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General review

Obstructive sleep apnea in drug-resistant epilepsy: A significant comorbidity warranting diagnosis and treatment

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ABSTRACT

Introduction. – Drug-resistant epilepsy is a debilitating condition that warrants new therapeutic options. The last two decades have seen a growing interest in the relationship between epilepsy and obstructive sleep apnea syndrome (OSAS), which could ultimately yield non-pharmaceutical treatment strategies. Based on a Medline search of the literature, this review develops lines of evidence for a clinically significant role of OSAS in refractory epilepsy.

State of the art. – OSAS is a primary sleep disorder that could presumably lower the seizure threshold via mechanisms such as sleep fragmentation, oxygen desaturation and chronic sleep deprivation. In comparison to the general population, patients with epilepsy probably have a higher prevalence of OSAS (9–33 % overall; 13–16 % with moderate to severe OSAS). Several common risk factors for OSAS have proven to be significant in patients with epilepsy, notably advanced age, male gender and obesity. Moreover, certain specific conditions, such as refractory seizures, antiepileptic polytherapy and vagus nerve stimulation, appear to render these patients particularly vulnerable to OSAS. Prospective data regarding the efficacy of continuous positive airway pressure (CPAP) therapy for seizure control is scarce. However, there is compelling retrospective evidence that severe OSAS can exacerbate the seizure burden and that CPAP may yield a pronounced reduction in seizure frequency, excessive daytime somnolence and, potentially, cognitive complaints.

Perspectives. – In the light of the severity of drug-resistant epilepsy and its impact on quality of life, our current knowledge justifies systematic questionnaire screening for OSAS and a low threshold for referral to sleep laboratory exploration. In the long run, a large prospective trial is needed to confirm the therapeutic interest of CPAP treatment for mild to moderate OSAS in patients with epilepsy.

Conclusion. – OSAS is a significant comorbidity of drug-resistant epilepsy that has the potential to yield new treatment options for better seizure control.

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1. Introduction

Drug-resistant epilepsy is a debilitating disease with ample repercussions on the patient's quality of life [1]. Substantial amounts of time and effort have been invested in research on pharmacoresistance, and on medical and surgical treatment options, but for many patients, only modest improvements are achieved [2]. There is growing awareness that obstructive sleep apnea syndrome (OSAS) may be a significant comorbidity [3] and that its treatment may lessen the seizure burden [4,5]. In fact, some clinical features of epilepsy, such as sleep deprivation as a precipitant [6–8], fatigue or somnolence [9,10] and cognitive dysfunction [1,11,12], can overlap with symptoms of OSAS [10]. Indeed, there is increasing evidence that both entities may influence each other [13], which could ultimately yield a promising non-pharmacological treatment strategy [14].

On the basis of a Medline search, the present review summarizes the current knowledge of the pathophysiology of OSAS and its link to seizures and, in particular, the prevalence of OSAS in adult epilepsy, its common and specific risk factors, treatment benefits and potential implications for patient care in the long run. In addition to previous, more general reviews on sleep disorders in epilepsy [6,10,15–22], the present report specifically focuses on the clinical implications of OSAS and epilepsy [13].

2. Methods

This review is based on a keyword search with the terms 'sleep apnea, epilepsy' in Medline. The search yielded 363 publications, 150 of which were more closely related to obstructive rather than central sleep apnea. Of these 150 publications, only those with an abstract in English were further evaluated. As regards to the question of prevalence and therapy efficiency, 43 original articles and group studies were included. Case studies were selected only if they conveyed specific pathophysiological insights on the relationship between OSAS and epilepsy.

As OSAS is associated with different comorbidities and with systemic disease in children compared with adults, this review is centered on adult epilepsy and OSAS. Pediatric studies were considered only if they helped to elucidate general mechanisms of OSAS and epilepsy.

3. Mild to severe forms of obstructive sleep apnea

OSAS is a primary sleep disorder defined by the occurrence of daytime sleepiness, loud snoring and sleep-related interruptions of breathing, due to collapse of the oropharynx and ensuing obstruction of the upper airways [23]. Cessation of airflow may be complete (apnea) or partial (hypopnea), and often results in choking, arousal or awakening [23]. By general consensus, these obstructive respiratory events have to last for at least 10 s and have a frequency of 5 events/h to fulfill the criteria of OSAS [20,23–25].

While questionnaires may be useful for estimating daytime sleepiness (Epworth scale) [26] and risk factors for OSAS such as snoring (Sleep Apnea Scale of the Sleep Disorders Questionnaire [SA-SDQ] [27], Berlin Questionnaire [27], STOP-Bang questionnaire [28]), polysomnography (PSG) remains the gold standard for the diagnosis of apneic events and their severity during sleep [25,29,30]. PSG detects apneas (Fig. 1) and hypopneas, which are grouped together in the apnea-hypopnea-index (AHI). More than 5 events/h are considered mild OSAS [24], more than 15 events/h moderate OSAS, and severe forms are defined as AHI $\geq$ 30 events/h [29].

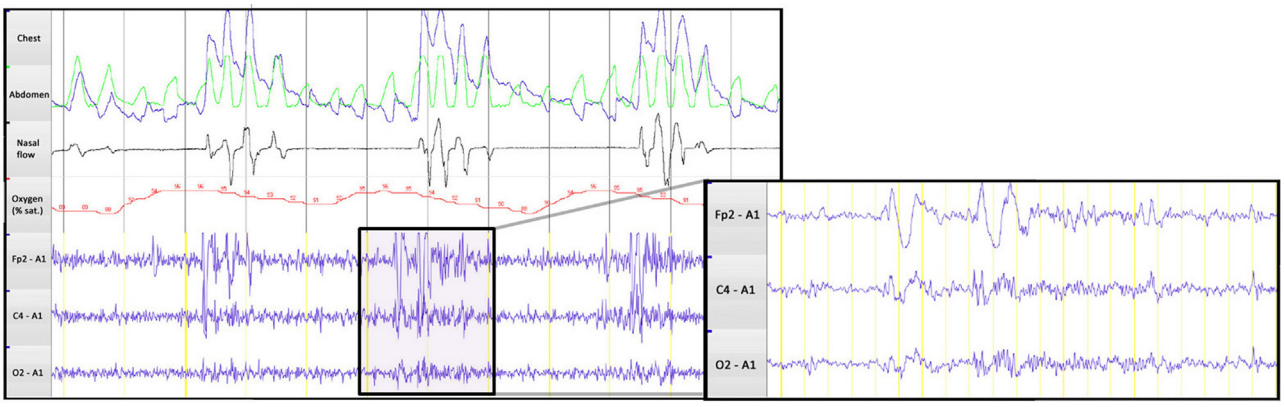

Fig. 1 – Example of obstructive sleep apnea with arousal on electroencephalography (EEG). This polysomnography (PSG) recording of a series of obstructive sleep apnea events in a patient with an AHI of 67 events/h shows that the chest (blue line) and abdominal (green line) movements, which are in opposite phase during airway obstruction, but are synchronized between apneic events. Nasal flow (black line) reveals cessation of airflow, followed by a lag of several seconds by oxygen desaturation (red line). The simultaneous EEG was recorded using right-sided frontal (Fp2), central (C4) and occipital (O2) electrodes with an auricular reference (A1). Time scale: 120 s (10 s interval between each vertical line). Inset shows the EEG arousal response as first and second K-complexes, the latter followed by a significant frequency shift best seen on the posterior electrodes. Time scale: 22 s (1 s interval between two vertical lines).