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Editorial

Sleep Disorders in Epileptic Patients: the Role of Epilepsy and the Role of AEDs

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Keywords

Epilepsy; Sleep disorders; Antiepileptic drugs

Abbreviations

AED: Antiepileptic Drug/drugs; EEG: Electroencephalogram; IEDS: Inter-icatl Epileptiform Discharges; OSAS: Obstructive Sleep Apnea Syndrome; FLE: Frontal Lobe Epilepsy; BECT: Benign Epilepsy with Centro-temporal Spikes; BECOP: Benign Epilepsy of Childhood with Occipital Paroxysms; LKS: Landau-Kleffner Syndrome.

Epilepsy and sleep disorders are major health problems and the prevalence of sleep disorders in children with epilepsy is under recognized. Childhood sleep disturbances may originate from factors aside from the primary neurological disorder. These include poor sleep hygiene, detrimental effects of seizures on sleep, effects of antiepileptic drugs and coexistence of primary sleep disorders or comorbid illnesses [1]. Children with epilepsy generally present alterations in sleep architecture, in sleep latency and spontaneous arousals with a higher incidence of sleep fragmentation and daytime drowsiness [2]. In particular NREM sleep is important for declarative memory consolidation whereas REM sleep is involved in non-declarative and emotional memory [3]. Sleep related paroxysmal disorders in infancy and childhood represent a significant challenge for clinicians with the distinction of nocturnal epilepsy from non-epileptic sleep disorders [4]. The American Academy of Sleep Medicine (AASM) elaborated in 2005 an international classification (ICSD-2) dividing sleep disorders mimicking epilepsy in three groups: NREM and REM parasomnias, sleep related movement disorders and other paroxysmal nocturnal events [5]. Sleep has a well-documented association with specific epileptic syndromes. The most important amongst these are nocturnal frontal lobe epilepsy (FLE), benign epilepsy with centro-temporal spikes (BECT), and benign epilepsy of childhood with occipital paroxysms (BECOP), Landau-Kleffner syndrome (LKS), infantile spams and electrical status epilepticus during slow wave sleep. The amount of baseline rhythmicity that occurs in the brain differs considerably between sleep and wakefulness. It is therefore not surprising that various types of seizures begin preferentially in specific sleep states [6]. The neurophysiologic process involved in the deepening of NREM sleep may also facilitate both seizures and inter-ictal epileptiform discharges (IEDS). NREM sleep represents a state of synchronization between the brainstem reticular activating system, thalamus and cortex. A progressive hyperpolarization of thalamo-cortical neurons is also determined by a reduction of the effect of acetylcholine that contributes to NREM sleep deepening [7]. In contrast, REM sleep tends to suppress IEDS and may restrict their field of distribution to the epileptogenic origin by inhibition of thalamo-cortical synchronizing mechanisms [8]. Seizures are most likely to occur as sleep becomes deeper. Patients with epilepsy generally have macrostructural sleep abnormalities such as increased number and duration of arousals during sleep, reduced sleep efficiency, reduced and fragmented REM sleep and increased stage shifts [8]. Among the causes of sleep fragmentation, sleep related breathing disorders could be considered a trigger for seizures and IEDS. This suggests that children with obstructive sleep apnea syndrome (OSAS) may have a dysfunction of the arousal system control which can be due to the effect of a primary brain insult as a predisposing factor for both OSAS and paroxysmal EEG activity [9]. Therefore treatment of these disorders may potentially improve seizure control. On the other hand antiepileptic drugs (AEDs) exert a beneficial action on seizures not only with direct effects on neuronal excitability but also by stabilizing sleep and reducing sleep transitions. Whether the improvement in sleep patterns is a direct consequence of the use of AEDs or the consequence of the suppression of epileptic manifestations is the object of many debates. The effects of AEDs on sleep have been studied showing both detrimental and beneficial effects. AEDs affect sleep architecture by inducing sedation or insomnia [10]. In addition some AEDs can cause weight gain, therefore predisposing to fragmented sleep [11]. Virtually all AEDs have effects on sleep architecture and many studies have analyzed these effects. In particular Class 1 studies in healthy adults suggest that phenobarbital and levetiracetam reduce REM sleep whereas it is enhanced by gabapentin [12-13]. Other studies demonstrate that clobazam decreases slow wave sleep in the same type of population while it is increased by levetiracetam, pregabalin and tiagabine. Clobazam also reduces sleep latency and arousals/wake time, which is also reduced by levetiracetam, phenobarbital, tiagabine and pregabalin [14]. Class 3 evidence based studies show that carbamazepine favors sleep efficiency and extends total sleep time increasing slow wave sleep in healthy subjects and reducing sleep latency, arousals, REM sleep and wake time [15]. On the other hand class 1 evidence based studies in epileptic adult patients show that pregabalin increases slow wave sleep that is instead reduced by levetiracetam [16]. Moreover phenobarbital and gabapentin reduce sleep latency and arousals. Regarding slow wave sleep it has been observed that carbamazepine and gabapentin have an enhancing effect contrarily to ethosuximide. Conflicting results were obtained with lamotrigine on REM sleep and slow wave sleep [17]. Phenobarbital and phenytoin caused a reduction in patients REM sleep that was not demonstrated with the administration of ethosuximide or gabapentin. Finally class 3 evidence based studies show that phenobarbital increases daytime sleepiness, an effect that was not seen when topiramate, lamotrigine, zonisamide or vigabatrin were administered to epileptic patients [18]. There are very few

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studies concerning epileptic patients with problems initiating sleep. On the basis of previously performed studies a reduction of sleep latency in this population could be obtained by using phenytoin, phenobarbital, carbamazepine and clobazam. Another domain where further clinical trials are required is that of epileptic patients with difficulty maintaining sleep. Gabapentin, tiagabine or pregabalin increasing N3 and having a positive effect on sleep consolidation could potentially achieve a good maintenance of sleep [19]. Another two aspects that could be explored are epileptic patients with insomnia and with excessive daytime sleepiness. In the first case these subjects could beneficiate from a therapy with carbamazepine, tiagabine or pregabalin; on the other hand it is important to avoid the association of phenobarbital, valproic acid and levetiracetam in patients with daytime drowsiness.

The complicated and reciprocal relationship between sleep and epilepsy is a topic that has been intriguing physicians and researchers for many years. Whether sleep affects epilepsy or epilepsy modifies sleep has been extensively evaluated [20]. Very little literature exists on the mutual interaction of epilepsy, AEDs and sleep disorders in the pediatric population. Future research should explore possible therapeutic applications of antiepileptic drugs in epileptic patients presenting sleep comorbidities [7].

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