, the localization and lateralization of interictal and ictal EEG of 304 patients with lesional TLE were analyzed. The probability of further contralateral ESPs was calculated based on a total of 1967 recorded ESPs, using Bayes' theorem.

Results: Two hundred seventy-one patients had unilateral TLE, and in 98% of them (265 of 271), IEDs were recorded during video-EEG monitoring. Purely unilateral temporal IEDs were present in 61% (166 of 271 patients). Ipsilateral temporal MRI pathology was found in 83% (138 of 166). Ictal EEG was concordant with the clinical side of TLE in 99% (136 of 138) of these patients. Two patients had discordant ictal EEG with both ipsilateral and contralateral ESPs. Epilepsy surgery with resection in the lesioned temporal lobe was still performed, and both patients remain seizure-free. Probability calculations demonstrate that at least 6 recorded unilateral ESPs result in a >95% probability for a concordance of >0.9 of any further ESPs.

Significance: The combination of purely unilateral temporal IED with ipsitemporal MRI pathology is sufficient to identify the epileptogenic zone, and the recording of ictal ESP did not add any surgically relevant information in these 138 patients. Rarely, discordant ESPs might be recorded, but the surgical outcome remains excellent after surgery on the lesioned side.

KEYWORDS

epilepsy surgery, ictal EEG, interictal EEG, MRI, predictive value, seizure pattern

1 | INTRODUCTION

Temporal lobe epilepsy (TLE) is one of the most common focal epilepsy syndromes, most patients are medically refractory[1] and epilepsy surgery is superior to drug therapy in these patients.[2–5] The presurgical evaluation aims at identifying the epileptogenic zone, using neuroimaging studies and long-term electroencephalography (EEG)–video monitoring (EVM), including semiology analysis and analysis of interictal and ictal EEG

Vollmar and Stred contributed equally to the manuscript.

patterns.[6] EVM typically lasts several days to record habitual seizures, which may be more violent, because antiepileptic drugs are typically tapered. Seizures during EVM may be associated with complications,[7] and this procedure is costly and time-consuming.

We therefore investigated whether ictal EEG yields new localizing information in patients who have unilateral temporal pathology on magnetic resonance imaging (MRI) and concordant purely ipsilateral temporal interictal epileptiform discharges (IED). We also determined which number of seizures with unilateral EEG seizure patterns (ESPs) needs to be recorded to ensure a high probability of concordant further ESPs.

Key Points

- Almost half of the temporal lobe epilepsy candidates for resective surgery have purely unilateral temporal spikes and a concordant MRI lesion
- In these patients, the combination of interictal EEG and MRI is sufficient to identify the epileptogenic zone
- The additional recording of ictal EEG did not yield any surgically relevant information
- In selected patients with temporal lobe epilepsy, ictal EEG recordings are not mandatory to proceed to resective surgery

2 | METHODS

We searched the database of the epilepsy monitoring unit of the University of Munich during the period between 1991 and 2005, for patients with medically refractory lesional TLE. Three hundred four patients with lesional TLE underwent presurgical EVM and were included, independent of whether surgery was eventually performed. The clinical classification of TLE and its lateralization was attained in an interdisciplinary patient management conference, based on the conclusive interpretation of all available clinical, EEG, and neuroimaging examinations. All data were reviewed and discussed by a panel of epileptologists, neurosurgeons, neuroradiologists, and neuropsychologists.

To investigate the question whether ESPs recorded during EVM add relevant new localizing information, we analyzed only the 275 patients classified as unilateral TLE (128 right TLE, 147 left TLE). The 29 patients classified as bilateral TLE were excluded. Four additional patients were also excluded due to missing ESP (n = 1) or MRI (n = 3), resulting in 271 included patients.

To address the question, how many seizures are needed to assume concordant further ESPs, 29 of the 304 TLE patients were excluded due to missing ESP (n = 3), only one recorded ESP (n = 20) or only nonlateralized ESPs (n = 6). Data from the remaining 275 patients with a total of 1967 recorded ESPs were used for further calculations.

This study complies with the rules for retrospective data analysis of anonymized patient data.

2.1 | EEG-video monitoring

All 304 patients underwent between 2 and 18 days of continuous noninvasive EVM with scalp electrodes using the international 10-10 electrode system[8] with 32-64 channel EEG machines (Vanguard, Cleveland, OH, USA). The duration of EEG recording ranged from 31 to 395 hours. The EEG data were evaluated in daily monitoring conferences. At least 2 observers had to agree on the classification and localization of the EEG findings. The whole EEG recording was reviewed by trained EEG technicians to identify IEDs. The localization of all IEDs was defined, and the relative frequency of IEDs at each location was calculated from periodically sampled EEG segments of 1-10 minutes per hour, during wakefulness and sleep, for the entire duration of the EVM recording. Patients were classified as having purely unilateral IED if 100% of their IEDs were unilateral and no contralateral, nonlateralized, or generalized IED were recorded.

A total of 39 patients were subsequently evaluated with semi-invasive and invasive electrodes (9 foramen ovale or epidural electrodes, 23 subdural grid and/or strip electrodes, 7 depth electrodes). The results of these invasive EVM also contributed to the final clinical classification of the epilepsy syndrome and lateralization in the patient management conference.

2.2 | MRI examination

All patients underwent cranial MRI with an epilepsy-optimized protocol. Each MRI included axial, coronal, and sagittal planes of T1-weighted, T2-weighted, and fluid-attenuated inversion recovery (FLAIR) images with a slice thickness of not more than 5 mm (1.0/1.5 Tesla Impact/Vision/Symphony; Siemens, Erlanagen, Germany). Additional coronal 3-mm T1, T2, and FLAIR images perpendicular to the long axis of the hippocampus and a high-resolution T1-weighted gradient echo sequence with an in-plane resolution and slice thickness of 1 mm were also acquired. Contrast medium was used only if inflammation or a tumor were suspected.[6]

2.3 | Additional examinations during the presurgical evaluation

All patients underwent a comprehensive presurgical evaluation and additional investigations were performed, such as

ictal single-photon emission computed tomography (SPECT; n = 191), interictal fluorodeoxyglucose–positron emission tomography (FDG-PET; n = 184), analysis of seizure semiology (n = 301), and neuropsychological testing (n = 137), in different combinations. Data from all these diagnostic modalities were routinely evaluated and could contribute to the clinical classification of TLE or lateralization of the epileptogenic zone, for example, by showing interictal temporal lobe hypometabolism. For the purpose of this study, though, only the diagnostic reliability of concordant MRI and IEDs was evaluated, independent of all other investigations.

2.4 | Statistical analysis

The correlation between purely unilateral IED and purely unilateral ictal EEG (100% vs <100%) was formally tested with the chi-square test, assuming statistical significance at $P < .01$.

For the analysis addressing the minimum number of ipsilateral ESPs needed to assume further concordant ESPs with a robust statistical certainty, a Bayesian analysis was performed based on a previous study.[9] Details are explained in Appendix S1. In short, the known distribution of concordant and discordant ESPs (Appendix S2: Table S1) was used to calculate the odds of recording discordant ESPs after a certain number of unilateral ESPs in this population.

3 | RESULTS

Two hundred seventy-one of 304 patients with medically refractory TLE undergoing EVM in preparation for epilepsy surgery had unilateral TLE and were included in the study. In 97.8% (265 of 271) of these patients, IEDs were recorded.

Purely unilateral temporal IEDs were present in 61.2% (166 of 271) of the patients, and in all of them, the side was concordant with the clinical classification. Ipsitemporal MRI pathology was found in 83.1% (138 of 166) of these patients. The most frequent MRI reported pathology was hippocampal sclerosis (44%); another 8% showed hippocampal atrophy without signal alteration, and 2% showed hippocampal T2 signal increase without volume loss. Other pathologies included neoplasia (22%), posttraumatic or postischemic defects (11%), vascular malformations (6%), and cortical dysplasia (1%). Some lesions could not be definitely classified in MRI (6%). In 98.6% (136 of 138) of these fully concordant patients, ictal EEG showed purely ipsilateral ESPs on the side of lesion. Only 2 of 138 patients (1.4%) had discordant ictal EEG and showed alternating ipsilateral and contralateral ESPs. Both patients had resective surgery ipsilateral and both remain seizure-free. Histopathology showed a pilocytic astrocytoma in one patient and an angioma in the other. In this group, there were no patients with only contralateral ESPs on ictal EEG, which would point to a contralateral epileptogenic zone. The identification of the epileptogenic zone through the combination of purely unilateral IEDs and ipsitemporal MRI pathology was excellent, with no clinically discordant patient found in our series ($P < .0001$).

In the remaining 99 patients (38.8%) additional, discordant IEDs were recorded. Most of those were contralateral temporal IEDs (99%), with only very few frontal IEDs (1%). The percentage of contralateral IEDs ranged from 1% to 93%, with an average of 27%; only 17 of 99 patients had the majority of IEDs contralaterally. A higher percentage of contralateral IEDs was associated with a higher chance of contralateral ESPs (Figure 1). There were no specific pathologic or clinical features associated with the occurrence of contralateral IEDs.

To address the question of how many unilateral ESPs need to be recorded during EVM to predict concordance of subsequent ESPs with adequate statistical probability, 275 patients with at least 2 recorded ESPs (range 2-58, total of 1967 ESPs) were included. When 6 unilateral ESPs are recorded, the probability of recording only additional

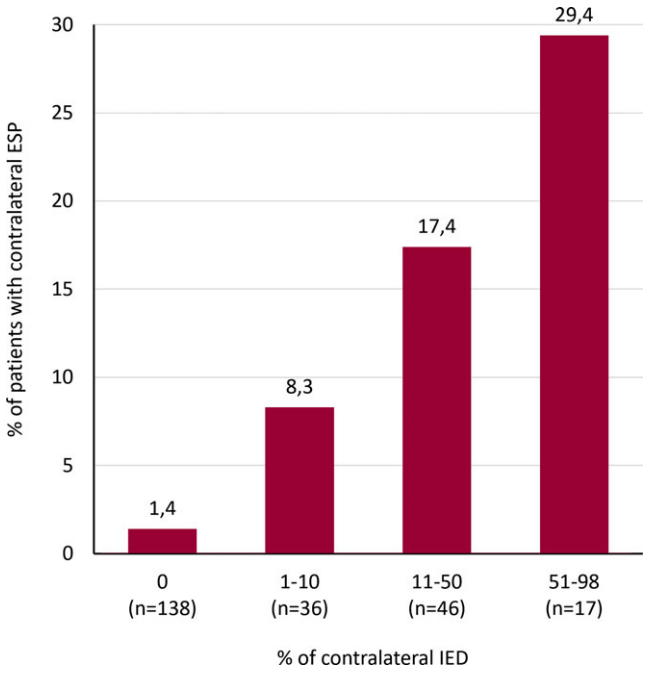

FIGURE 1 A higher percentage of contralateral IEDs (cIEDs) was correlated with a higher percentage of patients who also had contralateral ESPs (cESPs): in the main group with purely unilateral IED ("0") only 1.4% had cESPs. From the patients with 1%-10% cIEDs, 8.3% also showed cESPs, from those with 11%-50% cIEDs 17.4%, and from those with more than 50% cIEDs 29.4% also had cESPs

ipsilateral ESPs in subsequent EVM is 95.3% (bold figure in Appendix S2: Table S2), for a minimal concordance rate of 0.9. The occurrence of discordant ESPs increases the number of required EPS to achieve the same probability of further concordance: In case one discordant ESP is recorded, a total of 11 recorded ESPs are needed to achieve a concordance level of 0.9 with >95% probability.

4 | DISCUSSION

In the presurgical evaluation of patients with medically refractory TLE, a combination of purely unilateral temporal IEDs and concordant ipsilateral MRI lesion could correctly identify the epileptogenic zone in all 138 patients. This implies that the recording of seizures during EVM may not be necessary to proceed to resective surgery. We found only 2 patients (1.4%, 2/138) in our series with additional contralateral ESPs on ictal EEG. Both patients showed a clear ipsilateral temporal pathology on MRI and underwent resective epilepsy surgery on the side of the lesion and remain seizure-free. We suggest that these additional contralateral ESPs reflected fast propagation to the contralateral side, rather than independent contralateral onset, and therefore did not change the decision to proceed with resective surgery.

A high predictive value of unilateral IEDs in TLE associated with a favorable postsurgical outcome was described early on[10,11] and has subsequently been replicated in both lesional[12,13] and nonlesional[14–16] TLE patients.

Previous studies in patients with TLE and hippocampal sclerosis have shown that occasional discordant ESPs on ictal EEG are frequently recorded, but do not affect the odds of good postsurgical outcome.[12,17] The finding of ESPs arising predominantly or exclusively contralateral to the MRI lesion is rare and was not seen in our series. This has been described in the literature for 3 patients with gross focal lesions[18] and also for 5 patients with severe "burned out" HS.[19] In these patients, most likely, the lack of ipsilateral tissue volume prevents the generation of ESPs with a sufficient voltage initially, and the ESP is detected only in scalp EEG after propagation to the contralateral side, where more tissue can be involved. For all these patients, subsequent intracranial EEG could confirm seizure onset ipsilateral to the side of the MRI lesion[18,19] and seizure-free outcome after resection of the epileptogenic lesion confirmed the misleading lateralization of scalp ESPs. One study directly compared the predictive value of IEDs and ESPs and showed that concordance between side of the MRI lesion and interictal IEDs was a stronger predictor of good postsurgical outcome than the concordance between side of the MRI lesion and ESPs.[20]

These studies show, and our data confirms, that the relative contribution of recorded ESPs must be interpreted in the context of all clinical data, that ESPs can be discordant[21] and that the lateralization of recorded ESPs might not have an impact on the surgical management of some patients. Consequently, it may not be mandatory to record seizures in TLE patients with unilateral temporal IED and concordant MRI lesion.

Our finding in TLE patients with different pathologies supports the result of previous studies in patients with concordant hippocampal atrophy and ipsilateral IEDs that ictal EEG is not mandatory.[22,23] A considerable proportion of patients with TLE who undergo presurgical evaluation fulfill these criteria: 45.3% in our study, similar to 44.6% in a previous study looking at 184 patients with TLE.[23] For these patients, the potential harm through EVM,[7] its burden for the patient, and its associated effort and costs should be weighed against the potential additional diagnostic benefit.

Obviously, EVM provides much more information than just recording ESPs.[24,25] It allows a detailed assessment of the seizure semiology, the identification of additional nonepileptic seizures, and the recording and classification of multiple IEDs, and also ensures that all available data are thoroughly assessed by highly experienced staff in a specialized epilepsy center. A full EVM evaluation is therefore still recommended for all TLE patients if this is readily available. In this case, our results are relevant for up to 30% of patients[24–26] who may not have seizures during the limited time of their EVM admission, or where the recorded ESPs are artifact obscured or inconclusive. For them, the EVM admission might not have to be prolonged or repeated with the aim of recording a seizure and ESP. In resource-limited countries with restricted or no access to EVM, on the other hand, sufficient diagnostic confidence to proceed to epilepsy surgery might also be achieved through consistent clinical and neuroimaging data and repeated ambulatory EEG recordings analyzed by experienced epileptologists. If used with caution, this could facilitate access[27] and shorten the time to resective surgery for selected patients with unilateral temporal IEDs and concordant ipsilateral temporal lesion in neuroimaging.

For all patients in our study, multiple IEDs were recorded during several days of presurgical EVM. Our study does not address the question of how many IEDs are needed to safely assume "purely unilateral IEDs" and which duration or EEG recording is required to achieve this. We are not aware of any other study directly addressing this issue. Previous studies on IED lateralization did not report the total number of spikes that were analyzed and they were based on heterogeneous data. Some lateralized IEDs from just 1 hour of archived EEG recording[11] or from a few days of EVM admissions[10,12,22] and, more recently, a prospective study were based on at least 10 routine outpatient EEG recordings.[28] Approaches such as overnight sleep EEG[29] or 24-hour EEG recording[30] were

shown to increase the yield in relation to routine EEG, but also showed diminishing returns after 18 hours of EEG.[30] One study showed good concordance between IED lateralization in routine EEG and during EVM.[31] Based on this evidence, the minimum duration of EEG recording for reliable IED lateralization seems to be somewhere between a few routine EEG studies and 24 hours. Further studies are warranted to systematically address this question.

Similarly, the question of how many seizures should be recorded during an EVM admission is also not conclusively answered. Our statistical model of the patient population showed that 6 concordant ESPs are needed to predict with more than 95% probability that further recorded ESPs would also be at least 90% concordant. These data are in line with those of previous studies, concluding that 5 concordant ESPs are sufficient to predict unilaterality of further ESP in patients with nonlesional TLE,[9] or to rule out multifocal seizures.[32] However, after occurrence of one discordant ESP, both our and Blum's statistical model require a number of 11 ESPs to achieve the same probability of further concordance again. The recording of 11 seizures is certainly not easily achieved during a typical EVM admission, but any number below that would leave a higher uncertainty about the lateralization of the next potential ESP. Another study showed that due to seizure clustering, the first contralateral ESP may be recorded only as late as by the 13th seizure.[33] The fact, that a high reliability of concordant ESP lateralization can be difficult to achieve, even during a prolonged EVM admission, adds to the argument to put the relevance of recorded ESPs into the correct perspective if there is sufficient strong evidence on the epileptic zone from other diagnostic methods.

In conclusion, the recording of ictal ESPs did not yield new surgery-relevant lateralizing information in patients with purely unilateral temporal IEDs and concordant ipsilateral MRI lesion in our study. If EVM is not readily available, or in case no seizures are recorded during the EVM evaluation, epilepsy surgery is still an option, even without recorded ESPs.

DISCLOSURE OF CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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