Distribution of partial seizures during the sleep–wake cycle

Differences by seizure onset site

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Article abstract—*Objective:* To evaluate the effects of sleep on partial seizures arising from various brain regions. *Methods:* The authors prospectively studied 133 patients with localization-related epilepsy undergoing video-EEG monitoring over a 2-year period. Seizure type, site of onset, sleep/wake state at onset, duration, and epilepsy syndrome diagnosis were recorded. Periorbital, chin EMG, and scalp/sphenoidal electrodes were used. A subset of 34 patients underwent all-night polysomnography with scoring of sleep stages. *Results:* The authors analyzed 613 seizures in 133 patients. Forty-three percent (264 of 613) of all partial seizures began during sleep. Sleep seizures began during stages 1 (23%) and 2 (68%) but were rare in slow-wave sleep; no seizures occurred during REM sleep. Temporal lobe complex partial seizures were more likely to secondarily generalize during sleep (31%) than during wakefulness (15%), but frontal lobe seizures were less likely to secondarily generalize during sleep (10% versus 26%; $p < 0.005$). *Conclusions:* Partial-onset seizures occur frequently during NREM sleep, especially stage 2 sleep. Frontal lobe seizures are most likely to occur during sleep. Patients with temporal lobe seizures have intermediate sleep seizure rates, and patients with seizures arising from the occipital or parietal lobes have rare sleep-onset seizures. Sleep, particularly stage 2 sleep, promotes secondary generalization of temporal and occipitoparietal, but not frontal, seizures. These findings suggest that the hypersynchrony of sleep facilitates both initiation and propagation of partial seizures, and that effects of sleep depend in part on the location of the epileptic focus.

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Despite recent advances in therapy, nearly 30% of patients with epilepsy have seizures that are refractory to treatment.[1] Greater understanding of the factors, such as sleep, that modulate seizure timing and expression may provide insights into the pathophysiology and treatment of epilepsy. Different stages of sleep have opposing effects on interictal discharges, seizure threshold, and neuronal excitability. Non–rapid eye movement (non-REM) sleep, especially stages 3 and 4 (slow wave sleep), promotes interictal epileptic activity through increased neuronal synchrony.[2,3] REM sleep, in contrast, appears to inhibit the occurrence and spread of epileptiform discharges.[2,3]

Several studies have shown a marked effect of sleep on the timing of seizures,[4-7] especially primary or secondarily generalized seizures, and suggest that sleep increases partial seizure frequency, duration, and rate of secondary generalization.[4,8-10] Sleep and epilepsy interactions appear to differ according to site of seizure onset and epilepsy syndrome. In some idiopathic and genetic epilepsies (e.g., benign Rolandic epilepsy of childhood[11] and autosomal dominant nocturnal frontal lobe epilepsy[12]), sleep is well known to activate seizures. In cryptogenic and symptomatic localization-related epilepsies, however, this relationship remains incompletely characterized.

The aim of this study was to examine the influence of sleep and various sleep stages on partial-onset seizures recorded during continuous EEG monitoring. We hypothesized that sleep would increase seizure frequency, duration, and rate of secondary generalization and that these effects would differ according to sleep stage and the location of seizure onset.

Methods. We prospectively identified all patients with partial-onset seizures admitted for video-EEG monitoring over a 24-month period. The study included 133 consecutive patients with refractory complex partial seizures who were candidates for epilepsy surgery. Patients who had no spontaneous seizures or who experienced only auras during their admission, patients with intracranial electrodes, and patients with a final diagnosis not including localization-related epilepsy were excluded. In addition, we excluded patients who underwent prolonged sleep deprivation or withdrawal from benzodiazepines during the monitoring session. Patients were instructed to go to sleep at 11:00 PM, were awakened at 7:00 AM, and were not allowed to take daytime naps.

Patients. The characteristics of the patients in each group are summarized in table 1. All patients had simple or complex partial seizures or partial seizures with secondary generalization. All patients were receiving antiepilep-

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Table 1 *Patient characteristics*

Characteristic	TLE (all), n = 86	MTLE, n = 39	NTLE, n = 13	FLE, n = 20	OLE, n = 14
Sex, F (%)/M	51 (59.3)/35	20 (51.3)/19	7 (53.8)/6	11 (55.0)/9	7 (50.0)/7
Age, y, mean ± SD	41.3 ± 1.5	41.1 ± 2.2	41.7 ± 2.0	39.6 ± 3.5	37.3 ± 4.1
Median	38	42	37	37.5	32.5
Range	17–63	18–63	17–62	26–64	20–72
Lesional, n (%)	54 (62.8)	39 (100)	13 (100)	9 (45)	8 (57.1)
		38 MTS	5 Tumor	4 Tumor	5 Dysplasia
		1 Tumor	3 Trauma	2 Dysplasia	1 AVM
			3 Dysplasia	1 Trauma	2 Tumor
			1 Cavernous malformation	1 Encephalitis	
			1 Cyst	1 Infarct	
Intracranial EEG, n	3	6	3	3	
Surgery outcome, n	15 (13 Ia, 1 Ib, 1 II)	6 (5 Ia, 1 II)	3 (1 Ia, 1 II, 1 III)	4 (3 Ia, 1 II)	

Surgery outcome was scored according to Engel.[34]

TLE = temporal lobe epilepsy; MTLE = mesial TLE; NTLE = neocortical TLE; FLE = frontal lobe epilepsy; OLE = occipital or parietal lobe epilepsy; MTS = mesial temporal sclerosis; AVM = arteriovenous malformation.

tic drugs (AED), and most had their AED tapered during the monitoring session to facilitate recording of seizures. A standardized taper was not used. For most patients, AED were decreased by half at the time of admission, with subsequent further decreases as needed. The distribution of baseline AED was similar in the various patient groups.

The patients were retrospectively divided into four groups according to the location of seizure onset. The site of probable seizure onset was determined by using clinical and electrographic seizure characteristics, supplemented by interictal EEG, clinical history, and results of MRI, PET, and ictal and interictal SPECT, when available. Because most patients did not undergo intracranial EEG recording, these localizations are only best estimates of the ictal onset zone. Seventy-one patients (53.4%) had lesions visible on MRI. Seizure types[13] and epilepsy syndromes[14] were determined according to the International League Against Epilepsy (ILAE) classifications. In 13 patients (10%), definite seizure localization could not be determined; these patients were included in the overall analysis but excluded from the group analysis.

TLE group. The TLE group (86 patients) was heterogeneous. In 39 patients, clinical and electrographic seizures were consistent with mesial temporal onset,[15] and MRI showed mesial temporal sclerosis (hippocampal atrophy and increased signal)[16] or a mesial temporal lesion. These patients were classified as mesial temporal lobe epilepsy (MTLE). In 13 patients (NTLE), clinical and electrographic ictal characteristics suggested neocortical onset,[15] and MRI showed a neocortical temporal lesion. The other 34 patients clinically and electrographically had temporal lobe epilepsy, but onset could not be further localized on the basis of available information.

FLE group. We used widely accepted clinical and EEG criteria to classify seizures as frontal onset.[17] Nine patients (45%) had focal frontal lesions on MRI.

OLE group. Patients in the OLE group had either a focal occipital or parietal lesion (58%), an onset confirmed by intracranial EEG recordings (21%), or a clear visual aura at seizure onset (21%).

Video–EEG monitoring. Continuous recordings were performed over several days with scalp electrodes, video, and audio using commercially available technology (BMSI, Madison, WI). Scalp electrodes were placed by using collodion technique according to the 10-20 International System with additional T1, T2, and subtemporal electrodes; some patients with suspected temporal-onset seizures had sphenoidal electrodes as well. Chin electromyography (EMG) and periorbital electrodes were used in all patients to stage sleep. EEG was continuously screened with a spike- and seizure-detection program (Stellate Monitor), and all automatic seizure detections and seizures noted by the patient and staff were reviewed.

Patient-monitoring duration averaged 4.9 days (range, 1–18 days), and patients were almost never disconnected during the monitoring sessions. We limited analysis to the first 10 seizures for each patient to reduce bias that could be introduced by patients with large numbers of seizures. Only four patients had more than 10 seizures during their monitoring stay.

The following information was recorded for each partial seizure: (a) seizure type (simple partial, complex partial, partial with secondary generalization [2GTC], or subclinical); (b) site of onset if known; (c) epilepsy syndrome diagnosis; (d) time of seizure onset; (e) sleep/wake state at seizure onset; and (f) seizure duration. These determinations were made by attending epileptologists after the video-EEG recording sessions were completed. Sleep stage at seizure onset was determined by the criteria described by Rechtschaffen and Kales[18]. At the time of review, we analyzed at least 2 minutes of EEG before seizure onset by using both standard and polysomnographic montages to determine whether the patient was awake or asleep and, if asleep, the sleep stage. If sleep stage could not be determined from the EEG immediately preceding the seizure, additional EEG was reviewed until a definite stage could

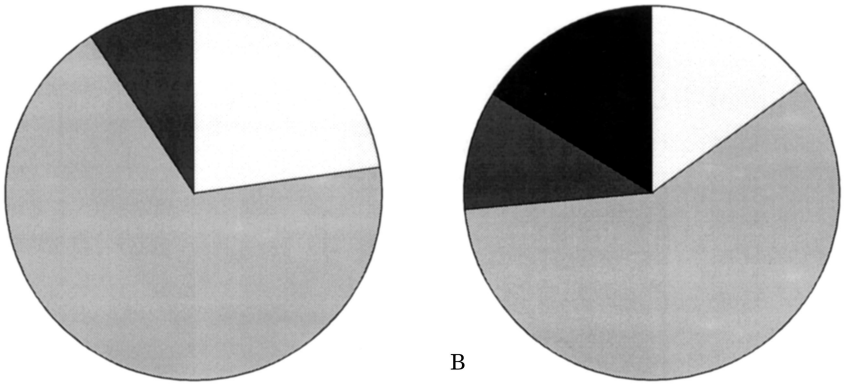

Figure 1. Proportion of partial seizures arising during various stages of sleep (A) compared with proportion of time spent in each stage of sleep in a subset of 34 patients undergoing all-night polysomnography (B). A: light gray, Stage 1 = 23%; medium gray, Stage 2 = 68%; dark gray, Stage 3/4 = 9%; REM = 0%. B: light gray, Stage 1 = 13%; medium gray, Stage 2 = 51%; dark gray, Stage 3/4 = 9%; black, REM = 14%.

be identified. Because surface EEG recordings may miss early electrographic discharges, seizures beginning within 30 seconds after an arousal from stable sleep were classified as beginning during sleep.

Polysomnography. All-night polysomnography was performed during video-EEG monitoring in a subset of 34 patients with temporal lobe epilepsy (TLE) to analyze the structure of sleep. We analyzed a total of 116 nights (average, 3.4; range, 1–7 nights per patient). The first night of admission was excluded from analysis. Patients were instructed to go to sleep at 11:00 PM, were awakened at 7:00 AM, and were not allowed to nap. Sleep stages were scored according to the criteria of Rechtschaffen and Kales[18] except that stages 3 and 4 were grouped together. For the purposes of this study, only the total sleep time and percentage of each type of sleep (NREM 1, 2, 3–4, and REM) were considered.

Variables and statistics. Student's *t*-test was used to determine significance of differences in means. Chi-square or Fisher's exact test was used to compare differences in proportions. Differences in medians of seizure duration (non-normal distribution) were analyzed by using the Mann-Whitney rank sum test and Kruskal-Wallis ANOVA on ranks. A p value of less than 0.05 was considered significant.

To determine whether seizures were distributed randomly during the sleep–wake cycle, we assumed that all patients' sleep was identical to that of the subset who underwent polysomnography. We then compared our observed numbers of seizures in each of these stages (wakefulness, stage 1, stage 2, stage 3/4, and REM) with the number expected if the seizures were randomly distributed during the sleep–wake and performed a chi-square analysis.

Results. *Overview of results.* A total of 613 seizures occurred in 133 patients (average of 4.5 seizures per patient; standard deviation, 2.6; range, 1–10). A total of 264 (43.1%) of 613 seizures occurred during sleep. All sleep seizures began during non-REM sleep and were more likely to occur during Stage 2 sleep. No seizures occurred during REM sleep (figure 1, top). Average sleep duration in the 34 patients undergoing polysomnography was 7.6 hours (31.6% of 24 hours). The proportion of time spent in each sleep stage was similar to that of normal controls (figure 1, bottom).

If seizures were randomly distributed, we would expect 68.4% of seizures to occur during wakefulness, (0.316) (0.13) in stage 1, (0.316) (0.51) in stage 2, (0.316) (0.09) in stages 3–4, and (0.316) (0.14) in REM sleep. The observed distribution of seizures during the sleep–wake cycle was different from this expected random distribution ($p < 0.0001$). More seizures occurred during light NREM sleep (Stage 1, $p < 0.005$; Stage 2, $p < 0.001$) than expected, and fewer seizures during REM sleep ($p < 0.001$). Seizures did not appear to be increased by slow wave sleep (Stages 3 and 4; $p < 0.9$), but the number of seizures recorded during slow-wave sleep was too small to reliably detect a difference. No significant difference in the proportion of seizures was seen between stages 1, 2, and 3–4 sleep, but all NREM stages showed an increase in seizures compared with REM (Stage 1, $p < 0.001$; Stage 2, $p < 0.001$, Stage 3, $p < 0.001$).

Because only patients with TLE underwent overnight polysomnography, we performed a similar analysis restricted to patients with TLE. A total of 363 TLE seizures was recorded, 199 during wakefulness, 35 in Stage 1 sleep, 115 in Stage 2 sleep, and 14 in Stages 3 and 4 sleep. Again, the observed distribution of temporal lobe seizures during the sleep–wake cycle was different from the expected distribution ($p < 0.0001$), because of an increase in seizures during light NREM sleep (Stage 1, $p < 0.05$, Stage 2, $p < 0.001$) and a decrease during REM sleep ($p < 0.05$), compared with wakefulness.

Table 2 shows that some seizure types occurred preferentially during sleep or wakefulness. Simple partial and subclinical seizures were relatively rare during sleep (35%), whereas secondarily generalized complex partial seizures occurred slightly more frequently during sleep (54.9%; $p < 0.05$).

Effect of sleep on seizure duration. Sleep may delay the clinical manifestations of complex partial seizures; therefore, seizure duration was defined as the interval from electrographic (EEG) onset to EEG offset. Simple partial

Table 2 *Proportion of seizures during sleep: seizure type*

Seizure type	No. of seizures	Sleep-onset seizures (%)
Simple partial	80	28 (35.0)
Complex partial	377	157 (41.6)
Complex partial, 2 GTC	122	67 (54.9)
Subclinical	34	12 (35.3)
Total	613	264 (43.1)

2 GTC = secondary generalization; $p < 0.05$.

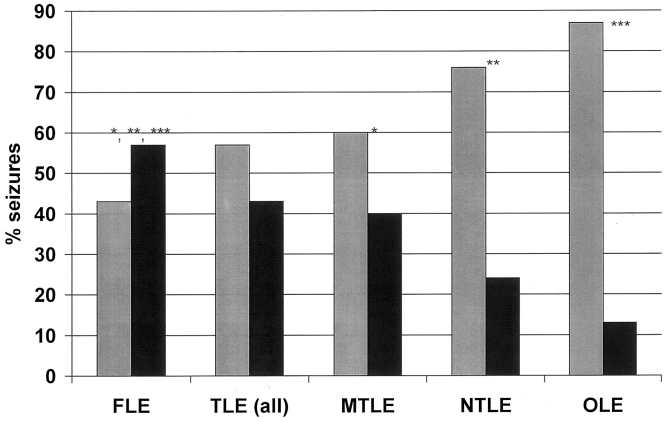

*Figure 2. Percentage of partial seizures arising during sleep from various seizure onset zones. Frontal lobe seizures were more likely to occur during sleep than seizures arising from other foci (p < 0.0001). FLE = frontal lobe epilepsy (n = 112), TLE = temporal lobe epilepsy (n = 382), MTLE = mesial temporal lobe epilepsy (n = 164), NTLE = neocortical temporal lobe epilepsy (n = 54), OLE = occipital or parietal lobe epilepsy (n = 45). Gray bars, awake; black bars, asleep. *p < 0.05; ***p < 0.001; ***p < 0.001.*

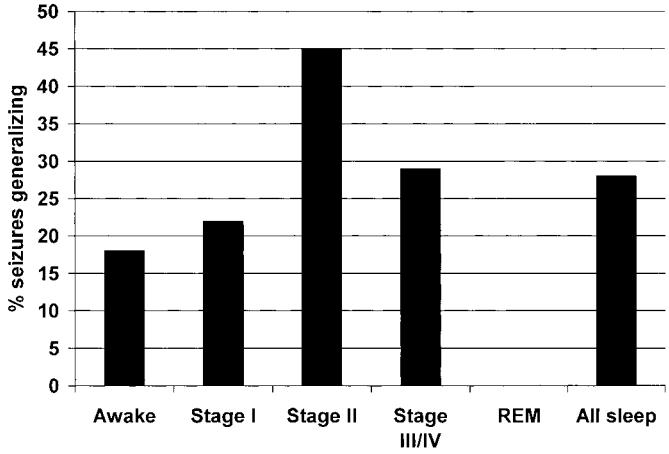

Figure 3. Percentage of partial seizures undergoing secondary generalization during various sleep stages. Although all NREM sleep stages appeared to promote secondary generalization, Stage 2 sleep had the most marked effect (p < 0.005). Black bars, complex partial seizures with secondary generalization.

seizures were excluded, because these were rare during sleep, often had no electrographic correlate, and usually had uncertain duration. Median seizure duration was not significantly different during wakefulness and sleep for all CPS (62 versus 64 seconds), CPS without secondary GTC (55 versus 51 seconds), and CPS with secondary GTC (93 versus 84 seconds). In addition, there was no significant effect of sleep stage on the duration of CPS.

Effect of sleep on seizures arising from different regions. All FLE, TLE (both MTLE and NTLE), and OLE partial seizures were included in this analysis, with or without secondary generalization. Frontal lobe seizures were more common during sleep (57.1%), whereas temporal lobe seizures, especially neocortical temporal lobe seizures, and occipitoparietal lobe seizures were more common during wakefulness (sleep onset seizures: TLE = 43.5%, MTLE = 40.2%, NTLE = 24.1%, OLE = 13.3%; $p < 0.0001$; figure 2). FLE seizures were significantly more common during sleep than MTLE, NTLE, and OLE seizures (figure 2). For all seizure onset zones, seizures were most likely to begin during stage 2 sleep and showed a similar proportion of seizures in each sleep stage.

Onset during sleep may be clinically useful in distinguishing frontal from temporal lobe seizures. We therefore analyzed patients with more than four recorded seizures and considered ≥75% of seizures occurring during sleep as a large proportion of seizures during sleep. Using these criteria, seven (50%) of 14 FLE patients, 14 (25%) of 55 TLE patients, and none of four OLE patients had a large percentage of seizures during sleep. There was no significant difference by Fisher's exact test, suggesting that although more patients with frontal lobe seizures have predominantly sleep-onset seizures, this nocturnal predominance is not diagnostically useful.

Effect of sleep on secondary generalization of CPS. Twenty-eight percent (67 of 236) of CPS beginning during sleep progressed to secondary GTC, compared with only 18% (55 of 298) of CPS occurring during wakefulness ($p < 0.01$). During sleep, 21.5% of CPS beginning in Stage I and 29.4% beginning in Stage III/IV secondarily generalized (no significant difference from wakefulness). Forty-five percent (51 of 112) of CPS beginning in Stage II sleep, however, underwent secondary generalization. This was higher than the proportion generalizing during wakefulness ($p < 0.005$) (figure 3).

The effect of sleep on rates of secondary generalization differed for frontal, temporal, and occipitoparietal lobe seizures. Overall, 14 of 80 (17.5%) of frontal, 80 of 363 (22.0%) of temporal, and 14 of 40 (35.0%) of occipitoparietal CPS progressed to secondary generalization, but this difference was not significant ($p = 0.09$). Sleep promoted secondary generalization of temporal lobe seizures (51 of 164, 31.1%), both MTLE (25 of 65, 38.5%) and NTLE (8 of 12, 66.7%), and occipitoparietal seizures (5 of 7, 71.4%), but not frontal (5 of 48, 10.4%) lobe seizures ($p < 0.005$) (figure 4). The effects of sleep on secondary generalization were significant for frontal versus mesial temporal, neocortical tempo-

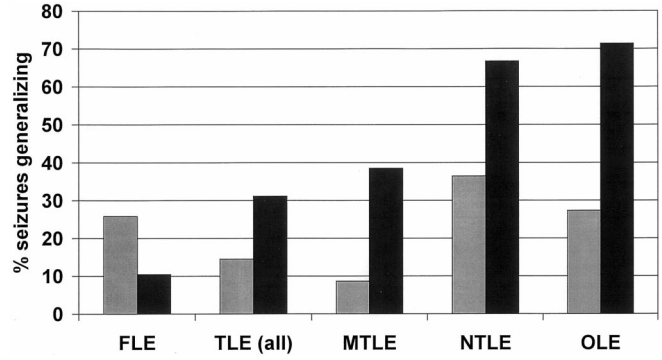

Figure 4. Percentage of partial seizures undergoing secondary generalization for various seizure onset zones. Sleep promoted secondary generalization of temporal lobe seizures (51 of 164, 31.1%), both MTLE (25 of 65, 38.5%) and NTLE (8 of 12, 66.7%), and occipitoparietal seizures (5 of 7, 71.4%), but not frontal (5 of 48, 10.4%) lobe seizures (p < 0.005). Gray bars, awake; black bars, asleep.

ral, and occipitoparietal lobe seizures, but not between other localizations (figure 4).

Discussion. Our study confirms previous well-accepted observations that NREM sleep, particularly Stage 2 sleep, facilitates partial seizures, whereas REM sleep appears to inhibit partial seizures.[4,8,10,19,20] More importantly, we showed a significant difference in both rate of initiation and rate of secondary generalization during sleep among seizures arising from different cerebral foci, suggesting that the synchronizing and activating effects of sleep may be different for frontal, temporal, and occipitoparietal lobes. Several studies have reported similar results.[10,19,20] In one study[20] of 30 patients with refractory partial epilepsy, most seizures occurred during NREM sleep Stage 2, with rare seizures during Stages 3–4 and REM. The percentage of frontal lobe seizures during sleep (61.1%) was similar to that in our study, but temporal lobe seizures were much less likely to occur during sleep (10.9%) than in our patients. Our current findings that more than 40% of temporal lobe seizures began during sleep do not support the authors' conclusion that all-night continuous EEG recordings are of little clinical utility for patients with suspected TLE. In addition, patients with either FLE or TLE may have most or all of their seizures during sleep. Therefore, an observation that an individual patient's seizures occur mostly during sleep is not diagnostically useful in determining the likely site of seizure onset.

The current study has several advantages over previous studies of the sleep–epilepsy relationship. First, use of continuous EEG monitoring with automated seizure detection allowed very accurate seizure counts. Rare seizures may have been missed by both staff and automatic seizure detection, but no additional subclinical seizures were detected in the subgroup of patients in whom all night polysomnography with analysis of every page of EEG was performed. Second, we classified our patients into several well-defined groups by probable site of seizure onset, using clinical, EEG, and neuroradiologic data. Rare patients may have been misclassified even using these criteria. Finally, we are the first to analyze partial seizures from multiple different onset zones.

The inclusion of polysomnography in a subset of patients with TLE allowed direct comparison of seizure frequency in each state. This analysis further emphasized the seizure-promoting effects of NREM sleep and the seizure-inhibiting effects of REM sleep. Because all-night polysomnography was performed only in patients with TLE, our assumption that sleep stage proportions are similar for all patients in the study may not be correct. Epilepsy disturbs sleep by increasing number of awakenings and total waking time after sleep onset (WASO), but does not significantly change the proportion of various sleep stages, including REM.[5,8] Changes in sleep structure also may have been induced by seizures themselves. Both diurnal and nocturnal seizures, especially secondarily generalized seizures, markedly decrease REM sleep and, if occurring before REM onset, prolong REM sleep latency.[21] Even very large reductions in REM sleep time, however, could not account for the total absence of REM-onset seizures seen in our study.

Several factors of study design may have influenced our results. Severe or refractory epilepsies are more likely to be diffuse epilepsies, with random distribution of seizures throughout the sleep–wake cycle.[22] Our cohort of patients may therefore be very different from the larger population of patients with epilepsy. We did not accurately assess the impact of changes in AED on seizure frequency and distribution during the sleep–wake cycle. AED are known to have significant effects on sleep structure[23] and may influence the timing of seizures. Finally, unequal numbers of seizures for each patient may have introduced bias. Patients with multiple seizures could bias the results by adding many more seizures to their category (FLE, TLE, or OLE), whereas patients with just a few seizures have less weight in the data analyses.

All seizures in our study occurred during NREM sleep, whereas none occurred during REM. NREM and REM sleep are determined by different mechanisms and have opposite effects on interictal and ictal discharges.[24] NREM sleep is characterized by cerebral hypersynchrony, mediated by interactions between the brainstem reticular activating system, the thalamus, and the cortex. During NREM sleep, oscillatory or bursting firing of thalamic neurons results in cortical synchronization.[25] REM sleep, however, is characterized by inhibition of thalamocortical synchronizing mechanisms,[26] a desynchronized EEG pattern, inhibition of spread of epileptiform discharges, and skeletal muscle paralysis.

Neurons in seizure foci may be hyperresponsive to synchronous excitatory synaptic inputs occurring during sleep.[27,28] Recordings from alumina gel–induced chronic neocortical epileptic foci in monkeys showed that normal neurons and grossly "epileptic" neurons did not change their firing pattern significantly during sleep, but neurons that were mildly epileptic during wakefulness greatly increased their firing frequency and synchrony.[29] Recruitment of these "mildly epileptic" neurons into synchronous firing patterns during sleep may promote initiation of ictal events.

Most seizures in our study occurred during Stage 2 sleep. Several studies have confirmed that interictal spiking rates increase as NREM sleep deepens, that is, as cerebral synchrony increases.[2,3] Most seizures do not occur during slow-wave sleep (Stages 3–4), but rather during Stage 2 or, less frequently, Stage 1 sleep.[10,20] Increases in cortical synchrony, therefore, cannot be the only factor at work during NREM sleep. A strong relationship has been noted between sleep spindles and epileptic activity.[30,31] Epileptiform discharges may represent an abnormal ex-

citatory response to the intrinsic thalamocortical volleys[25] that cause sleep spindles and delta waves during sleep. Similarly, a cyclic alternating pattern (CAP) of relative arousal (Phase A) followed by stabilization (Phase B) of sleep has been proposed as important for seizure initiation.[19] Most interictal and ictal discharges occur during the arousal phases of CAP during light stages of sleep.

Sleep had no effect on the duration of CPS with or without secondary generalization in this study. This is in contrast to the marked effect of sleep, particularly Stage 2 sleep, on rates of secondary generalization. Secondary generalization may depend on thalamocortical interactions,[25] which are facilitated during NREM sleep. Our data indicate that cortical regions with high secondary generalization rates have low seizure onset rates during sleep, and vice versa, suggesting that sleep may affect seizure initiation and seizure propagation mechanisms in different ways.

Most frontal lobe seizures occurred during sleep, mesial temporal lobe seizures occurred nearly equally during sleep and wakefulness, and neocortical temporal lobe and parieto-occipital lobe seizures occurred much more commonly during wakefulness. These results suggest that changes in neuronal excitability associated with sleep are different in each cortical region. Electrophysiologic and functional neuroimaging studies support this hypothesis. In one study of patients with partial epilepsy, depth and cortical electrode recordings during NREM sleep showed less activation of interictal spikes in occipital and parietal regions than frontal, mesial temporal, or neocortical temporal regions.[32] This agrees with our results that parietal and occipital regions were least likely to generate seizures during NREM sleep. Advances in functional imaging also support regional cortical differences during sleep. $H_2(15)O$-PET studies show decreased regional cerebral blood flow, resulting from increased neuronal synchrony, in the thalamus, prefrontal cortex, and temporal neocortex during NREM sleep, but little change in visual, auditory, and primary somatosensory cortices.[33] These regional differences in synchrony may explain our findings that frontal and temporal lobe seizures, but not occipitoparietal seizures, are activated by NREM sleep.

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CME

Multiperspective follow-up of untreated carpal tunnel syndrome

A multicenter study

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Article abstract—*Objective:* To assess the course of untreated carpal tunnel syndrome (CTS). *Methods:* The Italian CTS Study Group prospectively followed up (10 to 15 months) 196 untreated patients (274 hands) with idiopathic CTS with multiple measurements of CTS. Baseline factors were used to predict the evolution of untreated CTS in multiple regression analysis. *Results:* Comparison of baseline and follow-up data showed a significant spontaneous improvement of patient-oriented and neurophysiologic measurements. A significant correlation between evolution and initial severity of CTS was observed. CTS measurements improved in patients with more severe initial impairment whereas they worsened in patients with milder initial impairment. The main positive prognostic factor was short duration of symptoms. Similarly, spontaneous improvement was more frequently associated with young age. Conversely, baseline bilateral symptoms and positive Phalen predicted a poor prognosis. *Conclusions:* Some patients with CTS improve spontaneously without surgical treatment.

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Steroid treatment and noninvasive physical therapy may provide temporary benefit for carpal tunnel syndrome (CTS), but surgical decompression is considered the only definitive cure.[1-5] Many studies focus on the evolution of treated CTS and there are few data on the course of untreated CTS.[6-8]

During 1997, the Italian CTS Study Group studied patients with idiopathic CTS in 20 Italian centers.[9] In addition to the physician-centered and neurophysiologic traditional evaluations, we used a validated patient-oriented measurement to obtain more comprehensive and consistent data for the clinical picture. This type of measure is important in assessing the clinical picture of disease.[10-12]

Eight of the 20 centers that participated in the first study adhered to the follow-up study of the same sample. The aims were to evaluate the following: 1) the natural history of CTS; and 2) the predictive value of electrodiagnostic assessment and clinical picture at the time of the first diagnosis.

Methods. *Study design.* A careful review of clinical and neurophysiologic studies allowed the group to develop a unique methodology. An extensive and complete description of the study's design has been reported previously.[9,13] All centers adhered strictly to the protocol summarized here. The collaboration was performed according to the recently proposed guidelines for multicenter collaboration and clinical research in neurology.[14,15] The study was achieved following the literature classification criteria proposed by the American Academy of Neurology (AAN) and American Association of Electrodiagnostic Medicine (AAEM).

Data collection at the initial evaluation. Diagnosis of CTS was based on the AAN[1] clinical diagnostic criteria

See also pages 1431, 1565, and 1568

*See the Appendix on page 1466 for a list of members of the Italian CTS Study Group.

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