Sleep Disorders and Risk of Ischemic Stroke.

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Abstract
Sleep is a highly coordinated physiologic state, which is essential for the functional integrity of the neurons and brain. It is crucial for survival. Nonrapid eye movement sleep (NREM) vagal dominance enables the neural/cardiovascular axis to regenerate homeostasis after periods of stress or fatigue during wakefulness. Any reasons for sleep interruption or deprivation like periodic limb movements during sleep (PLMS), insomnia, shift work, and obstructive sleep apnea have a negative effect on cardiovascular homeostasis and restoration. Sleep disorders have a fundamental contribution to cerebrovascular and other cardiovascular diseases. The aim of this review is to highlight the role of sleep disorders in the risk of cerebrovascular ischemic stroke and help both neuropsychiatrists and our community to realize the great value of diagnosis and management of sleep disorders for effective prevention of ischemic stroke and proper care. Further attention and care should be given to the early identification of sleep disorders in risky patients to avoid major cerebrovascular and cardiovascular events.

Keywords: sleep disorders, ischemic stroke, risk factors, sleep apnea.

INTRODUCTION
Sleep is a composite behavioral and physiological state, needed for the integrity of cells (neurons) and organs (brain) and is crucial for the integrity of brain functions. However, thirty percent of the adult people have insomnia or other sleep troubles [1]. Sleep is a recurring process of cyclical changes from rapid-eye-movement (REM) to non-REM (NREM) sleep stages, which are strictly coordinated by the brain [2]. International Classification of Sleep Disorders classified sleep problems into six major groups [3]. Deprivation of sleep has been associated with several disorders, including cerebrovascular stroke as it prompts dysfunction of the autonomic nervous system, induces inflammation, stimulates oxidative stress mechanisms and disrupts coagulation [4].

Stroke is an ac cerebral circulatory disorder with temporary or persistent brain dysfunction. Stroke at according to the type of pathologic process into ischemic and hemorrhagic subtypes. Cerebral ischemic infarction occurs in more than 70% of cases and intracerebral hemorrhage accounts for 15-30% of stroke cases [5]. Stroke is a principal cause of mortality and a substantial long-standing disability all over the world. Stroke recurrence remains high and estimated at 17% over 5 years [6]. In our locality, stroke prevalence is high. It was estimated with a rate of 963/100,000 Egyptian population [7]. We will try to clarify the possible bidirectional causal relation between sleep disorders and stroke and how they can affect each other through the possible substantial effect of sleep disorders in the pathogenesis of
cerebrovascular events and the link of sleep disorders to stroke risk.

**Sleep disorders and stroke risk**

The cardiovascular system makes homeostatic balance during sleep by regulation of the autonomic system [8]. Lowering in the systolic and diastolic blood pressure throughout sleep periods, called “dipping,” is a marker for cardiovascular functional integrity, due to the effect of sleep and circadian rhythms [9]. During NREM sleep which constitutes 75-80% of sleep in normal adults, the autonomic nervous system has vagal predominance and elevated baroreceptor sensitivity, causing a lowering in blood pressure and cardiac rhythm, with marked lowering throughout deep sleep stages [9, 10].

On the other hand, REM which constitutes 20% of total sleep has pronounced variations in sympathetic and vagal balance which cause abrupt swings in cardiac rhythm and blood pressure [8]. Any cause of sleep disturbance has a negative effect on cardiovascular homeostasis by diminishing protective periods of NREM deep sleep. Sleep fragmentation, known by cortical EEG arousals, is a general feature of almost all sleep disorders and is associated with bouts in sympathetic hyperactivity [11].

Fragmentation of sleep causes non-dipping (Lack of reduction in blood pressure throughout sleep) [12-14] which is linked to cardiac, neurological, metabolic, and renal problems [15-19]. Non-dipping is prevalent in the elderly and is linked to an elevated stroke risk [20]. Lack of dipping is linked to brain atrophy, worsening functions, and compromised cerebral circulation [21].

Sleep disturbances can induce several pathologic mechanisms other than autonomic circulatory dysfunction including changes in intrathoracic pressure, fluctuant hypoxia, sympathetic overactivation, impaired endothelial function, and proinflammatory condition, insulin over resistance, activation of the axis of hypothalamic-pituitary-adrenal glands, blood pressure swings, cardiac dysrhythmia, and enhanced coagulability predisposing to cardiovascular diseases (atherosclerosis, arterial hypertension, cardiac arrhythmia, and stroke) [22, 23].

**Obstructive sleep apnea**

Obstructive sleep apnea (OSA) has recurrent pauses or reductions of airflow caused by partial or complete upper airway obstruction. Its prevalence in males 9% to 14% and 4% to 7% in females [24]. Several studies have provided evidence that OSA is a strong predictor for cardiac and cerebrovascular diseases, including stroke [22, 25, 26].

OSA is a leading biomarker for stroke susceptibility due to its hazardous effect on brain functions. Experimental animals exposed to intermittent hypoxia had executive dysfunction, excessive sleep, and hypersensitivity to sleep deprivation [27]. There is a proof of hippocampal neuronal damage [28], the base of the forebrain [29] and the wakefulness activating catecholaminergic mechanisms [30]. The proposed contributing techniques are through platelet overactivation, lipid oxidation, free radicals damage, nitric oxide overproduction, and programmed cell death [31]. However, mild hypoxia has a protecting influence on the cerebrovascular system by promoting vascular remodeling and other protective reactions, called ischemic preconditioning [32].

OSA is linked to ischemic changes in neuroimaging, including white matter changes and cerebral microbleeds [33, 34]. Moreover, OSA has been reported
to promote extracranial and intracranial atherosclerosis [35]. It has been reported that OSA is linked to hypertension and its severity [36] and is more common in patients with resistant hypertension [37]. Also, OSA may promote the risk of diabetes by enhancing insulin resistance and increasing cortisol hormonal secretion [26]. In agreement with this, OSA is also liked to cardioembolism. Nearly half of atrial fibrillation (A.F) problems happen at the periods between late night and early morning [38]. Patients with OSA have higher risk four times for A.F. Oxygen desaturation at night is a strong risk factor for newly developed A.F [39]. In a study by Cadby and their colleagues reported that OSA diagnosis and severity were significantly associated with A.F [40]. Furthermore, it was found that OSA magnifies the stroke risk in A.F patients [41]. Moreover, OSA mediates inflammation [42] dysfunction of endothelial cells [43] hypercoagulability [44] and cerebral hemodynamics disturbance [45]. Collectively, OSA was found to be a major stroke risk factor through different mechanisms including intermittent hypoxia, sleep fragmentation, and hemodynamic changes [22, 26]. OSA is much more prevalent in acute stroke, found in more than 50% of patients with acute cerebral infarction or transient ischemic attack, which is more than that seen in control individuals [46]. Furthermore, stroke and OSA share common risk factors such as hypertension, elderly age, obesity, smoking and male sex [47].

**Insomnia**

Insomnia prevalence is approximately 10% to 20% among adults [48]. Chronic insomnia is defined by difficulty starting and maintaining comfortable sleep, and earlier awakening than required for fully three nights per week for at least 3 months duration [3]. It has been reported that insomnia elevates cardiovascular risk and death probability [49]. Many studies found a major relation between lack of sleep insomnia and cardiovascular morbidities [50]. A study by Phillips and Mannino (2007), reported that insomnia was strongly related to hypertension and cardiovascular disease [51]. Insomnia with short sleep duration promotes the risk of arrhythmia, hypertension, diabetes, cognitive impairment, and mortality [52]. The cardiovascular effect of insomnia was suggested to be due to the hypothalamic-pituitary-adrenal axis and autonomic sympathetic hyperactivity [53].

**Duration of sleep**

The connection between the duration of sleep and cerebrovascular risk is U-shaped. Short and long duration sleep groups promote the risk for stroke [54]. Short sleep is a potential contributor to health; however, its role in predicting mortality associated with cardiometabolic risk factors remains poorly understood [55]. Short sleep (less than 5 hours of night sleep) elevates the incidence of cerebrovascular events, cardiovascular disease [56, 57]. Similarly, long sleep duration (9 hours or more of night sleep) elevates the risk of cerebrovascular and cardiac mortality [57-59]. The strong connection between cerebrovascular disease mortality and sleep duration and has been studied in many types of research [57, 60-62]. However, long sleep has more mortality risk than short sleep [63] which can be explained by that long sleep points to an increased sleep requirement, especially in elderly people, affected by comorbid pathological conditions [64].
Long sleep is a principal factor for future susceptibility to stroke [65, 66]. Enhanced inflammation and disturbed fat metabolism have been reported to be the mechanisms inducing stroke risk [67]. Long sleep was linked to carotid atherosclerosis [68], A.F [69] and white matter lesions [70]. Short sleep contributes to the development of obesity by elevating levels ghrelin which stimulates the appetite and reduced levels of leptin which antagonize the action of ghrelin [71].

Moreover, decreased mobility which presents with short sleep induce obesity by reducing energy consumption [72]. Furthermore, short sleep induces sympathetic hyperactivity [73] which contributes to impaired glucose metabolism [74] hypertension [75]. Sleep deprivation promotes inflammatory processes, leads to elevated interleukin6 and C-reactive protein levels [76]. In summary, prolonged and reduced sleep are promoting stroke and mortality. Simple interventions like weekend sleep expansion might have an influence on the population level. Many studies found that catch-up sleep at weekends reduces the risk of hypertension and weight gain [77].

**Periodic limb movements (PLM)**

PLM is distinguished by intermittent attacks of recurrent, stereotyped lower limb movements during sleep [3]. The average number of PLMs in an hour of sleep (PLM index) estimated the severity of PLM. Its prevalence among adult population (4.3% to 9.3%) [78]. It has been found that PLM has a positive relation with cardiovascular disease and higher risk associated with arousals combined with PLM [79]. PLM with awakening stimulates a sudden rise in blood pressure and heart rate by sympathetic overactivity [80].

**Restless leg syndrome (RLS)**

It is a chronic sensory and motor disorder characterized by an irresistible desire to move the limbs, worsens at rest, occurs at nighttime, and is relieved by walking around [81]. Its prevalence is 5-10% in adults [82]. It has been suggested that RLS elevates the risk of cerebrovascular diseases [83] Being RLS as a prognostic factor for stroke is a matter of controversy [84-86]. In a study, RLS was related to an elevation of the probability of cardiovascular mortality [87]. On the other side, other studies found contrast results [82, 88]. However, a recent study revealed that longer duration, more severe, and secondary RLS were linked to stroke risk [86]. Metabolic disturbance, sympathetic hyperactivity, and inflammation have been suggested as mechanisms linking between PLM/RLS and stroke risk [89]. Recurrent heart rate and blood pressure disturbance associated with PLM and repeated awakenings induce hypertension and elevating the risk for cerebrovascular diseases [90].

**Circadian rhythm disorders and stroke**

The internal 24-hour circadian pacemaker is regulated by external factors (light/dark cues, eating, exercise, and social interactions) [91]. Night work interferes with the blood pressure reduction at night, leads to an abnormal rise in blood pressure during the shift that continues to the next day [92]. Consequently, night workers are susceptible to hypertension, cerebrovascular disease, and mortality [93, 94]. A study by Brown and colleagues (2009) showed that, switching night shift work was significantly associated with a 4% rise in susceptibility of cerebral infarction for every 5 years of exposure [95]. Moreover, another study showed that shift work was positively correlated with cerebrovascular events [96].
Conclusion
Sleep disorders are underestimated pathological conditions in our locality despite the growing body of evidence of their great influence as important factors in cerebrovascular stroke susceptibility. They can be modifiable risk factors for cardiac and cerebrovascular diseases. OSA is a major susceptibility independent factor for cerebrovascular ischemic events. Future studies with improved treatment options are crucial. Duration of sleep and insomnia could be prognostic factors for cerebral ischemia and mortality. Furthermore, PLM and RLS, are also possible factors for stroke vulnerability. We recommend strong encouragement of systematized screening programs and suitable effective management of different sleep problems which can reduce ischemic stroke risk effectively among our population.

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