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IS THERE AN ASSOCIATION BETWEEN OBSTRUCTIVE SLEEP APNEA AND CEREBROVASCULAR INSULT?

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Obstructive sleep apnea (OSA) is highly prevalent in general population and has a bidirectional association with cerebrovascular insult (CVI), one of the leading causes of global morbidity and mortality. Untreated severe OSA doubles the risk for CVI. OSA may be associated with an increase of all-cause mortality and it may impair neurological outcome in CVI patients. Pathophysiological basis of the association and the possibilities of prevention and improvements of outcomes require further evaluation. Continuous positive airway pressure (CPAP) therapy during sleep is associated with a reduced risk of CVI in OSA patients, but the results are inconsistent. Treatment of post CVI OSA patients with CPAP therapy is recommended as part of the elimination of several risk factors involved in pathogenesis of CVI.
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Key words: *obstructive sleep apnea, cerebrovascular insult, continuous positive airway pressure therapy*

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Introduction

Obstructive sleep apnea (OSA) is a potentially fatal condition marked by intermittent hypoxia, sleep fragmentation, and sleep restriction (1). It is a multifactorial disorder and its basic feature is dynamic pharyngeal collapse during sleep (2).

Cerebro-vascular insult (CVI) is defined by the World Health Organization (WHO) as the fast onset of clinical signs of focal or global impairment of brain function, with symptoms lasting 24 hours or more, or with a death outcome, with no other evident cause other than vascular (3).

OSA is highly prevalent in general population and has a bidirectional association with CVI, one of the leading causes of global morbidity and mortality. According to Benjafield et al, 936 million persons aged 30 to 69 years old may have mild to severe OSA (4). CVI is the second leading cause of death and the second most common cause of Disability-Adjusted Life-Years (DALYs) worldwide (5). A typical OSA patient is an obese middle-aged man (6). CVI has a greater impact on younger people, and its prevalence is rising in this age cohort (7).

Pathogenesis

Pathogenic association between OSA and CVI is a direct link between the severity of nocturnal desaturation and intact carotid intima-media and/or atherosclerotic plaques in OSA patients, independent from systemic hypertension finding. During an apnea episode there are significant changes of intracranial pressure and cerebral flow. Mechanical effects of increased intracranial pressure during apnea and hypopnea episode reduce cerebral blood flow for more than 50%, thus predisposing ischemia, being in correlation with the duration of apnea/hypopnea and desaturation degree. Increased plasma fibrinogen and increased platelet aggregation in patients with OSA are associated with increased risk of developing CVI and other cardiovascular consequences. Cardiac arrhythmia, often associated with OSA, is a well-recognized factor of CVI development (6, 8-10).

On the other hand, three non-anatomic contributing factors for OSA onset (arousal threshold, muscle activity, loop gain) are controlled through the

brainstem. So, it is possible that brainstem lesions consequent to CVI may contribute to OSA onset. This can explain why patients with CVI have higher rate of OSA (11). The respiratory centers lesions within the medulla oblongata cause reduced chemosensitivity during wakefulness, sleep, even exercise (12). Several studies have shown that brainstem lesions affect pharyngeal muscle activities, resulting in dysphagia and may contribute to higher rate and severity of OSA. A few studies have investigated how CVI lesion size, regardless of hemorrhagic or ischemic origin, affect the frequency and type of breathing disturbance in sleep. Ahn et al. showed that bilateral hemisphere lesions resulted in significantly higher OSA severity in comparison to CVIs that occurred in a single region (13).

However, pathophysiological basis of the association and the possibilities of prevention and improvements of outcomes require further evaluation.

Current knowledge

Four scientific societies: European Academy of Neurology-EAN, European Respiratory Society-ERS, European Stroke Organization-ESO, European Sleep Research Society-ESRS, have established a working group of 15 experts in the fields of neurology, stroke, respiratory medicine and sleep medicine to critically evaluate evidence of potential links btween sleep and stroke diseases and the importance of therapy. A comprehensive search of the literature published between 1990 and 2019 was conducted. A total of 12.870 studies were reviewed, with 88 of them meeting the rigorous inclusion requirements. There were 13 research questions that were answered. The evidentiary basis for linking OSA to CVI is strongest in general, and it supports active diagnosis and treatment.

When it comes to the impact of OSA on CVI, it was concluded that untreated severe OSA doubles the risk for CVI, which is especially significant in younger and middle-aged patients. The available evidence, although still insufficient, indicates an increased risk of OSA caused by CVI in patients with coronary artery disease or atrial fibrillation, with the possible exception of elderly patients. Although observational cohort studies suggest that continuous positive pressure (CPAP) treatment during sleep is associated with reduced risk of CVI in OSA patients, the results are inconsistent, and meta-analyzes of RCTs do not find this association, however, at the same time, it is pointed out that patients adherent to CPAP therapy (> 4 h daily) may benefit. There is not enough evidence of the effectiveness of treatment options other than CPAP treatment.

At the second part of the association, the impact of CVI on OSA, it is pointed out that the prevalence of OSA in patients with CVI is high, about 50%, and 30% have severe OSA (AHI > 30). Respiratory polygraphy is sufficient to assess the presence and severity of OSA in these patients. The association between CVI parameters (type, severity, topography, etiology) and OSA severity in patients with CVI, as well as the predictors of OSA in patients with CVI, are poorly understood. The evolution of OSA throughout time is unpredictable. OSA is linked to an increased chance of recurrence of CVI or a transient ischemic attack (TIA), as well as an increased risk of death from any cause and a deteriorating neurological prognosis. Current evidence suggests that CPAP therapy is possible in patients with CVI and OSA. CPAP therapy in these patients can improve drowsiness, depression and neurological recovery and eliminate or improve several risk factors such as anticoagulant effect, atrial fibrillation, better control of hypertension and dyslipidemia, weight loss. Acceptance of CPAP therapy in acute CVI is limited, but when CPAP therapy is accepted, the compliance may be satisfactory. There is insufficient evidence to support the impact of other OSA treatment modalities on CVI outcome (14).

Conclusion

OSA increases the risk of CVI development. The outcome of CVI is worsened by OSA. OSA and CVI have a bidirectional relationship, approximately half of individuals with CVI also have OSA. CPAP therapy may help to lower the risk of CVI development and improve the prognosis of the condition. Future studies should look at the impact of different OSA phenotypes on this association, in addition to understanding the pathophysiological basis of the link between OSA and CVI.

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DA LI POSTOJI VEZA IZMEĐU OPSTRUKTIVNE APNEJE U SNU I CEREBROVASKULARNOG INSULTA?

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Opstruktivna apneja u snu (obstructive sleep apnea – OSA) veoma je rasprostranjena u opštoj populaciji i ima dvosmernu vezu sa cerebrovaskularnim insultom (CVI), jednim od vodećih uzroka morbiditeta i mortaliteta globalno. Nelečena teška OSA udvostručuje rizik od CVI-a. OSA može biti povezana sa povećanjem mortaliteta proisteklog iz svih uzroka i može negativno uticati na neurološki ishod kod bolesnika sa CVI-om. Patofiziološka osnova udruženosti i mogućnost prevencije i poboljšanja ishoda zahtevaju dalju evaluaciju. Terapija kontinuiranim pozitivnim pritiskom (CPAP) u disajnim putevima tokom sna povezana je sa smanjenim rizikom od CVI-a kod OSA bolesnika, ali rezultati su varijabilni. Lečenje post CVI OSA bolesnika CPAP terapijom preporučuje se u sklopu otklanjanja više faktora rizika uključenih u patogenezu CVI-a.

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Ključne reči: *opstruktivna apneja u snu, cerebrovaskularni insult, terapija kontinuiranim pozitivnim pritiskom tokom sna*