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Lateralizing Value of Interictal Spikes on Overnight Sleep-EEG Studies in Temporal Lobe Epilepsy

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Summary: *Purpose:* To determine the lateralizing value of interictal epileptiform discharges (IEDs) recorded during overnight sleep-EEG studies in temporal lobe epilepsy. Because IEDs are more prevalent in non–rapid eye movement (NREM) sleep than in wakefulness, overnight sleep-EEG recordings may contribute additional lateralizing information to the epilepsy surgery evaluation beyond daytime EEGs.

Methods: Twenty-four subjects with medically refractory temporal lobe epilepsy underwent continuous overnight sleep-EEG recordings. Subjects were seizure free ≥24 h before study and receiving stable doses of medication. The IED foci recorded on overnight studies were compared with daytime EEGs, interictal samples, and ictal recordings during long-term monitoring, brain magnetic resonance images (MRIs), and surgical outcome.

Results: (a) In all 24 subjects, including 13 without IEDs on daytime EEGs, temporal IEDs were present during NREM sleep and were exclusively or predominantly (>95%) unilateral in 15 and bitemporal in nine. (b) Unilateral NREM IEDs were concordant with surface or depth ictal-onset regions in 14 subjects, even if MRIs were normal (three subjects) or surface ictal-onset regions were bilateral (five subjects). Eleven of 12 subjects with unilateral concordant NREM IEDs who have undergone surgery are seizure free. (c) Bitemporal IEDs were associated with postoperative seizures in all subjects with normal MRIs or widespread MRI abnormalities. However, all subjects with bitemporal IEDs and MRI hippocampal abnormalities concordant with ictal-onset regions had good to excellent surgical outcomes.

Conclusions: When combined with other investigations, IEDs recorded on overnight studies add prognostic data to the epilepsy surgery evaluation not provided by daytime EEGs.
Key Words: Sleep—Epilepsy—Electroencephalography—Interictal epileptiform discharges—Surgery.

The activating effect of sleep on electroencephalographic (EEG) activity in epilepsy has been established for >50 years (1). Non–rapid eye movement (NREM) sleep increases interictal epileptiform discharges (IEDs) in partial epilepsy (2,3). In contrast, IEDs are relatively suppressed during rapid eye movement (REM) sleep. The activating role of NREM sleep on epileptic cortex has been attributed to increased neuronal synchronization within thalamocortical projection neurons, resulting from the neurochemical and neurophysiologic processes that initiate and maintain NREM sleep (4).

Although the usefulness of sleep-EEG recordings for the diagnosis of epilepsy is well established (5), few studies have examined the lateralizing value of IEDs recorded during overnight sleep. Daytime EEGs often contain drowsiness and may include NREM stage 2 sleep but rarely contain delta (NREM stages 3 and 4) or REM sleep. In comparison, NREM stage 2 sleep, delta NREM sleep, and REM sleep are routinely recorded on overnight continuous sleep-EEG recordings. Sammaritano and colleagues (3) found that IEDs were more frequent in delta NREM sleep and that NREM sleep extended and REM sleep restricted the IED field in subjects with temporal lobe epilepsy. By using log delta power to measure sleep depth in subjects with partial epilepsy Malow and co-workers (6) showed that the rate of IEDs increased in delta sleep and in deepening NREM sleep. Overnight continuous sleep-EEG studies, therefore, may provide useful information about IED foci that are not provided by daytime EEGs because (a) the IEDs are more likely to be recorded on overnight sleep-EEG studies than on daytime EEGs, and (b) the field of IED foci may be modu-

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lated by NREM and REM sleep (e.g., become independent bitemporal in NREM sleep and unilateral temporal in REM sleep).

Several investigators reported that IEDs have prognostic significance in the epilepsy surgery evaluation, especially when combined with other investigations such as brain magnetic resonance imaging (MRI). Although the majority of epilepsy centers require ictal recordings for all surgical candidates (7), some centers perform surgery on a subset of subjects without requiring long-term monitoring (LTM), provided that interictal EEGs demonstrate consistent, strictly unilateral, anterior–midtemporal epileptiform foci and that other imaging and functional tests are not discordant (8). The IEDs recorded on overnight continuous sleep-EEG recordings, in combination with other studies, have the potential to provide prognostic information in presurgical candidates and may help identify a subset of patients in whom costly and prolonged inpatient video-EEG surface or invasive intracranial monitoring may be minimized. We compared the IED foci recorded on overnight continuous sleep-EEG studies with those from daytime EEGs, interictal samples obtained during LTM, ictal recordings, brain MRIs, and surgical outcome in 24 subjects with medically refractory temporal lobe epilepsy to answer the following questions: (a) Do overnight continuous sleep-EEG recordings yield additional information about IEDs to daytime EEGs or interictal samples obtained during LTM? (b) How often are temporal IEDs recorded during NREM or REM sleep, and how common are unilateral versus independent bitemporal NREM or REM IEDs? (c) How well do unilateral or independent bitemporal sleep IEDs predict a unilateral ictal-onset region and surgical success when combined with information from other presurgical investigations?

METHODS

Subjects

Subjects 1, 2, and 10 (Table 1) were part of a pilot study to demonstrate the relation between IEDs and the depth of sleep, as measured by log delta power (6). From December 1995 to February 1997, all subjects who had complex partial seizures of temporal lobe origin (9) with or without secondary generalization during LTM and who met study criteria were approached to participate in the study. Twenty-one subjects or 57% of those eligible agreed to participate for a total of 24 participants when combined with the three subjects from the pilot study. Participants met the following criteria: age, 18–65 years; ability to give informed consent; a history of recurrent unprovoked focal seizures; ictal semiology and LTM

TABLE 1. *Subject characteristics*

Pt no.	Age/sex	NREM sleep-EEG IEDs[a]	REM sleep-EEG IEDs[a]	Daytime EEG IEDs	Interictal IED samples[b]	Ictal onsets	Brain MRI	Pathology	Outcome[c]
1	33F	LT	None	None	LT	LT (scalp)	L mts	Hip scler.	Sz free
2	43M	LT	None	None	LT	LT (scalp)	L mts	Hip. scler.	Sz free
3	52M	LT	LT	LT	LT	LT (scalp)	LT/LF glioma	Oligo.	Sz free
4	38M	LT	LT	LT	LT	LT (scalp)	L cav. angioma	Same	Sz free
5	20F	LT > RT	None	LT	LT	LT (scalp)	LT glioma	Gliosis	Sz free
6	25M	LT	None	None	None	LT (scalp)	L mts	Hip. scler.	Sz free
7	38F	LT	None	None	None	LT (scalp)	LT atrophy	Hip. scler.	Postop sz
8	32M	LT	LT	LT	LT	LT (scalp)	L mts	NA	Declined surg.
9	54F	RT	RT	RT	Bilat. temp.	80% RT (depth)	R hip. atrophy	Hip. scler.	Sz free
10	46M	LT	None	None	LT	77% LT (depth)	LT atrophy	WM gliosis	Sz free
11	47M	LT	None	LT	LT	LT (depth)	Normal	Min. neur. loss	Sz free
12	45M	LT	None	LT	None	LT (depth)	Normal	Hip. scler.	Sz free
13	20M	LT	LT	LT	Bilat. temp.	LT (depth)	Normal	Not avail.	Sz free
14	35M	Bilat. temp.	LT	None	Bilat. temp.	RT (scalp)	Normal	Min. neur. loss	Postop sz
15	39F	Bilat. temp.	None	None	Bilat. temp.	LT (depth)	Normal	Not avail.	Postop sz
16	39F	Bilat. temp.	None	Bilat. temp.	Bilat. temp.	LT (depth)	Normal	Hip. scler.	Postop sz
17	24M	Bilat. temp.	None	RT	RT	Bilat (depth)	RT enceph.	Hip. scler.	Postop. sz; sud
18	34F	LT	None	None	LT	LT (scalp)	Bilat. mts	Hip scler.	Postop. sz
19	21F	Bilat. temp.	None	None	RT	RT (scalp)	R mts	Hip. scler.	Sz free
20	44F	Bilat. temp.	None	None	Bilat. temp.	RT (scalp)	R hip. atrophy	Min. neur. loss	Sz free
21	18M	Bilat. temp.	Bilat. temp.	Bilat. temp.	Bilat. temp.	LT (depth)	L mts	Hip. scler.	Sz free
22	48F	Bilat. temp.	None	None	RT	RT (scalp)	R hip. atrophy	Hip. scler.	Rare sz
23	27F	Bilat. temp.	None	None	Bilat. temp.	Bilat (scalp)	R mts	NA	Declined ic. mon.
24	50F	RT	None	None	RT	LT (depth)	LT atrophy	Hip. scler.	Sz free

LT, left temporal; RT, right temporal; bilat., bilateral; temp, temporal; mts, mesial temporal sclerosis; LF, left frontal; cav., cavernous; hip., hippocampal; enceph, encephalomalacia; scler., sclerosis; oligo, oligodendroglioma; WM, white matter; min. neur. loss, minimal neuronal loss, NA, not applicable; not avail., not available; postop., postoperative; sud, sudden unexplained death; ic. mon., intracranial monitoring.

[a] Obtained during overnight continuous sleep-EEG studies.

[b] Obtained during long-term monitoring (LTM).

[c] Sz free, seizure-free >1 year.

consistent with complex partial seizures of temporal lobe origin (9); no evidence of psychogenic seizures; and no recent medication discontinuation. The most common reasons for nonparticipation included transportation difficulties, childcare or other family responsibilities, and inability to take time off from work. There were no significant differences between participants and nonparticipants in age, sex, years of seizures, brain MRI abnormalities, and ability to proceed to surgery without intracranial monitoring (skip candidacy).

Overnight continuous sleep-EEG recordings

Subjects underwent two consecutive nights of study in the General Clinical Research Center of the University of Michigan Medical Center with 21 channels of EEG and additional channels of electrooculogram (EOG) and chin electromyogram (EMG) to score sleep. Informed consent was obtained, and the studies were carried out under a protocol approved by the University of Michigan Institutional Review Board. The first night was an adaptation night. The 10–20 international electrode placement system was used (10); additionally, T_1 and T_2 electrodes were applied. A Digital EEG system (DEEG) was used for recordings (Telefactor Corporation, West Conshohocken, PA, U.S.A.). The EEG was digitized at 200 Hz, and filter settings were 0.3 Hz (low-frequency filter) and 70 Hz (high-frequency filter). Subjects were seizure free ≥24 h before study, most for at least a week, and were taking stable doses of medication. Antiepileptic medication (AED) trough levels were obtained in the morning after night 1. All subjects were taking at least one AED at therapeutic levels or doses. Because a first-night effect may occur during the initial night of study in a laboratory, resulting in a longer sleep latency and REM latency and an increase in the percentage of wakefulness and stage 1 sleep (11), night 2 was used for the determination of IED occurrence in 18 subjects. In four subjects, complex partial seizures occurred before or during night 2, and as IED rates may increase after seizures (12), the first night of study was used. Analysis of data in these subjects, however, showed that nights 1 and 2 were comparable; the occurrence of a seizure did not alter the lateralization or the NREM versus REM occurrence of IEDs. In two additional subjects, electrode artifact or loss of data interfered with the interpretation of night 2, and night 1 was used for analysis.

Sleep scoring and IED determination

Each patient's recording was partitioned into 30-s epochs for sleep scoring by using standard criteria (13). Visual determination of IEDs was performed after sleep staging had been completed by using the following reformatted montage: C3-T3, T3-T1, T1-T2, T2-T4, T4-C4, Fp1-F7, F7-T3, T3-T5, T5-O1, Fp2-F8, F8-T4, T4-T6, T6-O2, F7-Ez, T1-Ez, T3-Ez, F8-Ez, T2-Ez, T4-Ez (Ez is placed halfway between Cz and Pz). The inclusion criteria for IEDs were adapted from those of Gloor (14) and included (a) restricted triangular transient clearly distinguishable from background activity, with the spike component having an amplitude of at least twice that of the preceding 5 s of background activity in any channel of EEG; (b) duration of ≤200 ms; and (c) presence of a field, as defined by involvement of a second adjacent electrode. Our rationale for including the amplitude criteria was to interpret IEDs conservatively and to exclude questionable IEDs. Rare IEDs appeared in clusters and were counted as individual events. Benign epileptiform transients of sleep and wicket spikes were excluded, as were physiologic sleep transients, including vertex waves. Two authors (B.A.M. and M.S.A.) independently performed visual detection on one cycle of sleep within each subject's recording. The two authors had 100% agreement on the lateralization of IEDs (left temporal vs. right temporal vs. independent bitemporal). Bitemporal epileptiform activity was defined by the presence of any independent left and right temporal IEDs.

Analysis

Data were analyzed to determine (a) the occurrence and lateralization of IEDs during NREM and REM sleep, and (b) the relation of IED foci to surgical outcome (seizure free >1 year) and to presurgical studies, including daytime EEGs, brain MRIs, interictal samples and ictal recordings from LTM with surface and sphenoidal electrodes, and intracranial electrode monitoring performed in subjects in whom ictal-onset regions were not clearly defined by surface LTM. Ictal recordings were lateralized based on the presence of rhythmic theta activity and other established indicators of temporal lobe seizures (15). Daytime EEGs, performed on the day before the overnight continuous sleep-EEG recording, included wakefulness and drowsiness in all subjects and NREM stage 2 sleep in four subjects. Interictal awake and sleep samples (10–20 min day), obtained during inpatient admissions for LTM, were identified by using a spike detector (Telefactor Corporation) and validated visually. The decision to implant intracranial electrodes or to perform surgery without invasive monitoring was made at a weekly refractory epilepsy conference based primarily on the results of seizure semiology, surface ictal recordings, brain MRI and positron emission tomography (PET) studies, and neuropsychological and language evaluations. The results of overnight continuous sleep-EEG recordings were not available at the time of the conference and did not influence the decision-making process.

RESULTS

Overnight Continuous Sleep-EEG Studies

All stages of sleep were recorded in each patient. The mean recording time was 6.9 ± 1.0 h (mean ± standard

deviation). Stage REM sleep comprised 17% and NREM sleep comprised 83% of the asleep epochs; the majority of NREM epochs were stage 2 sleep.

Occurrence of IEDs during overnight continuous sleep-EEG studies

All 24 subjects had anterior temporal IEDs in NREM sleep (Table 1). The proportion of epochs containing IEDs and the average number of IEDs per minute was highest in NREM sleep stages 3/4 (0.87 IEDs/min), intermediate in NREM sleep stages 1 (0.3 IEDs/min) and 2 (0.45 IEDs/min), and lowest in REM sleep (0.12 IEDs/min). The IEDs were exclusively unilateral in 14 subjects, independent bitemporal in nine subjects (range, 51–92%), and predominantly (=99%) unilateral in one subject; because of the high unilaterality of the spikes in this one subject, she was grouped with the exclusively unilateral patients. Seven subjects had anterior temporal IEDs in REM sleep, which were unilateral in six subjects and independent bitemporal in one subject. In only subject 14 did independent bitemporal IEDs during NREM sleep became unilateral during REM sleep. No subjects had IEDs involving extratemporal regions. The relation of IEDs to sleep depth, as measured by log delta power, in 21 of the 24 subjects is detailed elsewhere (16).

Relation of IEDs recorded during overnight continuous sleep-EEG studies to daytime EEGs, interictal samples, and ictal onsets obtained during LTM, brain MRIs, and surgical outcome

The salient features of the data presented in detail in Table 1 are summarized. All subjects have been followed for ≥1 year after temporal lobe resections. Subjects 1–13, with unilateral temporal IEDs recorded on overnight continuous sleep-EEG studies that were concordant with (ipsilateral to) brain MRI abnormalities or who had normal brain MRIs, had a high proportion of seizure-free outcomes (>90% seizure free). Five of these subjects required intracranial monitoring because of bilateral temporal surface ictal onsets (subjects 9–13). In all five, sleep IEDs were concordant with the predominant (>75%) intracranial ictal-onset region and the side of successful surgical outcome. Several of these 13 subjects lacked IEDs on either daytime EEGs, interictal samples obtained during LTM, or both. Two subjects had independent bitemporal IEDs on interictal samples but unilateral IEDs on both the daytime EEG and the overnight sleep-EEG recording.

In contrast, subjects with independent bitemporal IEDs on overnight sleep-EEG recordings had a lower proportion of seizure-free outcomes (50% seizure free or rare seizures). Brain MRI findings were a major determinant of outcome in these subjects. Those with brain MRIs that were either normal or showed bilateral or widespread abnormalities had poor surgical outcomes (subjects 14–17). In contrast, those with focal brain MRI abnormalities had good to excellent surgical outcomes (subjects 19–22). In one subject with discordant sleep IEDs and brain MRI findings, the brain MRI was concordant with intracranial recordings and the side of successful surgical resection (subject 24).

DISCUSSION

Our findings show that overnight sleep-EEG studies in subjects undergoing presurgical evaluations provide lateralizing information about the epileptogenic region that contributes to the presurgical evaluation. Those subjects with sleep IEDs that were concordant with brain MRIs had a high seizure-free outcome, and even those with unilateral IEDs and normal brain MRIs were seizure free. In subjects requiring intracranial electrode monitoring because of bilateral surface ictal onsets, the unilateral sleep IEDs predicted the intracranial ictal-onset region and the side of successful surgical resection.

In contrast, overnight sleep IEDs could not be reliably used to predict ictal onsets if they were bilateral or discordant with brain MRI. Furthermore, subjects with bitemporal IEDs still had excellent surgical outcomes if focal brain MRI abnormalities were present. Overall, our findings support the principle that IEDs cannot be used in isolation to predict ictal-onset regions or surgical outcome and must be interpreted in combination with other data collected during the presurgical evaluation. Because our sample size is relatively small, our observations will necessitate confirmation in larger series examining the relation between IEDs recorded on overnight sleep-EEG recordings and surgical outcome.

In specific subjects, continuous overnight sleep-EEG recordings provided useful information not provided by daytime EEGs or interictal samples obtained during LTM. All subjects had IEDs during sleep-EEG recordings, whereas 13 subjects lacked IEDs on daytime EEGs, and three subjects lacked IEDs on interictal samples. In some subjects, the unilaterality or bilaterality of IEDs became apparent only on overnight recordings. For example, in subject 9, IEDs were independent bitemporal on interictal samples but, on overnight recordings and the daytime EEG, were unilateral and concordant with the side of the predominant intracranial ictal-onset region and of successful surgical resection. Conversely, in subject 17, who had bilateral intracranial ictal onsets and sudden unexplained death presumed to result from a seizure, IEDs were unilateral on daytime EEGs and interictal samples but independent bitemporal on overnight recordings.

Our data obtained during LTM were limited to interictal samples, and continuous sleep-EEG overnight studies were not performed. Our rationale for performing continuous sleep-EEG studies in the outpatient Clinical Research Center setting rather than during subjects' presur-

gical admissions for LTM was to minimize the possible confounding effects of AED reductions, seizures, and sleep deprivation on IEDs, potentially resulting in false lateralization of IEDs (e.g., expanding the field of IEDs beyond the epileptogenic region). Although two studies concluded that AED reduction does not affect IED occurrence, one of these studies did not control for sleep state and included both intracranial and surface IEDs (17). The second study limited IED sampling to the awake state and included only intracranial IEDs (12). The effects of sleep deprivation and seizures on IED lateralization also have been poorly defined. Although findings in our four subjects experiencing seizures before or during night 2 of study would indicate that lateralization of the sleep IED focus remains unchanged before and after seizure occurrence, one study reported that seizures may augment IEDs on the epileptogenic side postictally (18). Follow-up investigations are under way in our laboratory to determine if continuous sleep-EEG recordings obtained during LTM contribute useful and accurate lateralizing information about the epileptogenic region. These recordings can be performed by applying four additional electrodes (two EOG and two chin EMG electrodes) to the standard EEG coverage. Many digital EEG systems now allow sleep review. Given the ease of performing and reviewing these recordings, they may provide a cost-effective means to obtain valuable interictal data while ictal recordings are taking place.

Only two previous studies addressed the question of IED lateralization in relation to sleep state, although neither performed complete overnight EEG-sleep recordings. Sammaritano and colleagues (3) performed automated IED detection with visual validation on 4- to 8-h samples of sleep in 39 epilepsy surgery candidates undergoing continuous video-EEG monitoring. They found that the IED field was restricted in REM sleep and wakefulness and was extended in NREM sleep. Localization of the primary epileptogenic area was more reliable in REM sleep and least reliable in NREM sleep. Unfortunately, only 51% of their subjects had IEDs during REM sleep, compared with 68% of subjects with IEDs in wakefulness and 100% of subjects with IEDs in NREM sleep. Adachi and coworkers (19) examined the predictive value of NREM sleep recorded on routine EEGs in 83 subjects with temporal lobe epilepsy who were seizure free for >1 year. They reported that the accuracy of EEG recordings for prediction of lateralization increased from 51.8% during waking to 78.3% during sleep, and suggested that IEDs occurring in NREM sleep provide more accurate information for lateralization of epileptogenesis than do those occurring in wakefulness. In agreement with the work of these investigators and our previous work (6), we found that IEDs were more prevalent in NREM sleep, particularly delta NREM sleep (NREM stages 3 and 4) as compared with lighter NREM sleep, with REM sleep having the fewest spikes per epoch. The sampling of these deeper NREM sleep stages, combined with overall increased recording time, most likely contributes to the enhanced recording of IEDs on overnight sleep-EEG studies. Only 46% of our subjects had IEDs on daytime EEGs, and only 29% of our subjects had IEDs in REM sleep. Independent bitemporal NREM IEDs occurred in 38% of subjects. In the subjects presented in this study, REM sleep did not provide additional lateralizing information. The one exception in which REM sleep restricted the IED focus seen during NREM sleep was subject 14. He had unilateral IEDs during REM sleep that were contralateral to ictal scalp recordings, and postoperative seizures. However, his poor surgical outcome may be more related to the bilateral IEDs during NREM sleep combined with a normal brain MRI.

Our findings are timely, given several reports of the predictive value of unilateral temporal IEDs recorded during routine EEGs or LTM in relation to the ictal-onset region or surgical outcome (20–25). Because these studies did not include sleep recordings or included only samples of sleep recordings, without specifying the relation of IEDs to sleep state, they were not able to define whether sleep recordings added incremental information to the awake EEG. Two recent outcome studies assessed the contribution of IEDs in relation to brain MRI pathology. Gilliam and colleagues (26) found that concordance of MRI and interictal EEG, recorded during LTM, was the strongest predictor of surgical outcome in mesial-basal temporal lobe epilepsy. Radhakrishnan and colleagues (27) reported that unilateral hippocampal atrophy on brain MRI and concordance of IEDs (recorded during routine EEGs and LTM) with the ictal onset region were independently associated with excellent surgical outcome. Moreover, the highest probability of excellent outcome (94%) was achieved when both factors were present. It must be emphasized, however, that independent bitemporal IEDs may be associated with unilateral intracranial temporal lobe seizure onsets and a good surgical outcome (28,29). Holmes and colleagues (30) noted the importance of considering other prognostic variables, including brain MRI abnormalities, in the assessment of subjects with independent bitemporal IEDs. In our subjects, we also found that independent bitemporal IEDs, when combined with unilateral hippocampal abnormalities, were associated with good to excellent surgical outcomes.

We conclude that temporal IEDs recorded during continuous overnight-EEG studies contribute important lateralizing information to the presurgical evaluation of temporal lobe epilepsy beyond that provided by temporal IEDs contained in daytime EEGs or interictal samples obtained during LTM. Further investigations with larger numbers of subjects are necessary to determine the con-

ditions and combinations of studies needed to minimize costly surface or intracranial ictal recordings in the presurgical assessment of patients with temporal lobe epilepsy. Such investigations should pay careful attention to the lateralizing role of sleep IEDs, particularly when combined with awake EEGs, neuroimaging studies, and other aspects of the presurgical evaluation.

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