Epilepsy and Sleep Disordered Breathing

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Summary

Sleep-Disordered Breathing SDB (in particular obstructive sleep apnea/hypopnea -OSAH- syndrome), and epilepsy are two relatively common conditions in the general population. However, their co-occurrence seems higher than expected. In this article we summarize current evidences connecting SDB and epilepsy. In one sense, epilepsy can aggravate OSAH through relative increase of light sleep or indirectly via medication-related side effects (as increasing weight), and epileptic seizures can induce central apneas. On the other sense, SDB can impair the control of epilepsy through sleep disruption or repetitive hypoxemia. At present, there is some evidence suggesting that SDB treatment may contribute to a better seizure control. In addition, considering the general consequences of SDB (excessive daytime sleepiness, negative impact in psychosocial functioning, mood and cognition, increased cardiovascular risk) active screening of SDB in patients with epilepsy appears warranted, and moderate to severe cases should be treated. Further studies are required to better assess this relationship and the impact of treatment.

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Keywords: treatment, seizures, obstructive sleep apnea, hypopnea.

Epilepsie et troubles respiratoires lors du sommeil

Les troubles respiratoires au cours du sommeil (en particulier le syndrome d'apnées/hypopnées obstructives du sommeil) et l'épilepsie sont deux affections relativement fréquentes dans la population générale. Cependant, leur co-morbidité semble plus élevée que prévue. Dans cet article, nous résumons les indices actuels reliant ces deux maladies. D'une part, l'épilepsie peut aggraver les apnées/hypopnées obstructives par une augmentation du sommeil léger ou, indirectement, via les effets secondaires de certains traitements antiépileptiques (comme la prise de poids), et certaines crises d'épilepsie peuvent provoquer des apnées centrales. D'autre part, les anomalies respiratoires au cours du sommeil peuvent favoriser les crises d'épilepsie par la fragmentation du sommeil qu'elles induisent, ou par des épisodes répétitifs d'hypoxémie. A l'heure actuelle, quelques données suggèrent que le traitement des troubles respiratoires au cours du sommeil peut contribuer à un meilleur contrôle des crises. De plus, en considérant les conséquences des troubles respiratoires au cours du sommeil (somnolence diurne excessive, effets négatifs sur le fonctionnement psychosocial, sur humeur et la cognition, augmentation du risque cardiovasculaire) un dépistage actif chez les patients souffrant d'épilepsie semble justifié, et en cas de diagnostic positif un traitement adapté doit être proposé. D'ultérieures études sont néanmoins nécessaires pour mieux cerner cette co-morbidité et l'impact du traitement.

Mots clés : Thérapie, crises épileptiques, apnée obstructive, hypopnée

Epilepsie und Schlafapnoe

Schlafapnoe und Epilepsie sind zwei relativ häufige Erkrankungen in der Allgemeinbevölkerung, deren Ko-Morbidität aber häufiger als erwartet erscheint. In diesem Artikel werden aktuelle Daten über die Wechselwirkung zwischen Schlafapnoe und Epilepsie erwähnt. Zum einen kann sich Epilepsie durch eine relative Erhöhung von leichtem Schlaf, oder indirekt via Gewichtszunahme (Antikonvulsiva-NW) verschlechtern, und epileptische Anfälle können zu einer zentralen Schlafapnoe führen. Zum anderen kann Schlafapnoe durch Schlaf-Fragmentierung und wiederholte Hypoxämie eine optimale Epilepsie-Kontrolle erschweren. Es bestehen einige Hinweise, dass eine erfolgreiche Schlafapnoe-Behandlung zur Verbesserung der Epilepsie-Kontrolle beitragen kann. In Anbetracht der Rückwirkungen von Schlafapnoe (Schläfrigkeit tagsüber, psychosoziale Schwierigkeiten, Gemütsverschlechterung, und Erhöhung des kardiovaskulären Risikos) erscheint ein aktives Screening von Schlafapnoe bei Patienten mit Epilepsie als indiziert; moderate bis schwere Fälle sollten einer spezifischen Behandlung unterzogen werden. Weitere

Studien sind jedoch nötig, um die exakte Wechselwirkung zwischen diesen zwei Entitäten und den Stellenwert deren Behandlung besser zu erfassen.

Schlüsselwörter: Therapie, epileptische Anfälle, obstruktive Schlafapnoe, Hypopnoe

Sleep apnea

Sleep-Disordered Breathing (SDB) describes a group of disorders characterized by abnormalities of respiratory pattern during sleep. Obstructive sleep apnea/hypopnea (OSAH) is by large the most common of such disorders, which is characterized by repetitive episodes of upper airway obstruction during sleep, due to loss of pharyngeal dilatators muscle tone, resulting in cessation (apneas) or reduction (hypopneas) of airflow. The unsuccessful efforts to breath during obstructed events result in increased negative intrathoracic pressure, reduction of blood oxygen saturation, and, at the end, arousals from sleep that restore pharyngeal dilator muscle tone, and ventilation. However, pharyngeal obstruction recurs once sleep resumes, and recurrent arousals, although protective, disrupt sleep. Sleep gets lighter and less restorative. Thus, excessive daytime sleepiness is a common consequence, and a key factor, for example, in the increased occurrence of traffic accidents in OSAH patients [1]. But OSAH also significantly impacts various aspects of psychosocial functioning, mood and cognition. Deficits have been observed especially in the area of attention and memory. Furthermore, executive control impairments have been suggested, typically assumed to be related to prefrontal lobe dysfunction caused by sleep disruption and intermittent nocturnal hypoxemia [2]. It has been shown that OSAH has a major negative impact in the quality of life of affected patients [3]. In addition, hemodynamic changes induced by apneas/hypopneas and repetitive episodes of hypoxia and hypercapnia have been implicated in the occurrence of adverse cardiovascular events [4]: OSAH accelerates aterosclerosis [5] and is a recognized secondary cause of hypertension [6]. Several cohort studies have recently shown that severe OSAH is independently associated with an increased risk of myocardial infarction, stroke, and death from cardiovascular disease [7-9]. Finally, there is evolving evidence that SDB may contribute to insulin resistance and other components of the metabolic syndrome [10].

The presence of SDB is most reliably shown by attended overnight polysomnography in a sleep laboratory, in which continuous EEG, airflow, SaO2, ECG and respiratory movements of the rib cage and abdomen, are recorded. We still have a very incomplete understanding of the neurobiologic mechanisms responsible for the sleep-induced changes in upper airway motor control leading to pharyngeal collapse, but some factors have been identified to increase the risk of developing OSAH, in particular male gender, obesity, and age [11]: OSAH is two to three-times more common in men than in women, and its prevalence increases with age [12]; furthermore, a 10% weight gain increases the risk of developing OSAH by six-times. Nonetheless, OSA occurs in children and in individuals of normal weight, in whom other factors can contribute to pharyngeal collapsibility (e.g. large tonsils or macroglossia). Additional risk factors include nasal obstruction, the use of alcohol and sedatives and menopause in women.

Undoubtedly, the most important modifiable risk factor for OSAH is obesity, and weight loss has been shown to significantly decrease the severity of the condition [13]. In certain cases, avoiding the supine position during sleep (that can prevent the tongue and palate from falling backwards) can be an effective treatment. In mild or moderate cases, mandibular advancement splints that shift forward the lower jaw can be used to maintain open the airway during sleep. But the most widely accepted treatment for OSAH is continuous positive airway pressure (CPAP), which acts as a pneumatic "splint" by producing a positive pressure inside the airway, and thereby preventing upper airway collapse during sleep [14].

Central sleep apnea (CSA) describes a group of conditions in which cessations in air flow occur without respiratory effort [15]. This cessation of breathing results from a decrease in ventilatory drive. CSA can be idiopathic (e.g., primary central sleep apnea) or secondary. Examples of secondary CSA include Cheyne-Stokes respiration (related to heart failure), apneas due to high altitude periodic breathing, due to a medical condition (as brain stem lesions), or due to a drug or substance (as opioids) [16]. CSA is a less common form of SDB, and affects only 5-10% of this population. Initial treatment should be directed at any condition that may be causing or exacerbating the CSA. CPAP, bilevel positive airway pressure, adaptative servo-ventilation, supplemental oxygen or supplemental carbon dioxide are also possible treatments [17].

SDB is a common disorder, but estimates of its prevalence vary widely, between 2% and 20%, depending on the methodology [18, 19]. Conservatively, based on laboratory or portable home polysomnographies the prevalence of OSAH, defined as >5 apneas/hypopneas per hour of sleep, in middle-aged men and women in the Wisconsin cohort was 24% and 9%, respectively. If sleepiness was included in the definition, the prevalence of OSA was 4% in men and 2% in women [20].

Epilepsy

Epilepsy, occurring in 0.5%-1% of the worldwide population is also a common condition in the general population, with its prevalence showing a direct relationship with age [21, 22]. However, several observations suggest that their comorbidity is higher than ex-

pected: among patients with SDB, 5% were diagnosed with epilepsy [23]; conversely, SDB was found in one third of 39 patients with pharmacoresistant epilepsy undergoing presurgical evaluation [24], 10% of 283 unselected patients with epilepsy [25], and 20% of 40 children with epilepsy [26]; discrepancies may reflect different assessment methods and population selections. Excessive sleepiness is a common complaint in patients with both conditions, but interestingly, in subjects with epilepsy this symptom correlates independently with SDB and restless legs, but not seizure frequency, or medication [27]. In fact, SDB seems to be correlated with seizures: 7 out of 11 older subjects with incomplete seizure control had mild to severe (obstructive) SDB, versus 0/10 who were seizure free or had infrequent seizures [28].

Comorbidity and treatment

Multiple mechanisms may account for the higher than expected co-occurrence of epilepsy and SDB. While the latter may hinder the control of epilepsy through sleep disruption or repetitive hypoxemia [29], generalized or focal seizures can induce central apneas during the ictus [30], as well as obstructive events through increase of the proportion of light sleep [31], or medication side effects (e.g.: weight gain), thus generating a sort of vicious circle between the two conditions. A common hypothesis underlying seizures reduced central respiratory drive (particularly, the arousal response to hypercapnia), and even depression, may be represented by a dysfunction of serotonin pathways in the central nervous system. This could also have important implications for the sudden unexpected death in epilepsy (SUDEP) [32]. However, to date there is no clinical evidence that medication enhancing serotonin availability, such as SSRI, may be beneficial for the treatment of SDB or epilepsy, and this drug class is not recommended for their management [33].

Anecdotally, complete remission of SDB and seizures has been reported in a single patient after frontal lobe resection [34]: while this observation corroborates the relationship between these two entities, it does not prove any causality. On the other side, case reports [35] and observational studies have suggested improvement of seizure control following SDB treatment. Of 7 patients with moderate-severe SDB and epilepsy, 5 were treated with cPAP, and 2 were compliant; both experienced an improvement of seizure control [29]. In another study, cPAP was prescribed in 8/10 patients with epilepsy and SDB; 7 were compliant but only one improved in terms of seizures [36]. Among 444 adult and pediatric patients with epilepsy, 62 were suspected of suffering from SDB based on a questionnaire; of those, 9 had SDB confirmed by polysomnography, and 6 (with at least 4 seizures/month) underwent cPAP treatment or were prescribed a oral device; without change of AED, 4 patients showed a >45% seizures improvement [37]. An elegant Bernese study retrospectively identified 29 adults with SDB and epilepsy; 23 of whom were offered cPAP treatment [23]; good compliance was confirmed in 12 of them, and 4 experienced a >50% seizure reduction without medication changes over at least 6 months. In the study on older patients with epilepsy, of the 7 patients with SDB, 2 declined cPAP and 1 did not tolerate it; under cPAP for several months, 2 subjects did not report any change in seizures frequency, while 2 improved (one however after a medication change) [28]. These observations are summarized on **Table 1**. More recently, a careful pilot study has been described, in which patients with SDB and refractory epilepsy were randomized to receive effective vs. sham cPAP treatment [38]. Of 865 screened subjects, 68 were considered eligible, and 45 underwent PSG: 36 had obstructive SDB (excluding those with severe SDB for "safety reasons"), 22 were allocated to cPAP (19 completed the 8 weeks treatment period), and 13 to sham treatment (all completers). A >50% seizure reduction was observed in 5/19 (28%) of the cPAP vs. 2/13 (15%) of the control group (non-significant difference); of note, 4 patients on CPAP and one on sham treatment became seizure free, but 2/5 patients with a meaningful seizure reduction had an apnea-hypopnea index of just 5/h. This study, although interesting, does not appear generalizable in view of the strict selection criteria, and, intriguingly, has not been replicated/expanded to date (www.clincialtrial.gov, accessed October 21 2011).

Conclusion

There is some convergent but relatively low-level evidence suggesting that SDB may worsen seizures frequency, and that SDB treatment could therefore contribute to a better seizure control. While SDB seems to co-occur more frequently in patients with epilepsy as compared to the general population, only a minority of subjects with SDB experience improvement of seizure control under cPAP treatment, with a small subgroup becoming seizure free; however, patients remain on antiepileptic drugs. A further limitation is represented by the low baseline AHI indexes reported in several patients described to benefit from cPAP: these cases possibly represent "regressions to the mean" rather than reflecting a therapeutic impact of SDB treatment. At present, it seems reasonable to assume that SDB represents a modulating factor on epilepsy prognosis rather than an independent trigger. Since the proportion of "responders" (10%-20%) seems to be in the same broad range of a new antiepileptic drug trial, active screening for SDB of patients with epilepsy appears warranted; also in view of the general health implications of SDB (cardiovascular risk), patients with moderate to severe SDB should be offered a treatment attempt even in

Table 1: Studies investigating the impact of continuous positive airway pressure (cPAP) treatment in patients with epilepsy.

Study	Patients	cPAP prescribed	Compliant	>50% seizure reduction	% of total
Devinsky Neurology 1994	7	5	2	2	29%
Vaughn Seizure 1996	10	8	7	1	10%
Malow Sleep Med 2003	9	8	4	4	44%
Hollinger Eur Neurol 2006	29	23	12	4	14%
Chihorek Neurology 2007	7	5	4	2	29%

the absence of daytime sleepiness. Further studies are clearly needed to better assess the impact of specific SDB treatment in patients with epilepsy.

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