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Cognitive impairment in obstructive sleep apnea

Troubles cognitifs dans l'apnée obstructive du sommeil

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ABSTRACT

Obstructive sleep apnea (OSA) is characterised by repetitive cessation or reduction of airflow due to upper airway obstructions. These respiratory events lead to chronic sleep fragmentation and intermittent hypoxemia. Several studies have shown that OSA is associated with daytime sleepiness and cognitive dysfunctions, characterized by impairments of attention, episodic memory, working memory, and executive functions. This paper reviews the cognitive profile of adults with OSA and discusses the relative role of altered sleep and hypoxemia in the aetiology of these cognitive deficits. Markers of cognitive dysfunctions such as those measured with waking electroencephalography and neuroimaging are also presented. The effects of continuous positive airway pressure (CPAP) on cognitive functioning and the possibility of permanent brain damage associated with OSA are also discussed. Finally, this paper reviews the evidence suggesting that OSA is a risk factor for developing mild cognitive impairment and dementia in the aging population and stresses the importance of its early diagnosis and treatment.

RÉSUMÉ

L'apnée obstructive du sommeil est caractérisée par des pauses respiratoires ou des réductions du débit aérien répétées qui sont dues à une obstruction des voies aériennes supérieures. Ces évènements respiratoires entraînent une fragmentation chronique du sommeil et une hypoxémie intermittente. Plusieurs études ont montré que l'apnée obstructive du sommeil est associée à la somnolence diurne ainsi qu'aux dysfonctions cognitives incluant des déficits au niveau de l'attention, de la mémoire épisodique, de la mémoire de travail et des fonctions exécutives. Cet article examine le profil cognitif observé chez les adultes présentant l'apnée obstructive du sommeil. Les rôles spécifiques de l'altération du sommeil et de l'hypoxémie dans l'étiologie des dysfonctions cognitive seront également abordés. Les marqueurs de dysfonctions cérébrales tels que ceux mesurés en électroencéphalographie et en neuroimagerie seront aussi présentés. Les études examinant l'efficacité du traitement par pression positive continue afin d'améliorer les déficits cognitifs dans cette population seront discutées ainsi que la possibilité que l'apnée obstructive du sommeil puisse causer des dommages permanents au cerveau. Enfin, cet article présente les récents résultats concernant la relation entre l'apnée obstructive du sommeil et le risque de développer un trouble cognitif léger et une démence dans la population âgée et souligne l'importance d'un diagnostic précoce en vue d'initier un traitement de l'apnée obstructive du sommeil.

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1. Introduction

Obstructive sleep apnea (OSA) is a sleep disorder characterised by frequent breathing cessation and/or reduction of airflow due to partial or complete obstruction of the upper respiratory airways. These respiratory events occurring during sleep lead to intermittent hypoxemia and micro-arousals or awakenings. Sleep fragmentation is one of the leading causes of excessive daytime sleepiness, a predominant clinical manifestation of OSA. Daytime sleepiness in OSA is known to increase from two to seven times the risk of road accidents [1]. However, despite an increasing awareness of this health problem, 80% of individuals remain undiagnosed and untreated [2].

1.1. Night-time and daytime symptoms

Spouses or relatives sleeping in or near the bedroom of individuals presenting OSA usually report loud snoring that sometimes disturbs their own sleep. OSA patients report awaking breathless and choking during the night. In addition, they evaluate their sleep as non-restorative and report frequent awakenings overnight [3,4]. When waking up in the morning, subjects feel tired and may also have headaches and dry throat [3]. Most OSA patients complain of daytime sleepiness that usually occurs when performing tasks that require less attention (i.e. reading or watching television) [3,5]. With increasing OSA severity, sleepiness may occur while they drive, eat or work [3,5]. Most frequent cognitive complaints are a decrease in alertness, short-term memory problems, and lack of concentration [3,5]. However, our preliminary study recently showed a lack of insight in individuals with OSA with significantly more cognitive impairment [6]. Relatives and patients observe changes in their mood and personality, which includes irritability, depressed mood and anxiety. They often have sexual dysfunctions including loss of libido and impotence [3].

1.2. Diagnosis of obstructive sleep apnea

OSA is diagnosed through clinical history and polysomnography (PSG). Clinical history should include a complaint of excessive daytime sleepiness or two of the following symptoms: choking at night, recurrent awakenings, sensation of non-restorative sleep, and fatigue or inability to focus [5]. The PSG recording enables the confirmation of the OSA diagnosis. According to the recent update of American Academy of Sleep Medicine criteria, [7] obstructive apnea is a decrease greater than 90% of baseline airflow for at least 10 seconds, which is accompanied by a sustained or an increased respiratory effort. Obstructive hypopnea is a decrease greater than 30% of the airflow amplitude for at least 10 seconds accompanied with either a desaturation higher than 3% or an arousal. Frequency of respiratory events is measured by the apnea-hypopnea index (AHI) obtained by summing the respiratory events and dividing by the number of hours of sleep. Recommended criteria for the diagnosis of OSA are an AHI higher than 5 for young and middle-aged adults while criteria of AHI higher than 20 was suggested for the elderly [8,9]. OSA severity depends on the presence and intensity of daytime sleepiness and the frequency of respiratory events. The assessment of the severity of sleepiness relies on the type of task during which the episode occurs (i.e. reading vs. driving) and the impact of sleepiness on the social and functional aspects of life. The assessment of severity of respiratory events includes three levels in young and middle-aged adults: mild OSA (AHI between 5 and 15), moderate OSA (AHI between 15 and 30) and severe OSA (AHI higher than 30) [5].

1.3. Epidemiology

Epidemiological findings vary according to age, sex and apnea severity. When a criterion of an AHI $\geq$ 15 is used, the prevalence is estimated at 2 to 14% in middle-aged adults (39-59 years), but shows an increase to 20% in those aged 60 to 95 years. Some authors suppose that the increase in prevalence with age is due to anatomical changes in the upper respiratory airways or the coexistence of a medical disorder [10]. Others explain that OSA is more prevalent in elderly than in middle-aged individuals because OSA cases accumulate from a constant incident rate [2]. Moreover, the prevalence is twice as high among men (25%) than women (11%). Finally, in a population aged between 39 and 99 years old, mild OSA is more prevalent (29%) than moderate to severe OSA (18%) [2].

1.4. Pathophysiology

Partial or complete obstructions of the upper airway are due to the relaxation of the throat muscles and tongue, which collapse the airways during sleep. Airway obstructions create intermittent hypoxemia and hypercapnia. Peripheral (aortic) and central (medulla oblongata) chemoreceptors both stimulate respiratory centers to increase ventilation since they are sensitive to hypoxemia and hypercapnia. The end of respiratory events usually occurs through the occurrence of awakening or arousal and is associated with sympathetic activation [11]. OSA also creates inflammation and endothelial dysfunction, which reduce vascular elasticity and increase coagulation. Altogether, these factors predispose to atherosclerosis [11]. The combination of reduced oxygenation reaching tissues and vascular damages can lead to cellular dysfunctions in several organs such as the heart and the brain.

1.5. Risk factors and comorbidities

Overweight, obesity, central body fat distribution and large neck girth have been identified as important risk factors for OSA [12]. Morphological factors such as dimorphisms related to the size or position of the mandible or maxilla, narrow nasal cavity, a low soft palate, and enlarged tonsils also play an important role in the development of OSA [12]. Other factors may contribute to the risk of OSA, including hormonal changes, alcohol consumption, smoking and nasal congestion, but their causal role is not well established. Hypertension, diabetes, coronary heart disease, myocardial infarction, congestive heart failure and stroke were found to be associated with OSA. The emergence of these comorbid conditions may be due, in part, to common risk factors (i.e. obesity and hypertension), but OSA may also have a causal role in these diseases since hypoxemia and hypercapnia can lead to vascular dysfunctions [13]. Genetically, it has been reported that the isoform E4 from the *ApoE* gene, identified as a risk factor for Alzheimer disease, is more frequently found in OSA patients than in healthy control individuals, [14,15] but a meta-analysis based on published literature failed to support this association between ApoE4 and OSA [16].

1.6. Continuous positive airway pressure treatment

Continuous positive airway pressure (CPAP) improves overall OSA symptoms by keeping the upper airways open using air pressure, which consequently decreases hypoxemia and sleep fragmentation [17]. CPAP treatment globally improves subjective daytime functioning and performance in cognitive tests (see details in the following sections) [18–24]. In addition, CPAP treatment normalizes electroencephalographic (EEG) recordings performed during the waking state among OSA subjects and this normalization in EEG is associated with decreased daytime sleepiness [25,26]. However, CPAP should be used for at least four hours per night for a subjective effect on sleepiness, and a minimum of six hours per night for an effect on objectively measured sleepiness [27].