CONTROVERSY EXISTS REGARDING THE ROLE OF NON-RAPID EYE MOVEMENT (NREM) SLEEP VS. AROUSAL IN PROMOTING EPILEPTIC ACTIVITY. Previous investigators have demonstrated in feline models that spike-wave discharges evolve from the spindle rhythms of NREM sleep following intramuscular injection of penicillin.1 Steriade and colleagues have postulated that neurochemical processes underlying the facilitation of NREM sleep, including progressive hyperpolarization in thalamocortical projection neurons, induce a state of relative neuronal synchronization that facilitates epileptic seizures.2 Conversely, arousal from sleep may provoke seizure activity. Sudden synchronous excitatory input from waking-active neurons in the posterior hypothalamus, which project to the neocortical mantle, may facilitate seizures via exacerbation of cortical hyperexcitability.3 In his studies of primary generalized epilepsy, Niedermeyer introduced the term "dyshormia," or deviant arousal, to describe spike-wave activity seen in association with K-complexes.4 In temporal lobe epilepsy, sleep has been characterized by marked instability with a significant increase in the number and the duration of arousals and sleep shifts.5 These arousals from sleep may facilitate epileptic seizures.6 Terzano and colleagues have implicated arousal periods related to their "cyclic alternating pattern" in the activation of partial seizures.7 Analysis of the timing of epileptic seizure onsets in relation to sleep and arousal is limited because seizure onsets often have a delayed scalp representation. As demonstrated in a prior case report by Malow and Varma, the temporal sequence of seizures and arousals is often uncertain and may be impossible to determine based on scalp electroencephalogram (EEG) recordings alone.8 Seizure onset may

Study Objectives: The role of arousal from sleep in promoting epileptic seizures is controversial. To examine the question of whether seizures precede or follow arousals from sleep, we defined the timing of temporal lobe seizures in relation to sleep and arousal using combined scalp-intracranial electrodes.

Design: Retrospective review of 67 sleep-related mesial temporal lobe seizures in 14 subjects.

Setting: Inpatient epilepsy monitoring laboratory.

Patients: Subjects with medically refractory mesial temporal lobe seizures undergoing epilepsy surgery evaluations.

Interventions: None

Measurements and Results: Electroencephalographic (EEG) and/or polygraphic recordings and videotapes were independently reviewed to determine intracranial electrode seizure onset times and time of initial arousal from sleep. In 60 seizures in 13 subjects, intracranial ictal onsets always preceded clinical arousals from sleep. Electrographic signs of arousal in the scalp EEG, defined by the presence of sustained alpha or theta activity, either coincided with or followed, but never preceded, intracranial ictal onsets. In seven seizures in one subject with known seizures upon awakening, intracranial ictal onsets always followed clinical arousals and electrographic signs of arousal from sleep. Seven of the 14 subjects had electrocoelogram and chin electromyogram monitoring; in these subjects, no seizures occurred during REM sleep with the majority occurring during NREM stage 2 sleep.

Conclusions: Most sleep-related temporal lobe seizures occurred during NREM sleep and preceded arousals, supporting the premise that processes involved in the initiation and maintenance of NREM sleep play a greater role in facilitating temporal seizures than those involved in promoting REM sleep and arousal. However, arousal from sleep may provoke seizures in exceptional cases.

Key words: Seizures; sleep; arousal; epilepsy; intracranial electrodes; non-rapid eye movement sleep; rapid eye movement sleep; epilepsy surgery

INTRODUCTION

CONTROVERSY EXISTS REGARDING THE ROLE OF NON-RAPID EYE MOVEMENT (NREM) SLEEP VS. AROUSAL IN PROMOTING EPILEPTIC ACTIVITY. Previous investigators have demonstrated in feline models that spike-wave discharges evolve from the spindle rhythms of NREM sleep following intramuscular injection of penicillin.1 Steriade and colleagues have postulated that neurochemical processes underlying the facilitation of NREM sleep, including progressive hyperpolarization in thalamocortical projection neurons, induce a state of relative neuronal synchronization that facilitates epileptic seizures.2 Conversely, arousal from sleep may provoke seizure activity. Sudden synchronous excitatory input from waking-active neurons in the posterior hypothalamus, which project to the neocortical mantle, may facilitate seizures via exacerbation of cortical hyperexcitability.3 In his studies of primary generalized epilepsy, Niedermeyer introduced the term "dyshormia," or deviant arousal, to describe spike-wave activity seen in association with K-complexes.4 In temporal lobe epilepsy, sleep has been characterized by marked instability with a significant increase in the number and the duration of awakenings and sleep shifts.5 These arousals from sleep may facilitate epileptic seizures.6 Terzano and colleagues have implicated arousal periods related to their "cyclic alternating pattern" in the activation of partial seizures.7 Analysis of the timing of epileptic seizure onsets in relation to sleep and arousal is limited because seizure onsets often have a delayed scalp representation. As demonstrated in a prior case report by Malow and Varma, the temporal sequence of seizures and arousals is often uncertain and may be impossible to determine based on scalp electroencephalogram (EEG) recordings alone.8 Seizure onset may
appear to follow an arousal in the scalp EEG, yet simultaneously recorded intracranial EEG may demonstrate that seizure onset precedes the arousal. In addition, some sleep-related partial seizures lack scalp EEG correlates.

The purpose of this study was to define the timing of temporal lobe seizures in relation to sleep and clinical arousal in a larger subset of subjects than the one subject analyzed in the previous case report. We had the opportunity to analyze seizures in a unique group of patients—epilepsy surgery candidates undergoing invasive monitoring with combined scalp-intracranial recordings for clinical purposes.

METHODS

Subjects and Recordings

We reviewed the reports of all subjects undergoing long-term seizure monitoring with combined scalp-intracranial electrodes as part of their clinical evaluation for epilepsy surgery between January 1994 and July 1997. All of these subjects had previously undergone long-term seizure monitoring with scalp and sphenoidal electrodes in addition to routine electroencephalograms (EEGs), brain magnetic resonance imaging (MRI) studies, and neuropsychological and language testing. Based on the results of these initial studies, these subjects were considered to be candidates for epilepsy surgery, but required additional intracranial monitoring to define more precisely the brain regions where their seizures began.

Bilateral temporal depth electrodes were implanted in the hippocampus and parahippocampal gyrus from an occipital entry point. Bilateral temporal four-contact strip electrodes were also placed over the anterior lateral temporal and inferior temporal neocortex. Where clinically indicated, additional frontal depth electrodes and subdural electrode strips were also placed. Scalp electrodes included coverage of frontal, central, and temporal regions in all subjects. Additionally, eight subjects underwent electrooculogram (EOG) and chin electromyogram (EMG) monitoring to stage sleep. All subjects underwent recordings using a Telefactor Beehive System (Telefactor Corporation, West Conshohocken, PA).

Fourteen subjects were identified who had at least one sleep-related complex partial or secondarily generalized seizure. Seizures were defined as having both ictal electroencephalographic (EEG) patterns and behavioral correlates (e.g., arousals from sleep). Ictal EEG patterns were defined by the appearance of a persistent rhythmic discharge that evolved in frequency and amplitude and spread to adjacent electrodes. We excluded subclinical events, in which the EEG showed an ictal pattern but the subject remained asleep.

For review, data stored on videotapes were played back and digitized into a Telefactor Digital EEG System at 200 Hz with filter settings of 0.3 Hz (low frequency filter) and 70 Hz (high frequency filter). In all subjects, at least 15 minutes of data preceding the seizure were reviewed. The EEG recordings and videotapes were used for seizure detection. One author (BAM) independently reviewed all EEG recordings to determine intracranial seizure onset times, blinded to clinical arousal from sleep and scalp EEG channels. These seizure onset times were compared to those recorded in long-term monitoring reports. Two authors (BAM and RJB) independently reviewed videotapes, blinded to seizure onset, to determine the time of the first clinical arousal from sleep, which included such manifestations as eye opening and head lifting. Scalp EEG channels were reviewed separately to determine signs of electrographic arousal from sleep, defined by the presence of sustained alpha or theta activity. Isolated K-complexes without accompanying alpha or theta activity were not considered signs of electrographic arousal from sleep. Our definition of arousal was modified from the AASM criteria for EEG arousals.

RESULTS

All sleep-related and awake seizures began in the hippocampal depth electrodes. The average number of sleep-related seizures recorded in each subject was 4.8±3.6 (mean ± standard deviation) and ranged from 1 to 15. The intracranial seizure onset times determined by one of the authors and intracranial seizure onset times recorded in long-term monitoring reports were within three seconds in 62 (93%) of the seizures. In the other five seizures, onset times differed by six to ten seconds. When intracranial onset time differed, the average of the two times was used to calculate the difference between intracranial onset and clinical arousal. In all subjects except subject #14, in whom arousals from sleep always preceded intracranial onset times, both intracranial onset times preceded arousals from sleep. The clinical arousal times determined by the two authors were within five seconds in 59 (88%) of the seizures. In eight other seizures, the difference between the two arousal times was less than ten seconds. In every seizure where clinical arousal times differed, both clinical arousal times followed intracranial onsets with the exception of subject #14. When clinical arousal time differed, the average of the two times was used to calculate the difference between intracranial onset and clinical arousal.

In 13 of 14 subjects and 60 of 67 seizures, intracranial seizure onsets preceded clinical arousals from sleep, with an average seizure onset to clinical arousal time of 32.1±26.8 (mean±standard deviation) and range of 2-89 seconds. Figure 1A-B illustrates the evolution of a seizure in one of these subjects, with intracranial seizure onset followed by clinical arousal. The subject is in NREM stage 2 sleep prior to seizure onset. The open arrow indicates the intracranial electrode seizure onset in the left temporal
depth electrode contacts, characterized by the cessation of interictal epileptiform discharges and their replacement by high frequency sinusoidal activity that evolves in frequency and amplitude. The solid arrow indicates the clinical arousal from sleep noted on the videotape, marked by myogenic artifact. Note that the first representation of a sustained rhythmic discharge (ictal pattern) in the scalp electrodes follows the clinical arousal and is intermixed with the myogenic artifact. This scalp ictal pattern is delayed relative to the intracranial seizure electrode onset. Without the information provided by intracranial electrodes, one might erroneously conclude that the seizure followed, rather than preceded, the clinical arousal from sleep.8

In 13 of 14 subjects and 60 of 67 seizures, scalp electrographic correlates of arousal, defined by the presence of sustained alpha or theta activity, followed, rather than preceded, the intracranial seizure onsets. In a few instances, such correlates occurred simultaneously with the intracranial seizure onset. Scalp electrographic correlates of arousal were not uniformly present. As illustrated in Figure 1, in some seizures, an ictal discharge or myogenic artifact correlating with the clinical arousal from sleep dominated the scalp recording. Only one subject (#14) exhibited sleep-related seizures that followed clinical arousals from sleep. This subject had a history of complex partial seizures since childhood occurring every morning or every other morning upon awakening, and occasionally as he was awakening from a daytime nap. He was diagnosed with obstructive sleep apnea (respiratory disturbance index of 87 apneas and hypopneas/hour with minimum oxygen saturation of 83%) that resolved with continuous positive airway pressure (CPAP), although seizures persisted. Combined scalp-intracranial electrode monitoring revealed seven seizures localized to the right temporal lobe. In all seizures, the electrographic seizure onset followed the clinical arousal by 4 to 25 seconds. These arousals from sleep occurred following a variety of stimuli including a nurse knocking on the door to change an intravenous line, a hospital staff member delivering a breakfast tray, and a nurse arousing the patient to put his CPAP mask back on after it had fallen off. The patient underwent a right anterior temporal lobectomy and hippocampectomy four years ago with improvement in seizure control from several seizures per week to approximately one seizure per month.

Apart from subject #14, seven subjects had EOG and chin EMG placed during their monitoring admissions to assist in sleep scoring. In these seven subjects, in whom 38 seizures were recorded, all seizures began during NREM sleep. Thirty seizures occurred during NREM stage 2 sleep, seven seizures occurred during NREM stage 1 sleep, and one seizure occurred during NREM stage 3 sleep. No seizures occurred during REM sleep.

DISCUSSION

To our knowledge, this is the first study to explore the relationship between seizures and arousals from sleep in subjects with temporal lobe epilepsy undergoing monitoring with combined scalp-intracranial electrodes. Our results indicate that clinical arousals from sleep are more likely to follow seizures than to precede them. In 13 of our 14 subjects, clinical arousals from sleep occurred after seizures had begun in intracranial depth electrode contacts. The electrographic signs of arousal, measured in the scalp electrodes, either coincided with or followed seizure onsets. Only one of our subjects, with a history of seizures upon awakening, exhibited a pattern of arousal from sleep preceding epileptic seizures.

Our results suggest that processes involved in the initiation and maintenance of NREM sleep play a greater role in facilitating partial seizures of temporal lobe origin than...
those processes involved in promoting REM sleep and arousal. Both sleep and arousal-related mechanisms may be important in facilitating seizures, and mechanisms may differ among patients. Several partial epilepsy syndromes show a predilection to occur during NREM sleep, including autosomal dominant nocturnal frontal lobe epilepsy, benign rolandic epilepsy, and electrical status epilepticus of sleep. Other generalized epilepsy syndromes, such as juvenile myoclonic epilepsy and generalized tonic-clonic seizures upon awakening, may be precipitated by arousal from sleep. Janz differentiated patients who had a predilection for seizure occurrence during sleep and upon awakening. Reporting on a series of 2,110 subjects with generalized tonic-clonic seizures, he found that 45% had seizures during sleep and 34% had seizures upon awakening. Among those with complex partial and generalized tonic-clonic seizures who had temporal interictal epileptiform discharges, he found that 58% had seizures during sleep and 16% had seizures upon awakening. The prevalence of complex partial seizures upon awakening in subjects without generalized tonic-clonic seizures is unknown.

One limitation of our combined scalp-intracranial data is that all of our subjects had temporal lobe epilepsy. Subjects with generalized epilepsy are not candidates for surgical resections, and none of our patients had extratemporal lobe (e.g., frontal lobe) epilepsy. Therefore, we cannot comment on whether arousal mechanisms may be more important in facilitating seizures in these groups of subjects. Another limitation of our study is the definition of arousal from sleep. We defined clinical arousals from sleep by the first clinical sign of arousal on the videotape. Electroencephalographic (EEG) signs of arousal, present in the scalp electrodes, were not always present and may have been obscured by myogenic artifact. As our EEG electrode placement was limited to intracranial temporal and scalp EEG, we may not have captured the earliest EEG manifestations of arousal beginning in subcortical or other extratemporal brain regions. A related limitation is that our recordings emphasized EEG signs of arousal over other measures of arousal. Only eight of our subjects had EOG and chin EMG monitoring to aid in the scoring of arousals. We did not include non-EEG parameters, such as heart rate or variations in the microstructure of sleep, such as the "cyclic alternating pattern," in our definition of arousal.

We conclude that clinical arousals from sleep follow, rather than precede, seizures in the majority of cases of complex partial seizures of temporal lobe origin, although exceptions exist. Further studies will be necessary to determine the time sequence of seizures and clinical arousals in other types of epilepsies, such as extratemporal complex partial seizures or generalized seizures. In addition, experimental investigations will be needed to unravel the mechanisms underlying facilitation of seizures by sleep or arousal.

ACKNOWLEDGMENTS

We acknowledge the contributions of the epilepsy attending physicians and clinical neurophysiology fellows who cared for the subjects described in this manuscript. Dr. Diana Gomez-Hassan helped review neuroradiological studies. This work was supported by NINDS 1 K08 NS01840.

REFERENCES