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Obstructive Sleep Apnea: A Poorly Diagnosed Risk Factor for Stroke and Cardiovascular Disease

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Abstract: ***In this article we provide an overview of the current evidence based knowledge related to stroke and obstructive sleep apnea. A literature search was conducted in Medline and Pubmed of National Library of Medicine. We focused the search on the independent risk prevalence, mortality, relationship between OSA and stroke/TIA. Physiopathology mechanisms by which OSA might increase the risk for stroke, recurrence of OSA and recovery outcomes with CPAP therapy are also reported.***

Keywords: Sleep apnea syndrome (SAS); Obstructive sleep apnea (OSA); Stroke; Sleep disorders breathing (SDB)

Highlights

- Unrecognised and under-diagnosed risk factor worldwide, especially in low-income countries
- Obesity risk factor is becoming a global epidemic
- Optimal management of obesity can positively impact stroke incidence.

1. Introduction

Stroke is defined as a sudden neurological deficit resulting in neurological, sensory, language or visual sensory disturbances. It is the consequence of an obstruction or rupture of a cerebral blood vessel.

It is a global public health problem. Feigin et al (2014) [1] project that by 2030 there will be 12 million deaths from stroke, 70 million stroke survivors (prevalence), 200 million years lost due to death or residual disability from stroke.

Obstructive sleep apnea (OSA) is the most common component of SAS. It is defined by the American Academy of Sleep Medicine by 3 criteria "A" or "B" and or criteria "C",

Criterion "A": daytime hypersomnia not explained by other factors

Criterion "B": two or more of the following symptoms that cannot be explained by other factors: fatigue, choking or suffocation during sleep, repeated awakenings during sleep, non-restorative sleep, lack of concentration or attention, mood disturbance.

Criterion "C": A valid objective diagnostic test must demonstrate an apnoea-hypopnoea index (AHI≥5) per hour of sleep on the polysomnographic recording (PSG). Thus apnoea consists of a reduction of more than 90% of the respiratory signal for at least 10 seconds. Hypopnoea, on the other hand, is a reduction ≥30% in respiratory flow and thoracoabdominal movements compared to baseline, lasting at least 10 seconds accompanied by a desaturation ≥ 3% and/or a micro-arousal of 3 seconds. [2]

The aim of this article is to review recent publications related to this topic in order to raise awareness of physicians to screen for this risk factor before any stroke patient.

2. Methodology

We assumed that recent publications on the association between obstructive sleep apnoea and stroke were in English. We therefore selected the Medline database using the Pubmed search engine. The following keywords were used to access recent and relevant data: sleep apnoea syndrome (SAS), obstructive sleep apnoea syndrome (OSAS) and stroke. We eliminated a number of articles because their contents were similar to the most recent ones. We selected 22 articles based on their importance and relevance to this article.

Epidemiology

Stroke incidence in OSA-positive patients

Results from three cohort studies reported by Dae Lim Koo (2018) [3] show high incidences: Arzt et al (2005) OR 3.08 (ci: 0.74 - 12.81); Yaggi et al (2005) HR 1.97 (ci: 1.12 - 3.48); Redline et al (2010) RR 2.86 (ci: 1.1 - 7.39).

H. Lee Lau et al (2019) estimate a relative risk of independent association between SAS and stroke of 2.5 in a meta-analysis of 10 cohort studies [4]

Sherma (2016) analysing the Sleep Heart Health Study and Wisconsin studies gives the respective results: HZ =2.86 and RR = 4.48 (ci: 1.31 - 15.33) [5]

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Prevalence of OSA in stroke/TIA

The results of a meta-analysis and systematic review of 89 studies involving 7,096 patients by Andreas Seiler (2019) are as follows: for AHI >5 events/hour, the prevalence is 71% of patients, for AHI>30 events/hour, the prevalence is 30% of patients [6]. The observational polysomnographic study by Sebastian R. Ott (2020) gives a prevalence of 80.5% for an AHI > 5 events/hour and 25.4% for an AHI > 30 events/hour [7].

Mollie MC Dermotte (2020) confirms this high prevalence in the post-stroke period after reviewing recent relevant publications from the last 18 months.

Guevara R M et al (2020) report that any increase of one unit of AHI results in a 6% increase in stroke risk. [8]

Effects of OSA in post-stroke

Sleep apnoea syndrome (SAS) is responsible for a number of morbidities and mortality. For example, OSA increases the length of hospital stay. Graig Di Tommasso (2018); Claudio L.A. Bassetti (2020); duration of rehabilitation Graig Di Tommasso; Claudio L. A. Bassetti (2020); risk of stroke/TIA recurrence (Sharmas (2016); Bassetti (2019 , 2020); mortality rate (Mollie MC Dermott (2020), Basetti (2020) , Graig Di Tommasso (2012); dysthymia Graig Di Tommasso (2018) , H Lee Lau (2019) and negatively impacts the functional prognosis of stroke patients. [9-10-11]

Pathophysiology

The effects of apnoea/hypoxaemia cause stimulation of the sympathetic nervous system which releases catecholamines responsible for arterial hypertension which can be resistant, an increase in intra-thoracic pressure, cardiac rhythm disorders and altered cerebral haemodynamics [12-13].

The parasympathetic nervous system is also depressed. This inhibition contributes to the release of inflammatory markers. Il1, IL6, TNFα and interferon γ. These will damage the endothelial lining of blood vessels, which promotes platelet aggregation. The vascular damage thus created in OSA patients can lead to stroke. Apnea/hypoxia episodes are responsible for oxygen desaturation without compensatory mechanisms in an OSA patient. This leads to an overproduction of reactive oxygen species responsible for vascular and systemic inflammation. Oxygen desaturation and hypoxaemia further cause ischaemia in the brain leading to TIA and stroke.

OSA may be the causative factor for silent brain infarcts [12-13] In OSA, platelet hyperaggregability is present and is thought to be due to high secretion of catecholamines. Increased haematocrit, fibrinogen and blood viscosity contribute to the development of thrombosis and early atherosclerosis, Another pathophysiological mechanism found in subjects with OSA that contributes to atherogenesis is increased levels of pro-inflammatory adipokines. Studies have shown the deleterious effects of OSA-induced sympathetic hyperactivation on carbohydrate, lipid and liver metabolism. It has also been shown that intermittent hypoxia leads to inflammation of fatty tissue resulting in significant release of chylomicrons and circulating LDL-cholesterol contributing to atherogenesis [14].

3. Screening

Because the evidence for an association between OSA and stroke is sufficiently strong, screening for OSA is recommended for all patients with stroke/TIA. The test of choice for screening is polysomnography. 15] Unfortunately, this is a very expensive test and therefore inaccessible to populations in low- and middle-income countries. However, cardiorespiratory polygraphy would be sufficient to estimate the presence and severity of sleep-disordered breathing in stroke patients in medical practice according to Bassetti (2020)

Clinical questionnaires: Stop-Bang, Berlin and Epworth Scale and others lack sufficient data to prove their accuracy. They are used to quantify sleep disturbances and not to make the diagnosis of OSA. In addition, they have not always been correlated with PSG [16]. Despite these limitations, screening for OSA using questionnaires seems important because recurrence of post-TIA stroke or mild stroke is about 5% in the first week and then increases to 10% one month later, as PSG recordings take a long time to schedule even for those who can do it.

4. Treatment

Treatment of OSA with continuous positive airway pressure (CPAP) improves clinical outcomes in compliant patients. It reduces mortality and morbidity, post-stroke cardiovascular events and stroke/TIA recurrence [17]. It improves mood and functional recovery at 1 month [17] . CPAP should therefore be included in the therapeutic arsenal of post-stroke patients. Positional therapies would also have a positive impact on this patient population.

Gaps in current knowledge

OSA is a highly emerging disease worldwide. It needs to be detected and treated. In the US and Canada, screening is recommended, but elsewhere it is less so.

In OSA, Alberto R. Ramos (2017) [18] reports that the predictors of cerebrovascular and cardiovascular events are still poorly elucidated.

In 2017, the US Preventive Services Task Force (USPSTF) sought to make recommendations for screening for OSA and other sleep disorders in asymptomatic adults, but they did not find sufficient evidence to make a recommendation[19] This research group studied 2 questionnaires Berlin is the preferred multivariate apnea tool and concluded that the data provided by these tools lacks accuracy[19]

Objective sleep testing by monitors, which could replace the cumbersome and expensive PSG, lacks EEG to corroborate sleep.

With these devices, the AHI is calculated based on sleep duration and/or self-reported recording time, which generally underestimates the AHI [20]. The American Heart Association and the American Stroke Association in 2016 recommended PSG screening and treatment of OSA in

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stroke/TIA but did not give specific recommendations on how to screen and when to refer to PSG. There are no tools to help keep obstructive sleep apnoea in focus for clinicians. Without clear guidelines, physicians will question screening. Even if there is appropriate screening to refer patients for PSG, it may take several weeks or months to schedule this test, delaying treatment. This waiting period is crucial because recurrent stroke following a TIA or mild stroke is estimated to occur in about 5% of cases within the first week and then in about 10% of cases within a month of the first stroke. Furthermore, there are few studies defining the timing of OSA treatments that could affect early stroke recurrence, yet OSA, like other established risk factors, needs to be treated promptly [20]. The American Academy of Sleep Medicine, which does not support treatment of OSA based on questionnaires and Type IV testing, nevertheless believes that in the context of stroke, overnight oxygen desaturation has been shown to be a stronger predictor of stroke than AHI [21]. High resolution pulse oxygenation (HRPO) in patients hospitalised for stroke could be an interesting tool [21].

Regarding the treatment of OSA with CPAP, there is no evidence for primary stroke prevention. CPAP is a heavy treatment and difficult to tolerate in stroke patients who are usually on multiple therapies. There is therefore a need to research other types of treatment to offer [22].

5. Conclusion

Low-income countries are at a significant disadvantage in terms of OSA management and stroke prevention. They lack treatment centres and advanced screening tools for OSA and neurologists.

Efforts should be made to focus on information and treatment of OSA risk factors such as obesity, diabetes, hyperlipidemia and other modifiable factors as their treatment can contribute to a decrease in stroke incidence.

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