The relationship between sleep and epilepsy

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Abstract
Epilepsy and sleep have a close association and a two way interaction. Recognising this allows for a greater awareness of the importance of good quality sleep in epilepsy patients with potential benefits on seizure control and quality of life. This article reviews this complicated but fascinating area addressing diagnostic issues, the effects of epilepsy and its treatments on sleep, the effects of sleep disorders on epilepsy concluding with some practical advice on assessment.

Introduction

Sleep and epilepsy are intimate bedfellows, having an impact on each other and adversely affecting quality of life and daytime performance.[1] Sleep has an important role in memory consolidation.[2] Sleep deprivation impairs this process[3] and epilepsy can upset this delicate balance.[4] Sleep disorders are up to three times as common in epilepsy[5] and can be a major contributor to refractory seizures,[6] poorer quality of life[7] and possibly SUDEP.[8] Recognition of the comorbid sleep disorder and successful treatment can lead to significant improvements in seizure control.[9] Many patients with epilepsy have seizures in sleep, some exclusively so. Often diagnosis is difficult due to incomplete histories from sleep partners. Even when telemetry facilities are available, data can be difficult to interpret and EEG is not always diagnostic.[10] To add to this complexity, epilepsy treatments often have impact on sleep. Understanding this complex relationship can lead to better treatment outcomes for patients. This review will begin with diagnostic issues, moving on to the effects of epilepsy and its treatments on sleep, the effects of sleep disorders on epilepsy and concludes with practical advice on assessment.

Epilepsy Syndromes Closely Associated with Sleep

There are a small number of epilepsy syndromes which are predominantly or exclusively associated with sleep (Table 1). Seizures arising from sleep are almost always of focal onset. These include the childhood onset syndromes of benign childhood epilepsy with centrotemporal spikes (BCECTS, Rolandic epilepsy), benign childhood epilepsy with occipital paroxsysms (Panayiotopoulos syndrome) and the frontal lobe epilepsy syndromes (including autosomal dominant nocturnal frontal lobe epilepsy ADNFLE). Idiopathic generalised epilepsy syndromes (IGE) such as juvenile myoclonic epilepsy (JME) and generalised tonic clonic seizures on waking arise shortly before or after sleep onset but not from a sleep state.

Diagnosing Paroxysmal Nocturnal Events

Table 2 summarises clinically important details which help in differentiating epilepsy from other sleep disorders. Derry et al (2006 & 2009) have produced very useful clinical tools to help differentiate nocturnal seizures from other sleep disorders with diagnostic accuracy up to 94%[11,12,8] however comorbidity is common[13] and an awareness of the characteristic features of the more common conditions enhances the history taking process. During nocturnal seizures patients rarely leave the bed space, episodes are often brief and stereotyped and can cluster throughout the night (Figure 1). Incontinence, tongue trauma and seizures during daytime wakefulness are strong pointers. Postictal symptoms on waking such as generalised aching, headache and amnesia of the preceding day's events are strongly associated.

Parasomnia episodes are seen in either rapid eye movement (REM) or non-REM (nREM) sleep. REM parasomnia (REM behaviour disorder (RBD) is almost exclusively seen in elderly subjects with a male predominance, often associated with alpha synucleonopathies.[14] Dream enactment occurs due to a lack of muscle atonia during REM sleep. Episodes occur late in the sleeping period where a higher concentration of REM sleep is seen. Patients often recall their dreams, behaviour is often violent and episodes are repeated each night. The American Academy of Sleep Medicine suggests RBD is diagnosed with polysomnography (PSG) as it can sometimes be difficult to differentiate it from epilepsy on the history alone.[15]

Table 1: Epilepsy Syndromes Closely Associated with Sleep

Focal Onset Syndromes	Idiopathic Generalised Epilepsy Syndromes	Epilepsy syndromes of uncertain origin
Benign childhood epilepsy with centrotemporal spikes (BCECTS, Rolandic epilepsy)	Juvenile myoclonic epilepsy (JME)	Continuous spike and wave during slow wave sleep
Benign childhood epilepsy with occipital paroxysms (Panayiotopoulos syndrome)	Generalised tonic clonic seizures on waking	Landau – Klefner syndrome
Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)		
Nocturnal frontal lobe epilepsy		
Nocturnal temporal lobe epilepsy		

Figure 1: A video EEG image of a nocturnal seizure showing short lived dystonic posturing of the right hand seen immediately on waking. 30 stereotyped attacks were recorded over 2 nights. The EEG was normal throughout. Awareness was reported for most attacks although the hand posturing was not recalled by the patient.

nREM parasomnias generally arise in childhood, they are less frequent and usually singular during the early part of a sleeping period. Patients are more often amnesic to the event however, some recollection of the later stages of events is often reported due to awakening, often in a confused state. Injury is rare, behaviour is often complex and episodes can be prolonged but usually not more than 30 minutes. Excessive daytime somnolence (EDS) is generally not a direct consequence of nREM parasomnias but if severe one should consider comorbid sleep disorders such as obstructive sleep apnoea (OSA) and periodic limb movements in sleep (PLMS).

Night terrors and confusional arousals

Differentiating between these two types of common nREM parasomnias often causes difficulty. Night terrors are exclusively a paediatric condition and don't persist into adulthood. Although deeply asleep, the child appears awake and is inconsolably terrified, often screaming loudly. Events can last up to one hour but they are not remembered. Confusional arousals occur in adulthood when an abrupt but incomplete awakening occurs from slow wave sleep (SWS), often associated with distressing dreams which can be recalled, leading to confusion and sometimes injury.[16] Diagnostic difficulty can arise when the arousal is due to a short seizure and the confusion due to postictal phenomena.

The effects of epilepsy on sleep

The effects and consequences of epilepsy on the sleep EEG

Objective PSG assessments show that interictal epileptiform discharges (IEDs), increase in sleep[17] especially in N3 nREM sleep, although seizures seem to predominate in lighter nREM sleep.[18] Nocturnal seizures lead to reductions in REM sleep and increases in nREM sleep. These changes are also seen when a wakeful seizure has occurred the previous day.[19] Seizure types have differing relationships with sleep with focal epilepsies being more likely to disrupt sleep than IGE. Even in seizure free states, interictal temporal lobe epileptic discharges seem to disrupt sleep when compared with frontal lobe epilepsy (FLE) and IGE. Temporal lobe epilepsy (TLE) correlates with worse sleep efficiency and increased stage shifts and awakenings. Despite this, frontal lobe seizures are seen more commonly in sleep than temporal lobe seizures.[20] Uncontrolled epilepsy in sleep can lead to memory impairments[4] and excessive daytime somnolence (EDS).[5]

The effect of epilepsy treatments on sleep

AEDs (Table 3) and epilepsy surgery can affect sleep however the particular effects can be unpredictable.

AEDs

Few studies have been conducted in this complex area. Those which have are limited by short duration and inadequate controls for seizure types and polypharmacy. It appears that AEDs can improve sleep, however it is uncertain if this is due to improved seizure control or independent sleep consolidation.[8] Unfortunately, AEDs commonly produce daytime fatigue and at higher doses excessive daytime somnolence (EDS).[23] This can be an advantage in patients with insomnia. Some AEDs are associated with significant weight gain which can lead to OSA. Care must be taken when using sedating drugs such as the benzodiazepines (BZPs) in patients who may be prone to sleep disordered breathing as apnoeic episodes may increase.[24] Care should be taken when labeling EDS as a side-effect of AEDs as this risks under interpreting the disruptive effects of unrecognised nocturnal seizures or co-morbid sleep disorders. Polysomnography (PSG) may be required to differentiate between the two.

The effects of AED withdrawal on sleep must also not be overlooked. Withdrawal of a sedating drug may lead to reductions in sleep,[25] withdrawal of mood stabilising

Table 2: Clinical features of disorders commonly producing sleep attacks

Disorder	Age of onset	Patient Awareness	Leaves the bed	Stereotyped behaviour	Complex behaviours	Incontinence / tongue bites / injury	Daytime somnolence	No. of attacks per night	Typical duration of attack	Typical time of night
Epilepsy[8]	Any	Variable but usually poor	No	Yes (posturing, head version)	No	Yes	Variable	Often multiple	Seconds - minutes	Any
Non REM Parasomnia[8]	Childhood	None or very limited	Common	No	Yes (talking, walking, eating, intercourse)	No (rarely sustain injury)	Variable (if severe consider comorbid sleep disorders, OSA, PLMS etc)	Singular	< 30 minutes	Within 2 hrs of sleep onset
REM Behaviour Disorder (RBD)[12]	Middle age to elderly (mostly male)	Variable but can be significant (distressing dreams etc)	No	No	No	No (but injury sustained in violent acts)	No	Can be multiple	Seconds	> 4 hrs after sleep onset
Non -Epileptic / Functional attacks[8]	Young adult	Poor	Variable	No	Variable	Variable	Variable	Variable	Usually prolonged	Any
Periodic Limb Movements in Sleep	Elderly	Poor	Never	Yes (small amplitude flexion of legs)	Never	Never	Common	Numerous 10s – 100s)	Seconds	Any

Table 3: Common Effects of AEDs on Sleep Symptoms / Disorders		
AED	**Improves**	**Worsens**
Lamotrigine (LTG)	–	Insomnia
Levetiracetam (LEV)	–	Fatigue / Somnolence OSA [a]
Carbamazepine (CBZ)[8,21]	Insomnia[22]	Fatigue / Somnolence
Sodium Valproate (VPA)[21]	Insomnia	Fatigue / Somnolence
Phenytoin (PHT)[8,21]	–	Fatigue / Somnolence Insomnia
Topiramate (TPM)	OSA [b]	-
Pregabalin (PGB)	Insomnia[22,41]	Fatigue / Somnolence OSA [a]
Gabapentin (GBP)[21]	Insomnia[22]	Fatigue / Somnolence OSA [a]
Phenobarbitone (PHB)[21]	Insomnia	Fatigue / Somnolence OSA [a]
Lacosamide (LAC)	–	Fatigue / Somnolence
Zonisamide (ZON)	OSA [b]	Fatigue / Somnolence
Perampanel (PER)	–	Fatigue / Somnolence OSA [a]
Oxcarbazepine (OXC)	–	Fatigue / Somnolence
Ethosuxamide (ETH)[21]	OSA [b]	–
Benzodiazepines (BZP)[21]	Insomnia	Fatigue / Somnolence OSA
(a) – due to weight gain (b) – due to weight loss		

Table 4: Comorbid Sleep Disorders in Epilepsy Patients			
Sleep disorder	**Prevalence Rates**	**Reference**	**Commonly used non-AEDs which may worsen the disorder**
Insomnia	52% (vs 38% controls)	Khatami et al 2006[37]	Caffeine Stimulants (methylphenidate, modafinil, amantadine) Alpha-blockers Beta-blockers Corticosteroids SSRI antidepressants ACE inhibitors Angiotensin Receptor II Blockers Cholinesterase inhibitors H1 antagonists Statins
OSA	30%	Malow et al 2000[33,1]	BZPs
CSA	3.7%	Vendrame et al 2013[32]	BZPs
PLMD	17%	Malow et al 1997[40]	Antidepressants (except buproprion) Neuroleptics Antihistamines
RLS	18% (vs 12% controls) ns	Khatami et al 2006[37]	Antidepressants (except buproprion) Neuroleptics Antihistamines
EDS (>10 on Epworth Sleepiness Scale)	19% (vs 14% controls)	Khatami et al 2006[37]	BZPs Mirtazepine Tricyclic antidepressants Neuroleptics Dopaminergics
ns = non significant			

Table 5: Practical tips for the evaluation of sleep problems in epilepsy patients	
Diagnosis	FLEP scale,[11] CHIAD Tree analysis[12]
Clues regarding the onset of symptoms	Drug commencement, Drug withdrawal, Weight gain, Epilepsy surgery / VNS
Assess for comorbidity	RLS (IRLS scale),[42] OSA (Berlin questionnaire,[43] STOP BANG questionnaire), EDS (ESS)[44]
Optimise sleep hygiene	Regular bed and wake up times, Remove bedroom technology Avoid caffeine after 1800 hrs, Avoid large meals after 1800 hrs, Reduce evening fluid intake, No daytime naps

AEDs (i.e. VPA, CBZ, LTG, TPM) may lead to worsening depression and anxiety all of which can precipitate insomnia and nREM parasomnias. Withdrawal of TPM can lead to weight gain which may precipitate OSA.

Chronopharmacology

Chronopharmacology holds great potential when applied to the management of epilepsy; it recognises that circadian rhythms exist in absorption and metabolism of drugs. For example, it has been recognised that without changing the total daily dose of PHT and CBZ in epilepsy patients, serum levels increase and seizure control improves by administering proportionally higher doses at 2000 hrs compared with the morning.[26] This suggests that great benefits can be achieved by prescribing higher doses of AEDs later in the day.

Epilepsy surgery

Resective epilepsy surgery is now widely used to treat refractory epilepsy. However, only one study of 17 patients has evaluated sleep pre and post operatively using PSG. Although no overall benefit was seen, patients who attained better post operative seizure control had greater improvements in total sleep times and arousals.[27] Vagal nerve stimulation (VNS) has shown increases in SWS and nocturnal sleep latency in a study of 15 children with refractory epilepsy.[28] However, in adult populations it can lead to deterioration in sleep disordered breathing in up to 31% of patients[29] thus changes in snoring and EDS should be closely monitored post VNS insertion. Deep brain stimulation (DBS) is now a recognised epilepsy surgery technique however it may have deleterious effects on sleep as there is a small amount of evidence to suggest that anterior thalamic nucleus DBS has been found to increase electroclinical arousals on average 3.3 times more frequently during stimulation periods compared to non-stimulation periods in a study of 9 patients.[30]

The effects of sleep disorders on epilepsy

Sleep disorders are up to three times as common in patients with epilepsy compared with controls.[5]

Sleep deprivation is often associated with an increase in IEDs and poorer epilepsy control[31] with 77% of JME patients reporting more seizures when sleep deprived.[32] AEDs are associated with weight gain,[33] and mental health disorders[34] and both of these conditions predispose to sleep disorders. OSA is often caused or worsened by increases in the BMI and is known to have prevalence rates up to 30% in epilepsy populations[33] and is associated with worsening seizure control.[6] TLE has a greater association with OSA than extra temporal seizures.[35] Management of OSA with continuous positive airway pressure (CPAP) produces improvements in epilepsy control with seizure freedom seen in almost 20% in a randomised controlled trial of 68 using therapeutic vs sham CPAP.[7] Impressive responder rates (>50 % seizure reduction) have also been reported in trials of CPAP for OSA in epilepsy subjects (OR 32.2).[36] Mood disturbance is also very prevalent in epilepsy patients.[34] Sleep disorders are commonly associated with these mental health problems. Concurrent use of antidepressants is common, thus an awareness of the effects of these drugs is required when evaluating

sleep complaints in epilepsy patients to ensure their contribution is not overlooked (Table 4), in particular an awareness of the potential for precipitation of RBD, RLS and PLMD. RBD can be mistaken for epilepsy and can be effectively treated with removal of the antidepressant or the use of melatonin. RBD, restless leg syndrome (RLS) and periodic limb movement disorder of sleep (PLMD) are also commonly precipitated by antidepressant and neuroleptic drugs however RLS and PLMD occur in a primary form in the absence of pharmacological triggers and can significantly disrupt the quality of sleep although the evidence available suggests they are no more common in epilepsy subjects compared with controls.[37,38] There is no published evidence on the impact of treating RLS / PLMD on seizure control however this should be considered good practice.

Conclusions

Epilepsy and sleep and its disorders are very closely associated and improvements in the recognition and management of either will have beneficial effects on the other (see Table 5 for practical tips on clinical assessment). Research in this field is still in its infancy compared with other neurological conditions, however greater awareness and investment promises much for epilepsy patients.

Table 6: Abbreviations

ADNFLE – Autosomal dominant nocturnal frontal lobe epilepsy
AED – Anti epileptic drug
BCECTS – Benign childhood epilepsy with centrotemporal spikes
BMI – Basal metabolic rate
BZP – Benzodiazepine
CBZ – Carbamazepine
CPAP – Continuous positive airway pressure
CSA – Central sleep apnoea
DBS – Deep brain stimulation
EDS – Excessive daytime somnolence
ETH – Ethosuximide
FLE – Frontal lobe epilepsy
GBP – Gabapentin
IED – Interictal epileptiform discharges
IGE - Idiopathic generalised epilepsy
JME – Juvenile myoclonic epilepsy
LAC – Lacosamide
LEV – Levetiracetam
LTG – Lamotrigine
nREM – Non rapid eye movement sleep
OR – Odds ratio
OSA – Obstructive sleep apnoea
OXC – Oxcarbazepine
PER – Perampanel
PGB – Pregabalin
PHB – Phenobarbitone
PHT – Phenytoin
PLMD – Periodic limb movement disorder of sleep
PSG – Polysomnography
RBD – REM behaviour disorder
REM – Rapid eye movement sleep
RLS – Restless leg syndrome
SUDEP – Sudden death in epilepsy
TLE – Temporal lobe epilepsy
SWS – Slow wave sleep
VNS – Vagal nerve stimulation

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