



Narrative review of sleep and stroke

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Abstract: Sleep disorders, such as sleep-disordered breathing (SDB), insomnia or restless legs syndrome (RLS), are common in the general population and after stroke. In some cases, sleep disturbances are pre-existing, but can also appear *de novo* as a direct consequence of brain damage or due to stroke-related complications. Furthermore, some sleep conditions may act as a risk factor of stroke. This review explores the available evidence of the two-way relationship between sleep and stroke. Cardiovascular physiological changes during sleep are described, as well as the evidence on the relationship between stroke and sleep duration, SDB, RLS, insomnia, excessive daytime sleepiness (EDS), and circadian rhythm alterations. Potential changes on sleep architecture, and the links that may exist between sleep and functional outcomes after stroke are also discussed. Importantly, sleep-related disturbances may be associated with worse stroke recovery outcomes and increased cerebrovascular morbidity. It is therefore relevant that the bidirectional association between stroke and sleep is taken into consideration by clinicians taking care of these patients. Future research may focus on this mutual relationship for a better understanding of the impact of stroke on sleep, the importance of sleep in stroke incidence and recovery, and have further evidence on treatment strategies that may improve functional outcome after stroke.

Keywords: Stroke; obstructive sleep apnoea (OSA); restless legs syndrome (RLS); insomnia; excessive daytime sleepiness (EDS)

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Introduction

The relationship between sleep and stroke is complex and bidirectional (1). Physiological changes of the cardiovascular system associated to sleep, and also due to circadian variations, may play a key role on the aetiology and onset of stroke. Certain sleep disturbances may increase the risk for cerebrovascular events; obstructive sleep apnoea (OSA) and sleep duration have been considered as potential, often modifiable, stroke risk factors. Conversely, many sleep disorders, such as restless legs syndrome (RLS), periodic limb movements during sleep (PLMS), insomnia, sleep-

disordered breathing (SDB), excessive daytime sleepiness (EDS) and circadian anomalies, are frequently reported and diagnosed in patients having suffered a stroke. These sleep-related complaints, either as *de novo* presentation or because of their exacerbation after a stroke, may have an impact on the functional recovery of patients (2).

Importantly, stroke is a major cause of morbidity and disability, and is the second most common cause of death worldwide (3). Sleep disturbances are prevalent in the general population, and can affect performance, quality of life and associate a significant economic burden (4,5). It is therefore worthwhile to consider potential links between

these prevalent conditions.

We aim to review some of the most relevant aspects of the intricate relationship between sleep and stroke. We discuss circadian and sleep-wake cardiovascular changes that may act as facilitating pathophysiological factors for stroke, the current evidence on certain sleep disorders as potential stroke risk factors, and the most commonly reported sleep issues following stroke. Additionally, we summarise post-stroke sleep architecture changes, and the potential impact that sleep disturbances may have on functional recovery following a cerebrovascular event.

We present the following article in accordance with the Narrative Review reporting checklist (available at <http://dx.doi.org/10.21037/jtd-cus-2020-002>).

Methods

The authors included the following main topics in this narrative review: cardiovascular sleep-wake changes and stroke; stroke and SDB; sleep duration and risk of stroke; RLS, PLMS and stroke; post-stroke insomnia; post-stroke EDS and risk of stroke in sleepy patients; circadian rhythm disturbances, shift work and stroke; sleep architecture changes after stroke; and sleep and functional outcome from stroke.

A literature search was done between March and April 2020. Search strategies used included a combination of free text and specific terms related to stroke and the sleep disorders or disturbances outlined above. Published studies were identified from the National Library of Medicine, PubMed database. Abstracts or full papers in English language pertinent to the topics included were reviewed.

Cardiovascular sleep-wake changes and stroke

The incidence of stroke during sleep and its circadian variations have been widely studied. Initial studies reported that cerebral infarction occurred more often at night than during the daytime and that symptoms are usually noticed on waking (6). However, nowadays, it is known that several types of cardiovascular events, including stroke, acute myocardial infarction and sudden cardiac death, display significant circadian variation in symptoms onset (7-9). A meta-analysis (10) identified a 49% excess risk for ischaemic stroke between 6 am and noon compared with the number expected if there was no circadian predominance. Furthermore, in studies that analysed specifically whether strokes occurred during sleep, they described a decrease of

stroke frequency in the night sleep hours (11), therefore, proposing the idea of a protective effect associated with night sleep or an activator effect in awakening. Overall, about 25% of strokes occur during sleep (12,13), and a large proportion of them take place in the last part (14), when rapid-eye-movement (REM) sleep is more prominent. Changes during REM sleep stage may trigger mechanisms for thrombotic events, and may present clinically only after arousal (15).

Although the exact mechanisms are still not clear, there are several physiologic variations occurring during sleep and arousal that may predispose to a cerebrovascular event (16). These are discussed below.

Autonomic nervous system

Non-REM (NREM) sleep, is a period of relative autonomic stability, incorporating sympathetic inhibition, increased vagal tone with bradycardia (15,17) and enhanced respiratory sinus arrhythmia. Alternatively, REM sleep is predominantly a parasympathetic state (16), however, with phasic sudden bursts of sympathetic nervous system (SNS) activity (15,18), leading to complex fluctuations in autonomic function, with evidence of vagal discharges to the sinoatrial node, as well as abrupt sympathetic bursts. Additionally, as a result of rapid parasympathetic withdrawal and SNS activation (18,19), arousals are accompanied by substantial increases in blood pressure (BP), heart rate and transient hyperpnoea.

Renin-angiotensin-aldosterone system (RAAS) and catecholamines

There is a circadian variation in catecholamine metabolism (20), with maximal increase between 6 and 9 am, and lowest levels at midnight, confirming the activation of SNS. Similarly, also as a result of activation of the SNS, the RAAS is activated in the early morning before awaking (21), with increased production of renin and angiotensin II (22). In addition to vasoconstriction, angiotensin II brings vascular inflammation and increased risk of thrombosis (23).

Blood pressure

The Framingham study (24) showed that hypertension is the most powerful risk factor in the aetiology of stroke. Several studies have described a circadian variation in BP (25), as this reaches its highest in the mid-morning and then

progressively falls throughout the day, with its lowest at 3 am. There is emerging evidence that the absence of the expected nocturnal BP decline, as seen in “non-dippers” (such as patients with OSA), as well as an excessive BP decline during sleep (“extreme dipping”), may both have important cardiovascular implications (10). Furthermore, the activation of the SNS and RAAS just before arousal produces an early morning BP surge.

Platelet aggregability

Tofler *et al.* (26) found that the increase in platelet aggregability depended on the time of the subjects arousal, showing a peak at 6–9 am in those who woke up and started their daily activities, but not in those who remained at bedrest. This suggests that the increased morning aggregability is a response to some component of the process of awakening and, most probably, with the assumption of an upright posture (27).

Fibrinolytic factors

Under normal conditions, tissue-type plasminogen activator and its fast-acting inhibitor represent a potential fibrinolytic capacity (28), and their circadian variation is not associated with changes in effective fibrinolysis. However, in thrombotic states, the physiological drop of fibrinolytic activity in the morning hours may render incompetent to counterbalance the high level of fibrin generation and favour thrombus development.

Blood viscosity

Another factor that may contribute to the occurrence of stroke is increased blood viscosity. This reaches a maximum in the morning between 8 am and 12 pm and a minimum at 3 am (29).

Taken together, all these changes with a circadian predominance, happening during sleep or upon arousal, may play a role in the occurrence of a cerebrovascular event.

Stroke and SDB

The prevalence of OSA associated with daytime sleepiness is approximately 3% to 7% for adult men and 2% to 5% for adult women in the general population (30). In a population-based study, the overall prevalence of central sleep apnoea (CSA) on polysomnography was 0.9% (31),

and approximately half of the CSA cases were associated with Cheyne-Stokes respiration.

In a meta-analysis of SDB after ischaemic or haemorrhagic stroke and transient ischaemic attack (TIA) (32), 72% of patients had an apnoea-hypopnoea index (AHI) of at least 5 events/hour (ev/hr) but only 7% of patients had primarily central apnoeas.

The different forms of SDB have a mutual relationship with stroke, as they may both act as risk factor and arise as a consequence of cerebrovascular events (*Table 1*).

OSA as a risk factor of stroke

OSA is known to be an independent risk factor for stroke (33). The Sleep Heart Health Study (34), a prospective study spanning 7 years, discovered a direct relationship between OSA severity and risk of stroke. It found that men with moderate to severe OSA had a 3-fold risk of suffering a stroke, and that the risk of stroke rose by 6% for every unit on the AHI between 5 and 25 ev/hr. Among women, such increases in risk of stroke were observed only in those with an AHI at 25 ev/hr or higher. A meta-analysis (35) revealed that moderate to severe OSA significantly increased cardiovascular risk, in particular, the risk of stroke (relative risk, 2.02; 95% CI, 1.4–2.9).

From a pathophysiological perspective, the mechanisms underlying this increased risk of stroke are multifactorial (36). In patients with OSA, there seems to be a decreased cerebral blood flow during awake state compared with non-OSA individuals, and greater reductions in regional cerebral blood flow during NREM sleep (37). During apnoeas, there is a proven marked increase in intracranial pressure (38) and a secondary decrease in cerebral perfusion pressure. Additionally, abnormalities of cerebral vascular response to hypercapnia have been found in patients with OSA during wakefulness (39), which can impair the ability of cerebral vessels to adapt to rapid systemic pressure changes and to the metabolic needs of the brain. This abnormality in cerebral auto regulation may be corrected with the treatment of sleep apnoea with continuous positive airway pressure (CPAP) (40). As well as these changes in cerebral vascular responses, there is evidence that platelet aggregation is significantly enhanced in patients with severe OSA during the night compared with healthy individuals (41), and that the abnormality may be reversed with treatment of sleep apnoea with CPAP. The increased platelet aggregability is related to rising plasma norepinephrine and epinephrine levels (26) caused

Table 1 Sleep-related disturbances and their associations with stroke

Stroke and SDB

OSA is an independent risk factor of stroke

CPAP therapy in stroke patients with OSA may improve functional outcomes

SDB (OSA/CSA) may arise as a consequence of stroke

The presence of OSA in stroke patients is associated with worse functional outcome, early death and recurrent stroke

Sleep duration and risk of stroke

Both short and long sleep times have been proposed as potential risk factors for stroke

Cardiovascular, metabolic and inflammatory changes have been suggested as underlying mechanisms that associate sleep duration alterations and stroke

RLS, PLMS and stroke

RLS and PLMS may arise following cerebrovascular events involving strategic areas in the CNS

PLMS may be associated with an increased risk of stroke, whereas the evidence for this in patients with RLS is limited

Post-stroke insomnia

Insomnia is prevalent in stroke patients and is probably multifactorial

The effect of insomnia on the risk of stroke is uncertain

The presence of insomnia is related to greater disability following stroke

Post-stroke EDS and risk of stroke in sleepy patients

Investigating EDS in stroke patients is challenging due to heterogeneous definitions of sleepiness

Available evidence has focused in EDS associated to stroke involving strategic areas in the CNS

EDS has been proposed as a risk factor of stroke, however, there are several limitations related to EDS assessment and presence of confounding factors

Hypersomnia is associated with higher rates of disability after stroke

Circadian rhythm disturbances, shift work and stroke

Changes in levels of melatonin have been reported in the acute phase of stroke in some patients

Shift work might contribute to the risk of stroke

Sleep architecture changes and functional outcome after stroke

Alterations in sleep architecture, such as a reduction in total sleep time and sleep efficiency, have been reported in the acute phase of stroke

High sleep efficiency and low amount of wakefulness after sleep onset in acute stroke have been related to good long-term outcomes

Changes in REM sleep latency may play a role in stroke recovery, although data are contradictory

SDB, sleep-disordered breathing; OSA, obstructive sleep apnoea; CPAP, continuous positive airway pressure; CSA, central sleep apnoea; RLS, restless legs syndrome; PLMS, periodic limb movements during sleep; CNS, central nervous system; EDS, excessive daytime sleepiness; REM, rapid-eye-movement.

by activation of SNS due to both apnoeas and arousals during sleep. The high levels of sympathetic activity during apnoeas, also leads to surges in BP (42) (further enhanced by arousals and sleep fragmentation) responsible for the characteristic “non-dipping” pressure pattern observed in most patients with OSA (43). Along with direct increases in

oxidative stress, the effects of the OSA-related sympathetic activity likely contribute to sustained daytime hypertension and the occurrence of cardiovascular events. Lastly, plasma fibrinogen levels (believed to be associated with increased risk of stroke), have been shown to be elevated in patients with OSA and stroke (44), and to correlate with OSA

severity.

OSA can also increase the risk of stroke through effects on traditional stroke risk factors, especially hypertension. In the Wisconsin Sleep Cohort Study, a dose-response association was noted between the AHI at baseline and the development of hypertension, with a 3-fold probability of having hypertension at a 4-year follow-up in participants with moderate OSA (45).

Patients with OSA have an increased prevalence of systemic hypertension, heart disease, impaired vascular endothelial function, accelerated atherogenesis, diabetes, atrial fibrillation, prothrombotic coagulation shifts and proinflammatory state (46). In patients with atrial fibrillation, OSA has been independently associated with recurrent atrial fibrillation after cardioversion or ablation (47). Patent foramen ovale (PFO) has also been suggested as a possible mechanism for increased stroke risk since patients with OSA are about twice as likely as controls to have evidence of a PFO (48). Additionally, nocturnal apnoeas and pulmonary hypertension associated with OSA could increase right-to-left shunting (49), thereby increasing the risk of paradoxical embolism and stroke in patients with a PFO.

OSA following stroke

The estimated prevalence of OSA after stroke or TIA is over 70% (32). This may be due to several factors: brain damage per se can impair breathing control, similar risk factors are associated with stroke and SDB, there are stroke-related upper airway tone changes, and some of the patients with OSA detected after stroke may have had pre-existent undiagnosed OSA. To date, there is no conclusive link between the prevalence or severity of OSA and stroke subtype, topography, size or severity (50). SDB improves from the acute to the subacute phase of stroke, but about 50% of patients still exhibit an AHI 10 ev/hr 3 months after the event (51). Central events appear to improve more than obstructive events. Restitution of neurological deficits, improvement of lung function (e.g., recovery from pneumonia), and disappearance of acute cardiac complications like heart failure, as well as a decrease in time spent in supine bed position, may play a role in the SDB improvement.

Treatment of OSA in stroke patients

The gold standard treatment for OSA is CPAP (52). Other

modes of positive airway pressure administration include bilevel positive airway pressure (BiPAP), and autotitrating positive airway pressure. Although CPAP therapy has been demonstrated to successfully treat OSA, adherence to CPAP therapy is a significant issue. Compliance has ranged from 40% to 84% in the general population, but it was as low as 15% in the long term in stroke survivors (53).

In a prospective cohort study of patients with ischaemic stroke who underwent a sleep study, CPAP was offered to 58% of patients with an AHI of at least 20 ev/hr (54). After a period of 7 years, patients who could not tolerate CPAP had a nearly 3-fold increased risk of nonfatal cardiovascular events, particularly recurrent stroke, compared with those who were adherent to CPAP, those without OSA, or those with mild disease combined. The number needed to treat to prevent one nonfatal vascular event with CPAP was 4.9 patients (95% CI: 2–19).

Therefore, there seems to be a relationship between CPAP use and stroke outcome, but the poor tolerance and adherence that stroke patients present to treatment with CPAP renders challenging to analyse the full benefits on stroke recovery. In an effort to improve tolerance, some interventions have been suggested to optimise and encourage CPAP use (55), such as closer monitoring, education and continual CPAP adjustments. Alternatively, BiPAP has been used in OSA patients who do not tolerate CPAP, since BiPAP has been shown to be well tolerated in >90% of acute ischaemic stroke survivors with OSA (56).

Diet and physical exercise, to reduce obesity, may improve SDB in non-stroke populations (57); however, weight loss may be difficult to achieve and maintain due to functional consequences following stroke. There is limited evidence of other therapeutic options for OSA such as positional therapy, mandibular advancement devices or surgical interventions in stroke patients (50).

CSA and stroke

CSA episodes may be associated with increased risk of adverse cardiovascular outcomes since evidence from animal models have shown an increment of adrenergic hyperexcitation independent of arousals (58), as well as desaturation and hypoxia. Furthermore, a relationship between CSA and decreased ventricular function has been described in various studies (59), and it may serve as a marker of underlying cardiac vulnerability, predisposing to increased cardiac arrhythmias (60). CSA may also emerge as a consequence of stroke, and it has been observed in

patients with vascular injury to the respiratory centers in the medulla, infratentorial lesions, and bilateral hemispheric lesions (50).

CSA tends to improve after acute stroke (32). In a study of 161 patients with first-ever stroke or TIA who underwent sleep studies in the acute phase and again after 3 months, the rate of SDB decreased with a significant reduction in central but not obstructive apnoeas, suggesting that CSA following acute stroke is often self-limited (51).

The effects of CSA on stroke outcome and the role of early therapy for CSA after stroke are unclear, since it has been far less studied than OSA in stroke populations. Studies that described higher risk of death in stroke patients with OSA did not show the same trend in patients with CSA (61).

In regards to treatment, despite the prevalence of CSA, no study has attempted to treat CSA directly in stroke patients. CPAP is the preferred first-line therapy for symptomatic patients with CSA, but this recommendation is based on studies that focused on CSA in patients with heart failure (62). Other treatments such as adaptive servo-ventilation (63), BiPAP (64), acetazolamide (65) and phrenic nerve stimulation (66) have been tried in patients with CSA and heart failure, but to date, there is not enough evidence to recommend their use in stroke patients.

Sleep duration and risk of stroke

The relationship between long or short sleep duration and the risk of stroke has been widely investigated. Short sleep duration or sleep deprivation may increase the stroke risk due to its effects on the cardiovascular system and metabolism, leading to higher sympathetic activity, increased cortisol secretion and inflammation (67,68). The mechanisms that relate long sleep with a higher risk of stroke are not fully understood (69). A pro-inflammatory state (70), and higher risk to develop other cardiovascular risk factors (71-73) have been proposed as mechanisms that may underlie this association (Table 1).

In the study by Eguchi and colleagues (74), short sleep time (<7.5 h) was found to be an independent risk factor of stroke in hypertensive patients, when compared to those sleeping more than 7.5 h. The Postdam Study (75), demonstrated an increased risk of stroke in two subgroups, those sleeping less than 6 h and more than 9 h. A prospective study looking at fatal and non-fatal incident stroke at 9.5 years of follow-up (69), showed that 346 (out of 9,692 participants included) had at least one incident stroke. Long sleep (defined as >8 h) was associated with a

46% increase in risk of stroke after adjustment for other cardiovascular risk factors and comorbidities; there was a stronger association among women, and participants reporting substantially increased sleep duration over time had a higher stroke risk compared to those consistently reporting average sleep time. This work also reported the results from a meta-analysis on the association between stroke incidence and sleep duration, including 12 studies, which showed a pooled hazard ratio (HR) at 1.45 (1.30–1.62) for long sleep duration, and more modest effect of short sleep duration with a HR at 1.15 (1.07–1.24). Similarly, a recent review and meta-analysis evaluating the links between long sleep duration and health outcomes, showed that long sleep (>8 h) was significantly associated with incident stroke (RR =1.46; 95% CI, 1.26–1.69) (76). Additionally, a dose-response meta-analysis of prospective cohort studies (77), demonstrated that long sleepers had a higher predicted risk of stroke than short sleepers, and that the risk increased in 13% for every 1-hour increment above the reference of 7 h of sleep. A dose-response effect was also demonstrated on a recent systematic review and meta-analysis studying the relationship of sleep duration with risk of all-cause mortality and vascular risk factors such as stroke (78). This found a pooled RR for stroke at 1.05 (95% CI, 1.01–1.09) per 1-hour reduction and at 1.18 (95% CI, 1.14–1.21) per 1-hour increment in sleep duration.

The evidence on the association between short or long sleep duration and a specific type of stroke is contradictory. The Singapore Chinese Health study showed that both long and short sleep in hypertensive patients had a higher risk of ischaemic or unspecified, but not haemorrhagic, stroke mortality (79). However, the study by Leng *et al.* (69), found an association between short sleep and risk of ischaemic stroke, and long sleep and haemorrhagic stroke.

Studies including larger number of participants with each stroke subtype would be required to investigate further this matter and assess the pathophysiological causes of these possible associations.

RLS, PLMS and stroke

The prevalence of RLS in stroke patients has been estimated to be at around 2–12% (80-84). Importantly, the presence of post-stroke RLS seems to lead to worse reported quality of life, independently from functional situation and depression (85).

The location of the stroke may contribute to the development of RLS or PLMS. Areas such as the

brainstem, thalamus, basal ganglia, and corona radiata, have all been reported as probably involved in post-stroke RLS/PLMS, and may influence in the laterality of these (83,86). Subcortical stroke location has been associated with an increased risk of acute-onset RLS (80), and an involvement of the basal ganglia has been proposed in the occurrence of bilateral post-stroke RLS (86) (*Table 1*).

Unilateral or asymmetrical pre-stroke RLS was a predictor factor for stroke in the study by Gupta *et al.*, whereas Shiina and colleagues found that pre-stroke RLS patients had more often bilateral symptoms (81,84).

A cross-sectional study showed that RLS was more frequent among patients with stroke or TIA than in controls, and multivariate analysis found that this was independent from other cerebrovascular risk factors (87). However, its design does not allow to infer causality of this association. Furthermore, the findings from systematic reviews and meta-analyses do not demonstrate a higher incidence of stroke (88), or increased risk of cerebrovascular ischaemia when adjusting for confounding factors in patients with RLS (89). Hence, it is considered that there is insufficient evidence to suggest an increased risk of stroke in RLS patients (1).

In regards to PLMS, there is some evidence that these increase the cardiovascular risk due to repeated sympathetic activations and consequent increases of heart rate and BP (90). Although it has been pointed out the significant heterogeneity on previous studies assessing this relationship (91), a recent meta-analysis assessing the presence of stroke in individuals with PLMS, found an increased frequency of cerebrovascular events in patients with PLMS *vs.* controls (OR, 1.27; 95% CI, 1.04–1.54; $P=0.019$) (92).

Post-stroke insomnia

The prevalence of insomnia as a disorder has been estimated to be around 10% of the general population in several European countries (93). When considering insomnia symptoms (difficulties in initiation or maintenance of sleep, early awakening, non-restorative sleep) with no further criteria considered, about a third of the general population have at least one of these (94).

Post-stroke insomnia is often multifactorial. New onset insomnia following stroke may be partly related to the disrupting environmental factors on a stroke unit, the concomitant medical conditions and the fact that patients are bedridden. Furthermore, insomnia may be particularly

seen as a consequence of strokes affecting the dorsal/tegmental brainstem, paramedian or lateral thalamus, or subcortical areas. Some of these patients have an alternation of insomnia (and sometimes agitation) at night, with hypersomnia periods in the day (95).

A recent systematic review and meta-analysis on the incidence and prevalence of insomnia after stroke found a pooled prevalence of insomnia disorder or insomnia symptoms at 38.2% (CI, 30.1–46.5; $I^2=98\%$; $P<0.01$), generally with a female predominance (96). Those studies including information about comorbidities reported higher prevalence of depression or anxiety in participants with insomnia (or insomnia symptoms), reflecting that these conditions are probably bidirectionally related (96,97). Of note, in a significant proportion of stroke patients, insomnia may be a pre-existing condition (98). Importantly, the possible comorbid presence of other prevalent sleep-related disorders such as SDB or RLS should be considered when there are insomnia complaints in stroke patients.

Availability of systematic data on stroke outcomes after insomnia treatment is lacking (1).

Although there is some evidence of insomnia as a risk factor of cardiovascular events, including stroke (99-102), further assessment of their relationship would warrant prospective studies using objective measures (1) (*Table 1*).

Post-stroke EDS and risk of stroke in sleepy patients

There are numerous limitations in the assessment of sleepiness in patients that have suffered a stroke. Importantly, the definition of EDS is not the same as that of hypersomnia (103), however, these two terms are often used interchangeably. Also, both EDS and hypersomnia, are different from other symptoms such as fatigue or apathy that may also be described by stroke patients. Lastly, the assessment of EDS may be done with subjective measures such as the Epworth Sleepiness Scale (ESS) or objectively, *i.e.*, with the use of a mean sleep latency test (MSLT), leading to heterogeneous methodology and findings across studies.

Several factors may contribute to post-stroke EDS. The location of stroke, comorbid presence of sleep-related disturbances such as SDB or depression, side effects from certain medications, or a reduction on physical activity, may all lead to sleepiness in the day in these patients (104). Mostly, EDS in stroke survivors has been studied in relation to SDB. A recent study assessing the presence of EDS (defined as an ESS >10) in the acute phase post-stroke,

found that 10.5% of patients suffered from this symptom, with no correlation between the severity of EDS and that of stroke. However, a significant association was found between the values of the ESS and other factors such as RLS, body mass index (BMI) and the presence of diabetes mellitus (105).

A substantial amount of evidence on EDS or hypersomnia after stroke relates to the presence of these symptoms in patients with a cerebrovascular insult involving strategic areas, responsible for sleep-regulation and maintaining wakefulness, in the central nervous system. Bilateral paramedian thalamic stroke, as well as strokes involving other diencephalic, subcortical and pontine structures, have all been reported to lead to significant EDS or hypersomnia (104,106,107). These symptoms are prominent in the acute phase of stroke and seem to improve over time (106).

EDS has also been considered a potential risk factor for stroke. The Three City Study (108) demonstrated that, in the population studied (volunteers over 65 years old), the incidence of stroke was higher in those reporting frequent EDS at baseline point. The analysis included an adjustment by other health factors such as depression, snoring or BMI. The Northern Manhattan Study (109), estimated an increased risk of ischaemic stroke in patients that reported severe dozing in the day compared to those with no daytime dozing (HR, 2.74; 95% CI, 1.38–5.43). Similarly, previous studies have demonstrated higher incident cardiovascular disease (including stroke) in sleepy patients (110), and independent associations between higher ESS and stroke (111). However, it should be taken into account that the assessment of EDS is often subjective and that, frequently, these studies are not controlled for relevant factors such as sleep duration and shift work (*Table 1*).

Circadian rhythm disturbances, shift work and stroke

The presence of circadian anomalies in stroke patients has been the objective of numerous studies. There are several studies demonstrating significantly reduced levels of serum (112,113) or urine (114,115) melatonin in the acute phase post-stroke *vs.* controls. Nevertheless, an assessment of the possible influence of exposure to light during the day on these findings was not included (116). Of note, when compared ischaemic or haemorrhagic stroke survivor patients with those not surviving the vascular event, significantly higher levels of serum melatonin were observed

in non-survivors subjects, and those predicted mortality (117,118). The authors hypothesised that the increased melatonin levels can be related to an attempt to compensate a state of neuroinflammation and oxidation in such severe clinical situations. Additionally, a study suggested changes in self-reported circadian tendencies towards a more advanced and delayed chronotypes following anterior and posterior circulation strokes respectively (119). Whether these circadian alterations persist chronically or are only present in the acute phase after a stroke is yet unclear.

Circadian rhythm disturbances have also been proposed to potentially increase the risk of cardiovascular events. Evidence is scarce for the specific risk of stroke (*vs.* overall cardiovascular risk) among shift workers. Vyas and colleagues reported an attributable risk to shift work of 1.6% for ischaemic stroke (120); whereas another study showed a moderate increase in the risk of stroke, especially in women working prolonged periods of rotating night shifts (121). Additionally, working long hours (defined as over 40 h per week) was related with an increased risk of incident stroke with a dose response association (122) (*Table 1*).

Sleep architecture changes after stroke

Alterations in sleep architecture, such as a reduction in total sleep time and sleep efficiency, have been reported in the acute phase of stroke (123–125) (*Table 1*).

A recent study assessing the sleep-EEG changes within 9 days following an ischaemic supra or infratentorial stroke, showed a significant reduction in REM sleep (126), and reported that a prolonged latency to REM sleep was an independent predictor factor of poor functional outcome (modified Rankin Scale >2) (126). Of note, some of the patients included were taking antidepressants, and this was not taken into account when analysing effects in REM sleep stage. The opposite, a shorter REM latency predicting poor outcome, was found in another study (124) (*Table 1*).

Specific alterations may be more frequently seen in certain stroke locations. Sleep spindles seem particularly reduced in paramedian thalamic strokes (95,106), with an improvement in their number in the post-acute phase (106). However, a study excluding thalamic involvement, also demonstrated reduced sleep spindle frequency in stroke patients that improved over time in a follow-up polysomnographic recording >60 days post-stroke (125).

Loss of REM atonia leading to REM sleep behaviour disorder (RBD) (127,128), as well as both cataplexy and RBD (129), have been reported as a consequence of pontine

strokes.

Sleep and functional outcome from stroke

Sleep disorders may have detrimental effects during the acute phase of stroke, secondary to arousals and disturbed sleep-wake regulation causing fragmented sleep, elevated sympathetic activation, oxidative stress, inflammatory changes and evolution of the penumbra (130). Sleep-related disturbances after stroke may also have a deleterious effect during the subacute and chronic phases affecting neuroplasticity processes (131). Of note, sleep actively participates in the process of memory development and brain plasticity (132). Whereas total sleep time and sleep efficiency are lower in patients with poor short-term outcome after stroke (123), high sleep efficiency and low amount of wakefulness after sleep onset in the acute phase of stroke have been related to good long-term outcomes (133) (*Table 1*). After stroke, changes of sleep spindles in the acute phase have a positive correlation between ipsilesional spindle peak size and functional outcome after 12 months, whereas a slow wave activity increment is a predictor of poorer functional stroke outcome (125,133,134). As mentioned on the previous section, there are contradictory findings regarding changes in REM sleep latency and outcomes following stroke (124,126).

The presence of SDB in stroke patients provides a worse prognosis by predisposing to recurrent stroke, increasing the risk of short- and long-term mortality and worsening functional recovery (135). According to several studies in patients undergoing stroke rehabilitation, the presence of moderately severe OSA was associated with a significant increase in the risk of early neurologic worsening, worse functional outcome, early death and longer rehabilitation stay (61). These findings were independent of age, vascular risk factors, and other comorbidities. Moreover, possibly by contributing to cerebral small vessel disease (136), intermittent nocturnal hypoxia may increase the risk of vascular cognitive impairment including reduced attentional and executive functions, decreased learning and memory abilities and daytime sleepiness (137). These factors may adversely affect performance during rehabilitation training and, by extension, neural plasticity.

An association between insomnia and greater disability following stroke has been demonstrated (98,138), and both insufficient sleep and insomnia may lead to worse outcomes after stroke (98). In experimental stroke models (139), sleep deprivation was found to augment brain injury and

impair neuroplasticity, whereas drugs that promote NREM and REM sleep had a favorable effect on neuroplasticity and stroke recovery. Large-scale studies on the impact of insomnia on stroke outcomes in humans are lacking. However, insomnia patients show worse stroke recovery measured by functional independence scores, scores assessing activities of daily living, and health-related quality of life. Insomnia is frequently associated with poor life satisfaction and depression, conditions that may interfere with rehabilitation. Furthermore, stroke survivors with chronic insomnia seem to have lower probability to return to paid work by 12 months after the cardiovascular event (138).

RLS may also have an impact on stroke recovery (140). A study showed that stroke recovery evaluated by the modified Rankin Scale and Barthel Index was worse in RLS than non-RLS patients after adjustment for diabetes and BMI, but due to the limited size of this study, other risk factors could not be adjusted for. Patients with RLS presented daytime sleepiness and poor-quality sleep, potentially affecting their rehabilitation performance. Further studies to better understand the interplay between RLS and stroke are needed.

Hypersomnia or sleepiness following a stroke may affect functional recovery (141). In a cohort of stroke patients admitted to an acute rehabilitation unit, hypersomnia was associated with higher rates of nursing home discharges and higher disability at discharge, even after controlling for stroke severity at admission, age, stroke type, and time since stroke (*Table 1*). In a nationwide register, the presence of fatigue 2 years post-stroke was associated with nursing home referral and predicted mortality in the following year (142). This study did not adjust for medical conditions such as infections or cardiovascular diseases.

Sleep promotion should be part of stroke recovery treatment and stroke units environment should be optimised to help patients maintain adequate sleep-wake patterns. Early recognition and treatment of concomitant sleep disorders is relevant and may have an impact in the recovery process from stroke.

Summary

There is a mutual and intricate relationship between stroke and sleep (*Table 1*). Sleep disturbances, such as insomnia, RLS or daytime sleepiness, are frequently reported after having suffered a stroke. Also, sleep-related breathing disorders are commonly diagnosed in stroke patients. OSA and inadequate sleep duration seem to increase the risk of

stroke. Overall, the best quality of evidence is that assessing the links between OSA and stroke. However, there are limited data providing stronger evidence on other sleep conditions, such as RLS/PLMS and insomnia, acting as risk factors for cerebrovascular events.

The numerous links between sleep disturbances and stroke raises the importance of establishing more collaborations among clinicians of these disciplines, with the aim of improving prevention and outcomes of those prevalent disorders. Future research with prospective studies involving patients with sleep disorders and those having suffered a stroke seems warranted to further evaluate their potentially relevant associations, and to study treatment options which may improve functional outcomes after stroke.

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