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Mini Review

Stroke and Sleep Disorders

Mehmet Murat Sumer*

Health Sciences Faculty, Atilim University, Turkey

***Corresponding author:** Mehmet Murat Sumer, Health Sciences Faculty, Atilim University, Turkey

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Abstract

Sleep disorders are highly prevalent in patients at risk for stroke and may be modifiable risk factors for stroke. Obstructive sleep apnea increases the risk of stroke independently, but the reported lack of therapeutic effectiveness of Continuous positive airway pressure for stroke prevention and cardiovascular protection should be cautiously interpreted. Short or long sleep duration, and insomnia with objective short sleep duration, could be risk factors for stroke and mortality. Sleep-related movement disorders, including Periodic limb movement during sleep and Restless leg syndrome are also potential risk factors for stroke. The overall findings suggest that systematic screening and proper management of sleep disturbances can substantially contribute to stroke risk modification at the population level.

Introduction

Stroke, remains one of leading causes of death and significant disability worldwide although incidence and early stroke mortality have been decreasing [1-4]. Cardinal risk factors are hypertension, cardiac disorders mainly valve disorders and atrial fibrillation, hyperlipidaemia, diabetes, smoking [5,6]. Recently, the role of sleep pathology in the development of cardiovascular and metabolic diseases has been highlightted [7-9]. Sleep, although characterized by quiescence and diminished responsiveness, is not only simple state of rest, but rather a cyclic state of periodic transitions between rapid-eye-movement (REM) and non-REM (NREM) sleep, which are precisely regulated by the central nervous system [10]. Along with the brain and other organs or physiological streams, the cardiovascular system achieves homeostatic restoration during sleep, mainly through autonomic circulatory control [11]. The decrease in blood pressure during sleep, "dipping," is a key biomarker of cardiovascular health, secondary to changes in activity and posture and also under the influence of sleep and circadian rhythms [12].

During NREM or slow wave sleep, the largest portion (up to 80%) of normal adult sleep, the autonomic system is stabilized with vagal dominance, reduced sympathetic tone, and heightened baroreceptor gain, contributing to a significant reduction in blood pressure and heart rate, with the greatest drop occurring during NREM sleep [13,14]. REM sleep-occupying about 20% of total sleep-is dominated by marked fluctuations in sympathovagal balance (irregularly peaking sympathetic surges against a background of tonic vagal inhibition), which lead to abrupt changes in blood pressure and heart rate [11,15]. A compromised cardiovascular system is at risk for pathological events such as myocardial ischemia or arrhythmias during REM sleep. Sleep thus acts as a gatekeeper through cyclic oscillations between NREM and REM sleep. Non-dipping-loss of the typical blood pressure drop during sleep-is associated with a host of poor cardiac, neurological, metabolic, and renal outcomes [16]. Sleep fragmentation causes non-dipping [17]. Non-dipping is common in older adults and is associated with an increased risk of stroke [18]. Reduced dipping is associated with brain atrophy, worse functional status, and lower daytime cerebral blood flow [19]. Common sleep disorders such as sleep apnea, insomnia, and PLMS (Periodic limb movement during sleep) activate multiple mechanisms including intermittent hypoxia-reoxygenation injury, inflammation, insulin resistance, hypothalamic-pituitary- adrenal axis activation, hemodynamic swings, cardiac arrhythmia, and hypercoagulability, all of which have the potential to provoke cardiovascular diseases [20].

Obstructive Sleep Apnea (OSA) is the most frequent sleep disorder. The prevalence of moderate-to-severe OSA in the adult general population is 4-14% and increasing with age [21,22]. Experimental and observational studies have provided evidence that OSA promotes the development of cardiovascular diseases, including stroke [20,23]. Moderate to severe OSA is associated with silent ischemic changes, including white matter changes and lacunae as well as cerebral microbleeds [24,25]. Carotid and intracranial atherosclerosis are also accelerated in OSA [26]. It is unclear whether continuous positive airway pressure (CPAP) has a therapeutic effect on these changes [27]. Hypertension and insulin resistance might mediate the development of stroke in OSA. Moderate-to-severe OSA is significantly associated with prevalent and incident hypertension [28]. Effective CPAP therapy, alone or in addition to antihypertensive medication, significantly reduces blood pressure [29,30]. OSA may also increase the risk for development of type 2 diabetes by mechanisms such as increased insulin resistance and high cortisol secretion [31]. Concomitant obesity might have

a stronger effect than OSA, not mitigated by CPAP therapy. OSA is also associated with the risk for cardio embolism. People with OSA have four times the odds of atrial fibrillation [32]. Nocturnal oxygen desaturation is an independent risk factor for new onset atrial fibrillation [33].

Sleep apnea is associated with inflammation, endothelial dysfunction, hypercoagulability, and cerebral hemodynamic changes [34-41]. Recent studies reported that OSA was significantly associated with incident stroke [42]. The relationship between sleep duration and stroke incidence is U-shaped in general; the risk for stroke is elevated in both short and long sleep groups [43-45]. Short sleep, commonly defined as <5 to 6 hours of nocturnal sleep, increases the risks of stroke, coronary heart disease, and death [44,46]. Sleep deprivation leads to increased levels of the appetite stimulating hormone ghrelin and reduced levels of the anti-appetite hormone leptin [47]. Furthermore, reduced physical activity associated with sleep deprivation leads to weight gain by decreasing energy expenditure [48]. Short sleep is also associated with sympathetic overactivity, which leads to impaired glucose metabolism hypertension, and non-dipping of blood pressure [49-51]. Long sleep duration (more than 9 hours of sleep) is also associated with stroke and cardiovascular mortality [52]. The linking mechanisms between long sleep and stroke are still elusive, but increased inflammation and abnormal lipid profiles in long sleepers have recently been reported [53,54].

Insomnia is prevalent in approximately 10% to 20% of the adult population, with approximately 50% having a chronic form. Chronic insomnia disorder is characterized by a complaint of difficulty initiating sleep and maintaining sleep and waking up earlier than desired. The diagnosis of chronic insomnia requires occurrences on at least three nights per week for at least 3 months. Insomnia was found to be a risk factor for cardiovascular events and death [55]. Elevated sympathetic and hypothalamic-pituitary-adrenal axis activity has been proposed as a mechanism for the cardiovascular effect of insomnia [8].

The defining feature of PLMS is periodic episodes of repetitive, highly stereotyped limb movements during sleep, which mostly occur in the lower extremities and can be associated with cortical arousal. A positive relationship between PLM and cardiovascular events or mortality has been demonstrated in observational studies, and a greater risk attributed to PLM combined with arousals [56,57]. PLM with arousal induces an abrupt increase in blood pressure and heart rate through sympathetic overshoot. Sympathetic overactivity, metabolic dysregulation, inflammation, oxidative stress, peripheral hypoxia, and hypothalamic pituitary-adrenal activation have been proposed as possible linking mechanisms between PLM/RLS (Restless leg syndrome) and cardiovascular diseases [58]. Repeated nocturnal fluctuations in heart rate and blood pressure that are associated with PLM and related microarousals cause daytime hypertension, subsequently increasing the risk for cerebrovascular diseases [58,59].

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