

## Sleep disorders and acute stroke: profile and research opportunities

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Stroke is the leading cause of disability and mortality worldwide. More than half of stroke patients have sleep disorders, including sleep breathing disorders, non-apnea sleep disturbances, and circadian rhythm disruption. Therefore, sleep disturbances, particularly obstructive sleep apnea (OSA), have long been speculated as new preventive and therapeutic targets for stroke. Whether the specific roles of the above sleep disorders in stroke outcome or the efficacy of OSA treatment with continuous positive airway pressure (CPAP) therapy to prevent cerebrovascular events remains uncertain yet. It is noteworthy that there are important limitations among these studies. Here, we briefly reviewed representative studies and subsequently addressed the opportunities mainly for clinical research. The main recommendations are outlined at the end.

There are two main types of sleep-disordered breathing: obstructive and central. The literature investigating stroke-related sleep disorders in human has primarily focused on OSA.<sup>[1-4]</sup> Most of them found a correlation between OSA and ischemic stroke. The estimated prevalence of post-stroke OSA is greater than 70%,<sup>[5]</sup> which might have to do with positional sleep apnea, stroke-related upper airway tone changes, and untreated OSA preceding the stroke. A prospective study evaluating sleep apnea before and after stroke showed a similar frequency of OSA, indicating OSA is the condition before stroke rather than the consequence of infarction in most patients.<sup>[1]</sup> Furthermore, population-based cohort studies have confirmed that OSA independently leads to an increased risk of ischemic stroke.<sup>[2]</sup> The mechanisms underlying the phenomenon might be through the hypoxia-reoxygenation mechanism and sleep fragmentation, which increase the expression of proinflammatory markers, oxidative stress, endothelial damage, and sympathetic hyperactivity. In addition, OSA can increase the risk of stroke by affecting vascular risk factors such as hypertension. Regarding stroke recovery and recurrence, several cohort studies have indicated that, in the post-

stroke population, OSA patients are more likely to have a higher rate of recurrent strokes, a higher risk of mortality, and a worse functional recovery than non-OSA patients.<sup>[3]</sup> Several high-quality cohort studies have provided relatively sufficient and reliable evidence regarding the effects of OSA on stroke. However, limited evidence exists concerning the effects of central sleep apnea (CSA) on stroke. Isolated retrospective studies suggest central respiratory events are common after stroke where there is infarction of special areas (brainstem and interbrain) regulating the respiratory system.<sup>[4]</sup>

Rapid eye movement sleep behavior disorder (RBD) is a parasomnia, characterized by vivid dreams accompanied by attacks of vigorous and dangerous motor activity. Additionally, restless leg syndrome (RLS) is a disorder that causes uncomfortable sensations in the legs, typically worse during periods of rest. Both are rarely associated with sleep apnea in terms of etiology; therefore, classified as non-apnea sleep disorders. As a topical issue in the research field of Parkinson disease and related disorders for many years, the roles of RBD and RLS in cerebrovascular disease have been rarely reported. Only a few small cohort studies have shown that non-apnea related disturbances are associated with an increased risk of stroke.<sup>[6-8]</sup> Excessive sympathetic activation and the lack of dopaminergic neurotransmitters might be the potential mechanisms. However, most of the studies were of poor quality, with small samples and insufficient follow-up periods; thus, they should be interpreted with precaution.

A meta-analysis of 11 studies showed that risk of stroke increased 17% per hour of sleep increment in those with sleep duration >7 h/d compared with those within 7 h/d.<sup>[9]</sup> But another meta-analysis found that short sleep duration was associated with a higher risk for stroke.<sup>[10]</sup> Besides, the latest cohort study with 8-years follow-up period in China

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suggested that both short and long sleep duration increased risk of stroke.<sup>[11]</sup> Overall, there might be a U-shaped association between sleep duration and risk of stroke. Possible explanations might involve proinflammatory markers, atrial fibrillation, and arterial atherosclerosis. However, the current studies on this issue have some limitations. First, the definitions of long sleep duration vary from study to study. Second, few studies have included depression and anxiety, which might be potential confounding factors as co-variables in multivariate analyses. Third, the methods utilized in these studies were self-assessment questionnaires, lacked objective data. Given the high prevalence of insomnia (56.7%) and excessive daytime sleepiness (EDS) (28.0%) in the post-stroke population,<sup>[12,13]</sup> sleep misperceptions might lead to the inaccuracy of subjective questionnaire. On the one hand, there was an intriguing category which is the negative sleep state misperception (people who underestimated their sleep) among insomnias subtypes.<sup>[14]</sup> On the other hand, daytime sleepiness was associated with positive sleep state misperception (people who overestimated their sleep).<sup>[15]</sup> The inability to perceive sleep correctly might be a critical factor limiting the utilize of sleep-related self-assessment questionnaires.

No study has investigated the effects of sleep structure on acute ischemic stroke. Only one study has examined brain lesions at autopsy in 167 participants who had undergone polysomnography (PSG) before death, indicating that greater slow-wave sleep is associated with less brain atrophy, a feature of cerebral small vessel disease.<sup>[16]</sup> The evidence is insufficient, but multiple studies have investigated the effects of ischemic stroke on sleep structure, although no consistent associations were found. Compared with the controls, the ischemic stroke groups showed statistically significant reduction of the sleep architecture, including sleep efficiency, total sleep time, non-rapid eye movement sleep 1 (NREM1), NREM2, slow-wave sleep, and REM.<sup>[17-19]</sup> The cause might be the effects of ischemic injury on projection from the thalamus to the cortex, which regulates the sleep-wake cycle. Such a large difference in conclusions may be related to the heterogeneity of etiology, ischemic site, volume, and timing of infarction among different studies.

No study has investigated the effects of circadian rhythm disruption on ischemic stroke and, thus far, the evaluation of circadian rhythm in stroke patients is in the initial phases. Further, only a few studies have shown a decrease in melatonin after ischemic stroke.<sup>[20,21]</sup> These studies have several limitations. First, no pre-stroke melatonin concentration was measured and no causality could be found. Second, it remains unclear whether the circadian rhythm disruptions were due to a direct effect of stroke or by environmental light exposure. Third, a large heterogeneity is observed among stroke patients due to the differences in etiology, topography, and severity, which are likely to interfere with the conclusions of related studies. Future studies should measure daytime light exposure and the pre-stroke melatonin concentration. In addition, stratified analysis should be performed in enrolled patients according to the different etiology, topography, or severity.

Of all sleep disorders, OSA might be the most closely associated with stroke. CPAP therapy is the gold standard for the treatment of moderate to severe OSA. Whether CPAP can effectively reduce the risk of stroke and become a non-invasive and relatively inexpensive method of secondary prevention has aroused more discussions in recent years. The sleep apnea cardiovascular endpoints trial, an important evidence in the field, pointed out therapy with CPAP with the low compliance (3.3 h/night) did not prevent cardiovascular events in patients with moderate-to-severe OSA and established cardiovascular disease.<sup>[22]</sup> Besides, Gonzalo Labarca *et al*<sup>[23]</sup> conducted a systematic review including eight randomized controlled trials and 5817 participants and showed no evidence that CPAP therapy improves stroke outcomes. Considering that CPAP adherence and OSA severity may have reduced the benefit from CPAP, Lin *et al*<sup>[24]</sup> divided the studies into subgroups based on CPAP adherence status and baseline OSA severity and revealed significant stroke risk reduction in the good CPAP adherence group and the moderate to severe OSA group. CPAP therapy is a promising secondary prevention method for stroke. The key is to improve the detection of apnea severity in the post-stroke population and compliance of CPAP treatment. The long-term adherence to CPAP in the post-stroke population might be lower than that in the non-stroke population, the reasons for which are possibly related to the lack of typical symptoms of OSA and lack of positive concepts of secondary prevention. No evidence has been reported that other treatments for sleep disorders are equally effective in preventing stroke.

Our recommendations are as follows: (1) Further research is needed to verify the association between CSA and stroke, as previous studies have mostly focused on the association of OSA and stroke. (2) Studies focus on the relation between non-apnea sleep disorders (RBD, RLS) and stroke need a sufficient sample size and an adequate follow-up period. (3) Sleep duration can be analyzed as a continuous variable, not merely as a categorical variable; depression and other psychiatric comorbidities should be included for adjustments; objective sleep duration should be measured by PSG. (4) Analysis of sleep structure-related variables stratified by etiology and location of stroke is necessary. (5) The investigation of circadian rhythms in ischemic stroke is an emerging field in its infancy. A standardized measurement of circadian rhythms remains to be determined. (6) Observational studies targeting the causes of low adherence to CPAP in the post-stroke population should be encouraged. The development of appropriate strategies to improve the adherence to CPAP may be an area of research worth exploring.

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### Conflicts of interest

None.

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