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Review

Sleep and epilepsy

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ABSTRACT

The intimate relationship between sleep and epilepsy has long been recognized, yet our understanding of the relationship is incomplete. In this article we address four key issues in this area. First, we consider the reciprocal interaction between sleep and epilepsy. Sleep state clearly influences seizure onset, particularly in certain epilepsy syndromes. The converse is also true; epilepsy may disrupt sleep, either directly through seizures and epileptiform activity, or indirectly through medication-related effects. Unraveling the influences of sleep stage, epilepsy syndrome, and drug effects is challenging, and the current state of knowledge is reviewed. Secondly, accurate diagnosis of sleep-related epilepsy can be difficult, particularly the distinction of nocturnal frontal lobe epilepsy (NFLE) from arousal parasomnias. The challenges in this area, along with work from the authors, are discussed. Thirdly, we will explore the putative relationship between obstructive sleep apnea (OSA) and epilepsy, including the effect of OSA on quality of life; this will lead us to a brief exploration of the effects of OSA on neuroendocrine function. Finally, we will review the evidence surrounding the role of sleep in sudden unexpected death in epilepsy (SUDEP).

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1. Introduction

The intimate relationship between sleep and epilepsy has long been recognized, yet our understanding of the relationship is incomplete. In this article we address four key issues in this area.

First, we consider the reciprocal interaction between sleep and epilepsy. Sleep state clearly influences seizure onset, particularly in certain epilepsy syndromes. The converse is also true; epilepsy may disrupt sleep, either directly through seizures and epileptiform activity, or indirectly through medication-related effects. Unraveling the influences of sleep stage, epilepsy syndrome, and drug effects is challenging, and the current state of knowledge is reviewed.

Secondly, accurate diagnosis of sleep-related epilepsy can be difficult, particularly the distinction of nocturnal frontal lobe epilepsy (NFLE) from arousal parasomnias. The challenges in this area, along with work from the authors, are discussed. Thirdly, we will explore the putative relationship between obstructive sleep apnea (OSA) and epilepsy, including the effect of OSA on quality of life; this will lead us to a brief exploration of the effects of OSA on neuroendocrine function. Finally, we will review the evidence surrounding the role of sleep in sudden unexpected death in epilepsy (SUDEP).

For the sake of clarity, we have used the 1981 and 1989 ILAE classifications [1,2] for seizures and epilepsy in this article, as most work to date has used these classification systems.

2. Sleep and epilepsy — pathophysiologial interactions

2.1. The effects of sleep on epilepsy

The 19th-century neurologist William Gowers first highlighted the effects of sleep on seizures. In a study of institutionalized patients, he observed that in 21% of patients, seizures occurred only at night, in 42% they occurred only during the day, and in the remaining 37% they occurred randomly either during the day or at night [3]. This led to the concept of the 'pure sleep epilepsy', a term that is still used to describe patients in whom seizures are limited exclusively to sleep. Pure sleep epilepsies comprise about 6% of epilepsy patients according to one study from a tertiary referral center, although this figure rises to around 10% of epilepsy patients when individuals with occasional daytime seizures are included [4]. A variety of syndromic and non-syndromic epilepsies can present as pure sleep epilepsy, but focal epilepsies most commonly present in this way [5]. Pure sleep epilepsies often respond well to treatment with antiepileptic drugs [6], although the reasons for this are unknown.

A more recently described concept, first reported by Janz, is that of the 'awakening epilepsy' [7]. In this, seizures tend to occur around awakening, usually within the first hour or two after arousal. This is usually a feature of idiopathic generalized epilepsy syndromes such as juvenile myoclonic epilepsy.

Outside these clear temporal relationships between sleep and epilepsy, however, the electroclinical characteristics of many types of epilepsy are modified by the sleep-wake cycle. Electroencephalogram abnormalities, seizure types, and seizure frequencies may all be

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influenced by the sleep-wake state in a variety of ways. This relationship is complex and depends upon two principal factors: epilepsy syndrome and sleep stage.

2.1.1. Effects of sleep according to epilepsy syndrome

The electroclinical features of a number of syndromic and non-syndromic epilepsies are characteristically modified by the sleep-wake cycle. These are listed in Table 1, and discussed below.

2.1.1.1. Idiopathic generalized epilepsies (IGE). Broadly speaking, the seizures of idiopathic generalized epilepsy occur during wakefulness and include 'awakening epilepsies' as described by Janz [7,8]. In particular, the syndromes of juvenile myoclonic epilepsy and epilepsy with generalized tonic-clonic seizures on awakening are classical awakening epilepsies. Seizures in these syndromes also occur more commonly following nights of sleep deprivation, for reasons that are not well understood. On EEG, generalized epileptiform discharges tend to be most frequent during NREM sleep and least frequent in REM sleep [9–12]. The spike-wave discharges are most prominent in stage 2 sleep, where they are often seen in conjunction with K-complexes. According to Niedermeyer, these K-complexes may have an abnormal morphology with a frontal predominance, and he has proposed that this pattern represents 'dyshormia', or disordered arousal [9].

A minority (less than 10%) of individuals with IGE may present as pure sleep epilepsies, with generalized tonic-clonic seizures restricted to sleep. In these individuals, EEG abnormalities are often only seen during sleep [4,13].

2.1.1.2. Symptomatic generalized epilepsies (SGE). In contrast to IGE, seizures in SGE typically occur in both wakefulness and sleep. However, the electroclinical manifestations are significantly influenced by the sleep-wake state. In West syndrome, the characteristic high amplitude 'hypsarrhythmic' interictal EEG pattern is seen most prominently in early NREM sleep [14]; infantile spasms in West syndrome occur predominantly on awakening or during drowsiness before sleep onset, although they are uncommon during sleep itself [15]. In contrast, the tonic seizures of Lennox–Gastaut syndrome (LGS) occur much more frequently during NREM sleep than wakefulness. They may be very subtle or clinically silent during sleep but are often very frequent, being associated with characteristic paroxysmal fast activity on EEG; such sleep-related tonic seizures are seen in over 90% of patients with LGS [16]. In addition to the influence of sleep on seizures in Lennox–Gastaut syndrome, there is facilitation and modulation of the interictal slow spike-wave pattern during NREM sleep [17].

2.1.1.3. Idiopathic focal epilepsies. Seizures in the idiopathic focal epilepsy syndromes of childhood have a marked tendency to occur during sleep. Benign childhood epilepsy with centrotemporal spikes is associated with partial or secondarily generalized seizures, which occur exclusively during sleep in 70–80% of cases [18]. On EEG, the interictal epileptiform discharges of this condition are often infrequent or absent during wakefulness but are markedly activated during drowsiness and light NREM sleep [14]. In benign childhood epilepsy with occipital paroxysms (particularly of the Panayiotopoulos syndrome subtype), partial seizures, sometimes with secondary generalization, may also occur during sleep. Likewise, the interictal occipital sharp waves are accentuated by NREM sleep [19]. In autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), seizures occur exclusively during sleep in the majority of affected individuals [20].

2.1.1.4. Symptomatic and cryptogenic focal epilepsies. Around 80% of all "pure sleep epilepsies" are focal epilepsies [6]. Interestingly, idiopathic or lesion-negative focal epilepsies appear more likely to remain strictly nocturnal than those with an associated lesion [21] and often appear to have a relatively benign outcome with a good response to antiepileptic drugs [22].

Frontal lobe seizures have a strong preponderance to occur during sleep and occur more commonly during sleep than temporal lobe seizures (although the latter are more likely to secondarily generalize in sleep) [23–25]. Most individuals with frontal lobe epilepsy will have a significant proportion of their events during sleep, and many will have their seizures exclusively during sleep. Individuals in whom over 90% of their seizures arise during sleep are said to have nocturnal frontal lobe epilepsy (NFLE) [26]. It should be noted that the clinical syndrome of NFLE, although implicating frontal lobe structures in seizure semiology, does not always indicate a frontal lobe *onset* for seizures; recently, NFLE with established seizure onset outside the frontal lobes (for example in the temporal lobes or insular cortex) has been reported [27,28]. A syndrome of nocturnal temporal lobe epilepsy is described [29] but is uncommon.

From the electrographic perspective, NREM sleep (particularly stages 3 and 4) is an effective facilitator of focal epileptiform discharges in focal epilepsies [11,30], resulting in more frequent discharges with more extensive field [11]. In contrast, discharges in REM sleep have a more restricted field; some authors have asserted that the field in REM sleep is the most reliable interictal indicator of the epileptogenic zone [11,31].

2.1.1.5. Epilepsies undetermined as partial or generalized. The syndromes of epilepsy with continuous spike–waves during slow-wave sleep (CSWS) and Landau–Kleffner syndrome, show a striking response to the sleep-wake state. Both disorders are characterized by an almost continuous subclinical spike-wave activity on EEG during sleep, accompanied by neuropsychological deterioration, and represent age-related epileptic encephalopathies. In CSWS, this activity is associated with predominantly nocturnal focal motor seizures, although absences may also be seen in wakefulness in some patients [32]; the neuropsychological impairment may be global or selective for cognitive or expressive functions, and motor deficits such as ataxia, dystonia or hemiparesis may occur [32]. Landau–Kleffner syndrome is characterized by a specific neuropsychological deficit, verbal auditory agnosia, which is sometimes seen in conjunction with other types of aphasia [33]. Seizures are not invariably seen, and the EEG findings are very similar to those of CSWS; the commonalities between these two disorders have led some authors to suggest that they are in fact different subclasses of a single condition [34,35].

Table 1
Epilepsy syndromes with a clearly recognized relationship with sleep.

Idiopathic focal syndromes	Idiopathic generalized syndromes	Symptomatic focal epilepsies	Symptomatic generalized syndromes	Syndromes unclear whether focal or generalized
Benign childhood epilepsy with centrotemporal spikes	Juvenile myoclonic epilepsy	Frontal lobe epilepsy	Lennox–Gastaut syndrome (tonic seizures)	Epilepsy with continuous spike–wave during slow-wave sleep
Benign childhood epilepsy with occipital paroxysms	Epilepsy with generalized tonic-clonic seizures on awakening	Nocturnal frontal lobe epilepsy	West syndrome (infantile spasms)	Landau–Kleffner syndrome
Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)		Temporal lobe epilepsy (including nocturnal temporal lobe epilepsy)		