SHORT REPORT

Do seizures in patients with refractory epilepsy vary between wakefulness and sleep?

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Aim: To determine the effects of sleep and wakefulness on seizures in patients with refractory epilepsy recorded while undergoing video-electroencephalography (EEG) telemetry.
Methods: The video-EEG data of patients who had two or more seizures during video-EEG telemetry (n = 270) were reviewed. Fifty seven patients who had seizures both in wakefulness and sleep were identified. The video and ictal EEG data were reviewed, paying specific attention to type of seizures, duration, semiology, lateralisation and number of seizures.
Results: Three hundred and sixty two seizures were recorded; 237 seizures while awake and 125 while sleeping. Secondary generalisation occurred more often in sleep than in wakefulness ($p<0.01$). Overall, there was no significant effect of sleep on the duration of seizures or ictal EEG change. Sleep and awake seizures differed in only eight patients.
Conclusion: Secondary generalisation occurred more often in sleep than in wakefulness, perhaps due to the facilitated spread of seizures during sleep. For the most part, however, seizures recorded during sleep did not differ from those recorded during wakefulness.

The interaction between sleep and epilepsy has been recognised as far back as Hippocrates. Recent research has further elucidated this complex relationship. Epilepsy and epileptic drugs can have a profound effect on the sleep–wake cycle and sleep architecture. In addition, sleep can affect seizure occurrence, threshold and spread. Interictal electroencephalography (EEG) abnormalities are often potentiated during sleep, suggesting a change in seizure threshold.[1–5] The sleep–epilepsy relationship varies, however, according to the epilepsy syndrome; in some, such as the frontal lobe epilepsies, sleep may facilitate seizures,[6] whereas in others, sleep may protect against epilepsy. The finding that frontal lobe seizures have a greater chance of occurring during sleep whereas temporal lobe seizures are more likely to occur during wakefulness implies that sleep has distinct effects on seizure threshold in different brain regions.[6] Furthermore, sleep can influence the extent of seizure spread, such that seizures in temporal lobe epilepsy are more likely to secondarily generalise during sleep than during wakefulness.[6 7] These observations suggest that sleep may influence the pattern and extent of seizure spread, and therefore the electroclinical characteristics of the seizures. If true, this has critical implications for presurgical assessment, because seizures recorded during the day may yield different information from those recorded during the night. There have, however, been few studies on the influence of time of day on seizure semiology beyond the observation of the increased likelihood of secondary generalisation. The aim of this study was to determine retrospectively the effects of sleep and wakefulness on seizures in individual patients with refractory epilepsy undergoing presurgical assessment in a video-EEG telemetry unit.

MATERIALS AND METHODS

This was a retrospective analysis of patients undergoing presurgical video-EEG telemetry at a tertiary referral centre. Two of us (SS, MB) independently reviewed the video-EEG telemetric data of all patients with medically refractory epilepsy who had two or more seizures during video-EEG telemetry from January 2002 until September 2004 (n = 270). These findings were crosschecked by the other two authors (CAS, MCW), especially when there were differences in opinion between the two observers or a difference reported between awake and sleep records. These patients had longstanding uncontrolled seizures and were on multiple drugs for epilepsy. Patients with non-epileptic episodes or non-epileptic episodes in addition to epileptic episodes were excluded. Wake–sleep states were determined using well-established EEG criteria.

Fifty seven patients in whom seizures were recorded in both wakefulness and sleep were identified, permitting within-subject seizure comparison. Drug doses for epilepsy were reduced (halved or quartered) in 30 patients, whereas they were unchanged in 27 patients. In addition, sleep deprivation was carried out in 19 patients. Video of the seizures was shown to relatives or carers in all cases to confirm that the seizures recorded were the habitual seizures. We reviewed the video and ictal EEG data of these patients, with specific attention to type and number of seizures, duration, semiology and evidence of lateralisation. Statistical analysis was carried out using unpaired, paired Student's t test or χ^2 test as appropriate. $p<0.05$ was considered to be significant.

RESULTS

The mean (standard deviation (SD)) age at evaluation of the 57 patients in whom both awake and sleep seizures were recorded was 34.4 (12.7) years. There was slight male predominance (M:F ratio = 31:26). A total of 362 seizures were recorded; 337 (93%) of these were complex partial seizures and 25 (7%) were secondary generalised seizures; 237 (65.5%) seizures were recorded while the subject was awake and 125 (34.5%) while sleeping. Forty two patients (132 awake seizures, 74 sleep seizures) had temporal lobe epilepsy and 15 patients (85 awake seizures, 71 sleep seizures) had frontal lobe epilepsy. Overall, frontal lobe seizures were briefer ($p<0.05$) and more likely to secondarily generalise ($p<0.001$) compared with temporal lobe seizures.

Secondary generalisation occurred more often in sleep than in wakefulness ($p<0.01$). Complex partial seizures were more frequent during the awake state ($p<0.01$). Sleep deprivation was carried out in 19 patients. Secondary generalised seizures while awake occurred in six of these patients, whereas they occurred in only two patients without sleep deprivation ($p<0.001$). Arousal with α rhythms on EEG before onset of seizure was evident in only 12 (21%) patients. Seizures were

Abbreviations: EEG, electroencephalography; REM, rapid eye movement

Table 1 Comparison of some parameters during awake and sleep states (n = 57)

Parameters	Awake	Sleep	Statistics
No of episodes	237	125	—
No of partial seizures	229	108	$p<0.01$ (χ^2)
No of generalised seizures	8	17	$p<0.01$ (χ^2)
Duration of clinical episodes (SD)	196.8 (349.3)	161.04 (249.9)	NS (paired Student's t test)
Evidence of lateralisation	27	29	NS (χ^2)
Duration of ictal EEG change (SD)	63.5 (1)	69.1 (71.8)	NS (paired Student's t test)

EEG, electroencephalography; NS, not significant; SD, standard deviation. Duration is in seconds.

recorded from various stages of sleep—I: 19.2%, II: 55.2%, III: 8.8% and IV: 16.8%. Interestingly, no seizures were recorded during rapid eye movement (REM) sleep.

Sleep had no significant effect on the duration of seizures or ictal EEG change (table 1). No difference was found in the semiology between sleep and awake seizures in 49 (86%) patients. The semiology of sleep and awake seizures differed in only eight patients. These differences were, however, subtle and consisted of the presence of lateralising signs during sleep, but not during awake seizures (n = 5); the presence of lateralising signs during awake, but not during sleep seizures (n = 1), much briefer nocturnal seizures than daytime seizures (n = 1; sleep: 360 s *v* awake: 600 s) and distinct differences in the semiology of awake and sleep seizures (n = 1). This last patient had bilateral hippocampal sclerosis (left more affected than right) and the daytime seizure had signs consistent with left temporal involvement with marked aphasia, whereas the nocturnal seizure had signs indicative of right temporal involvement with dystonic posturing of the left hand, and automatisms affecting the right hand. The ictal EEG was not lateralising.

DISCUSSION

The relationship between sleep and epilepsy shows the delicate association of brain physiology and dysfunction. Sleep affects the distribution and frequency of epileptiform discharges in humans and influences the rate of kindling in animals. Epileptic discharges, on the other hand, alter sleep regulation and provoke sleep disruption.[3] In this study, we asked to what extent sleep modified the electroclinical characteristics of seizures. Apart from the finding that secondary generalisation occurred more often during sleep than during wakefulness, the sleep–wake state had little influence on seizure semiology. Indeed, in only eight patients could we detect subtle differences between awake and sleep seizures, usually consisting of the presence of lateralising signs during sleep, but not during wakefulness.

There may be several confounding factors in our study. Seizure semiology can be more difficult to determine at night than during the day. Secondly, although we recorded seizures during sleep, they were preceded by evidence of arousal and the emergence of α rhythms in about one fifth of the patients. This may explain the similarity in daytime and nocturnal seizures in those patients, but would not explain this finding in the majority who did not have arousals evident on the EEG (we cannot, however, exclude a brief arousal, obscured by movement artefacts in a few).

Sleep may influence seizures in a variety of ways. One of the well-accepted phenomena is that sleep deprivation can exacerbate most seizure types[8] (this is especially so with idiopathic generalised seizures). The effects of sleep itself are, however, dependent on the epilepsy syndrome.[6] Frontal lobe seizures occur more often during sleep. Temporal lobe seizures start more often while awake, but generalise more so when asleep.[6 7] The stage of sleep may also have different effects on seizures. Non-REM sleep exacerbates seizures by synchronisation of EEG, resulting in more frequent and widespread interictal epileptiform discharges. The reverse is true for REM sleep.[3] A similar finding was noted in our study, in which we observed no seizures arising from REM sleep. About three quarters of the seizures in this study were recorded during light sleep (stages I and II). Although we did not analyse the time spent in each stage of sleep, this is consistent with the observation that seizures arise more often during light rather than deep sleep.[9]

Neural generators of synchronous EEG oscillations—including tonic background slow waves—and phasic ''arousal'' events (sleep EEG transients such as sleep spindles and K-complexes) combine to promote electrographic seizure propagation during non-REM and drowsiness, and antigravity muscle tone permits seizure-related movement.[2 3] In keeping with this, we found that sleep has a pronounced effect on secondary generalisation of partial seizures, especially those of temporal lobe origin; this finding is consistent with other studies.[6 7] We further hypothesised that sleep would influence the semiology and electrographic characteristics of the seizure. In contrast, however, we found that in most cases sleep has a minimal effect on seizure characteristics. This finding suggests that although there may be an overall change of seizure threshold during sleep, resulting in more frequent seizures in frontal lobe epilepsy and more frequent secondary generalisations, the pattern of spread and the distributed networks involved in determining seizure semiology remain unchanged. This has important implications for presurgical assessment, as it implies that the quality of the data obtained should not be substantially influenced by the time of day at which it is recorded.

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REFERENCES

1 **Sterman MB**, Shouse MN, Passouant P, eds. *Sleep and epilepsy*. New York: Academic Press, 1982.
2 **Baldy-Moulinier M**. Inter-relationships between sleep and epilepsy. In: Pedley TA, Meldrum BS, eds. *Recent advances in epilepsy*. Edinburgh: Churchill Livingstone, 1986;**3**:37–55.
3 **Vaughn BV**, D'Cruz OF. Sleep and epilepsy. *Semin Neurol* 2004;**24**:301–13.
4 **Sammaritano M**. Sleep and epilepsy. *Epilepsy Curr* 2001;**1**:50.
5 **Crespel A**, Baldy-Moulinier M, Coubes P. The relationship between sleep and epilepsy in frontal and temporal lobe epilepsies: practical and physiopathologic considerations. *Epilepsia* 1998;**39**:150–7.

6 **Herman ST**, Walczak TS, Bazil CW. Distribution of partial seizures during the sleep-wake cycle: differences by seizure onset site. *Neurology* 2001;**56**:1453–9.
7 **Bazil CW**, Walczak TS. Effects of sleep and sleep stage on epileptic and nonepileptic seizures. *Epilepsia* 1997;**38**:56–62.
8 **Nakken KO**, Solaas MH, Kjeldsen MJ, *et al*. Which seizure-precipitating factors do patients with epilepsy most frequently report? *Epilepsy Behav* 2005;**6**:85–9.
9 **Minecan D**, Natarajan A, Marzec M, *et al*. Relationship of epileptic seizures to sleep stage and sleep depth. *Sleep* 2002;**25**:899–904.

NEUROLOGICAL PICTURE

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Torcular Erdheim–Chester disease

Erdheim–Chester disease (ECD) is a rare non-Langherans histiocytosis associated with multiple organ systems. Typical features include osteosclerotic lesions in the metaphysis of long tubular bones, exophthalmia, pulmonary and retroperitoneal fibrosis,[1] which highlight the diagnostic difficulties that ECD presents. Intracranial association is exceptional and its treatment is controversial.[2]

We present the case of a 52-year-old man with a history of progressive visual deficit, pseudotumour cerebrums and diabetes insipidus, who presented with a tumour in the torcular region; the lesion included the falx, transverse sinuses and straight and superior sagittal sinuses and had the radiological features of a meningioma (fig 1). Angiography of the cerebrum showed thrombosis of both transverse sinuses, with a narrowed anterior superior sagittal sinus but no hypervascular tumour stain. The lesion infiltrated the posterior falx and tentorium with a nodule indenting, but not infiltrating, the left cerebellar hemisphere. After subtotal resection of the mass, histological examination showed numerous lipid-laden histiocytes and scattered multinuclear Touton-type giant cells (fig 2) and rare eosinophils. The diagnosis was a xanthogranuloma of the Erdheim–Chester type. Further imaging showed multiple lesions in both femurs, pleural and retroperitoneal fibrosis with the kidneys being affected. The patient had a progressive worsening of respiratory and renal functions and died 6 months after diagnosis.

Most reported cases of intracranial ECD are dural granulomas affecting the brain stem, cerebellum and vertebral and basilar arteries.[1–5] Diabetes insipidus and cerebellar signs are the most common neurological symptoms.[3 4] A characteristic feature on MRI is the prolonged retention, even after several weeks, of gadolinium; this may be because of the abnormal content of histiocytes in the lesions.[5] In this unusual case, ECD was diagnosed after resection of the intracranial mass. The progression of neurological symptoms further distinguishes this case from previous reports.

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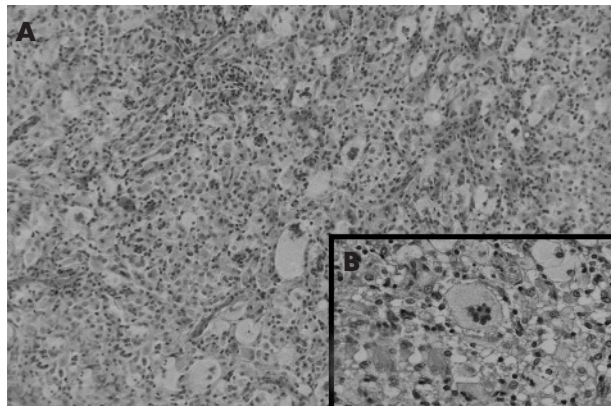

Figure 2 (A) Mixed, chronic inflammatory infiltrate of lymphocytes and foamy histiocytes; some of the histiocytes are multinucleated giant cells, original magnification ×250. (B) High-power view of (A). Touton-like multinucleated giant cell is readily identified, original magnification ×400.

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References

1 **Wright RA**, Hermann RC, Parisi JE. Neurological manifestations of Erdheim-Chester disease. *J Neurol Neurosurg Psychiatry* 1999;**66**:72–5.
2 **Bohlega S**, Alwatban J, Tulbah A, *et al*. Cerebral manifestation of Erdheim-Chester disease: clinical and radiologic findings. *Neurology* 1997;**49**:1702–5.
3 **Fukazawa T**, Tsukishima E, Sasaki H, *et al*. Erdheim-Chester disease and slowly progressive cerebellar dysfunction. *J Neurol Neurosurg Psychiatry* 1995;**58**:238–40.
4 **Oweity T**, Scheithauer BW, Ching HS, *et al*. Multiple system Erdheim-Chester disease with massive hypothalamic-sellar involvement and hypopituitarism. *J Neurosurg* 2002;**96**:344–51.
5 **Rushing EJ**, Bouffard JP, Neal CJ, *et al*. Erdheim-Chester disease mimicking a primary brain tumor. Case report. *J Neurosurg* 2004;**100**:1115–8.

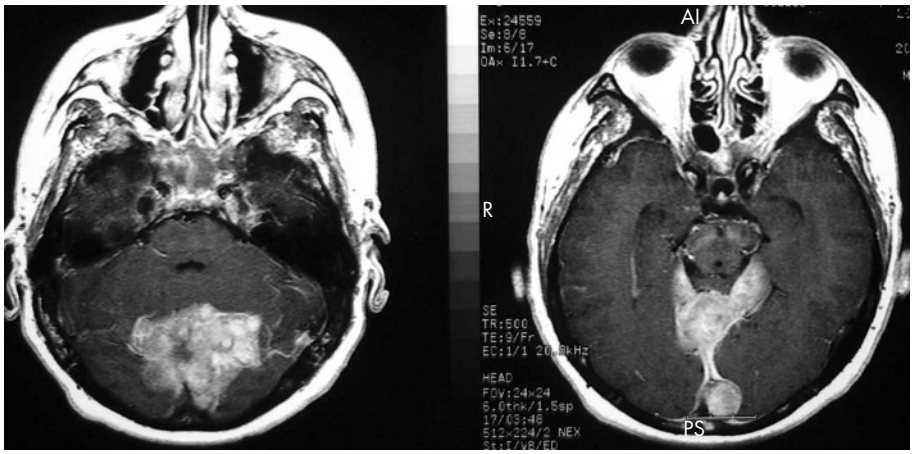

Figure 1 Brain MRI axial T1-weighted postcontrast image shows abnormal homogeneous infrasupratentorial tumour at the level of the torcula.