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POSSIBLE SLEEP QUALITY FACTORS PREDICTORS OF WAKE-UP STROKES

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Abbreviations

AF – Atrial fibrillation

AVC – Acidente Vascular Cerebral

BMI – Body mass index

BP – Blood pressure

CHF – Congestive heart failure

CT – computed tomography

DBP – Diastolic blood pressure

DM – Diabetes mellitus

ESS – Epworth Sleep Scale

HBP – High blood pressure

ISI – Insomnia Severity Index

NIHSS - National Institutes of Health Stroke Scale

NREM – Non-Rapid Eye Movement

NWUS – Non-Wake-up stroke

OSA – Obstructive sleep apnea

REM – Rapid eye movement

SBP – Systolic blood pressure

SD – Standard deviation

SDB – Sleep disordered breathing

WUS – Wake-up stroke

Resumo

Os Acidentes Vasculares Cerebrais (AVC) do despertar ocorrem quando o doente adormece sem qualquer sintoma e acorda com clínica de AVC. A fisiopatologia deste tipo de AVCs ainda não é totalmente compreendida, contudo, alguns estudos apontam para uma possível associação entre os AVCs do despertar e o sono.

O principal objetivo deste estudo é comparar as características clínicas de doentes com AVCs do despertar e de doentes com AVCs durante a vigília, de forma a inferir sobre possiveis relações entre AVCs do despertar e sono.

Métodos: Foi realizado um estudo observacional prospetivo incluindo todos os doentes internados em enfermaria de Neurologia vascular com o diagnóstico de AVC. Excluimos 221 doentes por apresentarem AVC hemorrágico, afasia, incapacidade de cooperaçao ou recusarem participação. Foi aplicado um questionário sistemático das características do sono, incluindo escalas validades. As características clínicas, exames complementares de diagnóstico realizados e terapêutica de reperfusão instituída foram registados e analisados.

Resultados: A amostra é constituída por 81 doentes (53% do sexo masculino), 15 dos quais (18.52%) correspondem a AVCs do despertar. A idade média da população estudada é de 73.7 ± 12.9 anos. Comparando AVCs do despertar com instalações noutras horas do dia, a pontuação NIHSS foi superior nos doentes com AVC ao acordar (9.73 ± 4.25 vs. 6.65 ± 4.81, p=0.008). O perímetro cervical foi medido em todos os doentes, revelando uma média de 39.8 ± 3.64 cm e revelou ser significativamente maior nos doentes com AVCs do despertar (43.6 ±2.44 vs. 39.0 ± 3.32, p<0.001). Foi igualmente encontrada uma diferença estatisticamente significativa entre os doentes com AVC do despertar e os AVCs na vigília relativamente à sonolência diurna (53.3‰ vs. 25.8%, p=0.037). Nenhuma diferença estatisticamente significativa foi encontrada em escalas específicas caracterizadoras do sono antes do AVC.

Conclusão: O conhecimento da fisiopatologia dos AVCs do despertar, bem como a identificação dos possíveis fatores de risco poderá otimizar as estratégias de prevenção deste tipo de AVC. O nosso estudo reporta uma associação entre os AVCs do despertar e o perímetro cervical e a sonolência diurna, o que poderá indicar que algumas doenças do sono são subdiagnosticadas em doentes com este tipo de AVC.

Palavras-chave: AVC do despertar, Sono, Qualidade do Sono

Abstract

Wake-up stroke is a phenomenon that occurs when patients go to sleep without any symptom and awake with clinical manifestations of stroke. The physiopathology of this type of stroke is not completely understood but previous studies have reported a possible association between Wake-up stroke and sleep.

The main objective of this study is to assess the clinical characteristics of patients with wake-up stroke and compare them with those of patients with non-wake-up stroke, to evaluate possible connections between wake-up stroke and sleep.

Methods: A prospective observational study was conducted including every patient admitted in the Neurology department with the diagnosis of stoke. We excluded 221 patients as they presented hemorrhagic stroke, aphasia, were uncooperative or refused to participate in our study. A questionnaire was answered by 81 patients (43 men and 38 women). The clinical manifestations, complementary diagnostic exams performed, and instituted therapeutics were registered and analyzed.

Results: Within the 81 patients that constitute our sample, 15 (18.52%) of them correspond to Wake-up strokes. The mean age of the studied population was 73.7 ± 12.9 years old at the onset of symptoms. When comparing the two groups, NIHSS score was higher in Wake-up stroke (WUS) (9.73 ± 4.25 vs 6.65 ± 4.81, p=0.013) when compared to Non Wake-up stroke (NWUS) patients. Cervical perimeter was measured in all patients showing a mean (+SD) of 39.8 ± 3.64 cm. When comparing the two groups of our study, cervical perimeter was found to be higher in patients with WUS (43.6 ±2.44 vs 39.0 ± 3.32, p<0.001). There was also a statistically significant difference between patients with WUS and patients with NWUS regarding daytime sleepiness. (53.3% vs. 25.8%, p=0.037). No statistically significant difference was found regarding specific sleep characterization scores assessing pre-stroke condition.

Conclusion: Knowing the physiopathology of this type of stroke and possible risk factors may optimize prevention strategies. Our study found a significant association between WUS and cervical perimeter and daytime sleepiness, which may indicate that sleep disorders are underdiagnosed in patients with WUS.

Keywords: Stroke, Wake-Up Stroke, Non-Wake-Up Stroke, Sleep Quality

Introduction

The World Health Organization definition of stroke is: “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin, with motor, sensitive and cognitive consequences, according to the area and extent of the lesion“ (1) Annually, 15 million people worldwide suffer a stroke. Of these, 5 million die and another 5 million are left permanently disabled, placing a burden on family and community. The burden of stroke is greater in younger people and the incidence of stroke is increasing in this group(2), however, older people are still the most affected group by this disease as our study showed.

According to the national health authorities, stroke is the primary cause of death and incapacity in Portugal(3). It is caused by an acute decrease in cerebral blood flow, regularly by the blockage of a blood vessel (ischemic stroke) or by the rupture of it (hemorrhagic stroke).

The risk of stroke is affected by non-modifiable factors such as age and gender and modifiable factors such as hypertension, smoking, diabetes, dyslipidemia, atrial fibrillation and other cardiovascular diseases(4). In people who have experienced a previous episode of stroke, the risk of further episodes is significantly increased.

Diagnosis should be suspected by the clinical features of the patient through anamnesis and physical examination, which may demonstrate a focal neurological defect with an acute onset, that is then confirmed through neuroimaging with a Computerized Tomography (CT). After the diagnosis, evaluation and management of an acute stroke is fundamentally based on time from symptom onset, which makes it extremely important to know the exact time of symptom onset or the time when the patient was last seen normal is crucial.

Patients who go to sleep normal and awaken with stroke symptoms, a phenomenon known as “wake-up stroke” (WUS), present a management dilemma for acute stroke providers(5). Sometimes the period of sleep is short, and a patient can still be eligible for thrombolytic therapy based on standard time-based criteria; however, when the time at which the patient was last known to be normal is the night prior to a morning presentation, which is often the case, the time of symptom onset could be higher than the recommended time for safe thrombolytic intervention, which limits the available therapeutics (6).

Amongst all strokes, nearly 20% occur during sleep, and their pathophysiology is incompletely understood. What seems clear, though, is that wake-up strokes are not random events occurring in a day but likely the result of circadian changes in coagulability, serum catecholamine levels, and autonomic tone(7,8). The hemostatic system exhibits a circadian rhythm that is characterized by morning increase in platelet aggregation, coagulation factors, fibrinolytic activity, plasma viscosity, and morning endothelial dysfunction has also been reported(9,10). Much like cardiac events, there is a preponderance of strokes of all subtypes in the morning as compared to evening onset(11)

Some studies have pointed towards an association between WUS and sleep, however, existing literature on this matter is still scarce and there is no conclusion about this possible association. Previous studies have reported an association between Obstructive Sleep Apnea (OSA) and WUS(12–14), while others stated that this association only happens in men and not in women(15–17), as OSA tends to be more severe in men. On the other hand, there are also reports of no association between OSA and WUS(9,18). Finally, other studies have also pointed out that people that sleep more have also a higher risk of stroke(19).

That being the case, studying the possible association between these two concepts is highly important. The main objective of this study is to assess the clinical characteristics of patients with WUS and compare them with those of patients with NWUS to evaluate possible connections between WUS and sleep.

Methods

Study design

A prospective observational cohort study was conducted in the Neurology department including all patients with the diagnosis of stroke, who were willing to participate

Study inclusion, data collection and application of questionnaires were applied 3 to 10 days after stroke onset during the period between November 1st 2021 and February 28th 2022

Study population

The inclusion criteria of the study group were admittance to a Neurology ward due to acute stroke. We excluded patients with hemorrhagic stroke, impaired language function or patients in disagreement with the written consent

The algorithm for patient inclusion is presented in Fig.1

Data collection

In association with the referred questionnaire, which evaluated pre-stroke sleep characteristics including total sleep duration, sleep latency, night time awakenings, notion of repairing sleep, napping, nycturia, snoring, respiratory pauses during sleep, dyspneic awakenings, daytime sleepiness, xerostomia, morning headaches, concentration deficit, orthopnea and confusional awakenings, other scales such as STOP-BANG, Epworth Sleep Scale (ESS) and Insomnia Severity Index (ISI) were also calculated in all the patients. The STOP-BANG scale predicts the risk of having OSA (Intermediate risk=3-4; High risk=5-8), ESS evaluates daytime sleepiness (Mild sleepiness=11-14; Moderate sleepiness=15-17; Severe sleepiness=18-24), and Insomnia Severity Index (ISI), which indicates the existence of clinical insomnia (Moderate clinical insomnia=15-21; Severe clinical insomnia=22-28).

Demographic data such as age and sex as well as clinical data including alcoholic habits, smoking, comorbidities like high blood pressure (HBP), Diabetes Mellitus (DM), Atrial Fibrillation (AF) and hyperlipidemia and objective measures, namely cervical and abdominal perimeter, Body Mass Index (BMI), initial NIHSS initial, systolic and diastolic blood pressure (BP) and glycaemia were also registered, based on the patients' clinical file.
Imaging characteristics (ASPECTS in baseline CT and occluded vessel in baseline CT-angiography) were also collected, from the patients' medical file.

Statistical analysis

This study included 81 patients, 43 men and 38 women. From the studied population, the study group relative to WUS included 15 patients, 7 men and 8 women.
The data was stored in an anonymous database, and it was analyzed using the SPSS software.

Qualitative data was handled by means of observed absolute (n) and relative (%) frequencies, while quantitative data was presented either by its mean ± standard deviation or median and interquartile range, according to the observed distribution of the variables.

The statistical analysis was based on the following tests: t-student for quantitative variables, Mann-Whitney U for ordinal variables and Chi^2 for dichotomic variables. Logistic regression was used for multivariable analysis.

The study was submitted and approved by the local ethics committee (OBS.SF.181/2021)

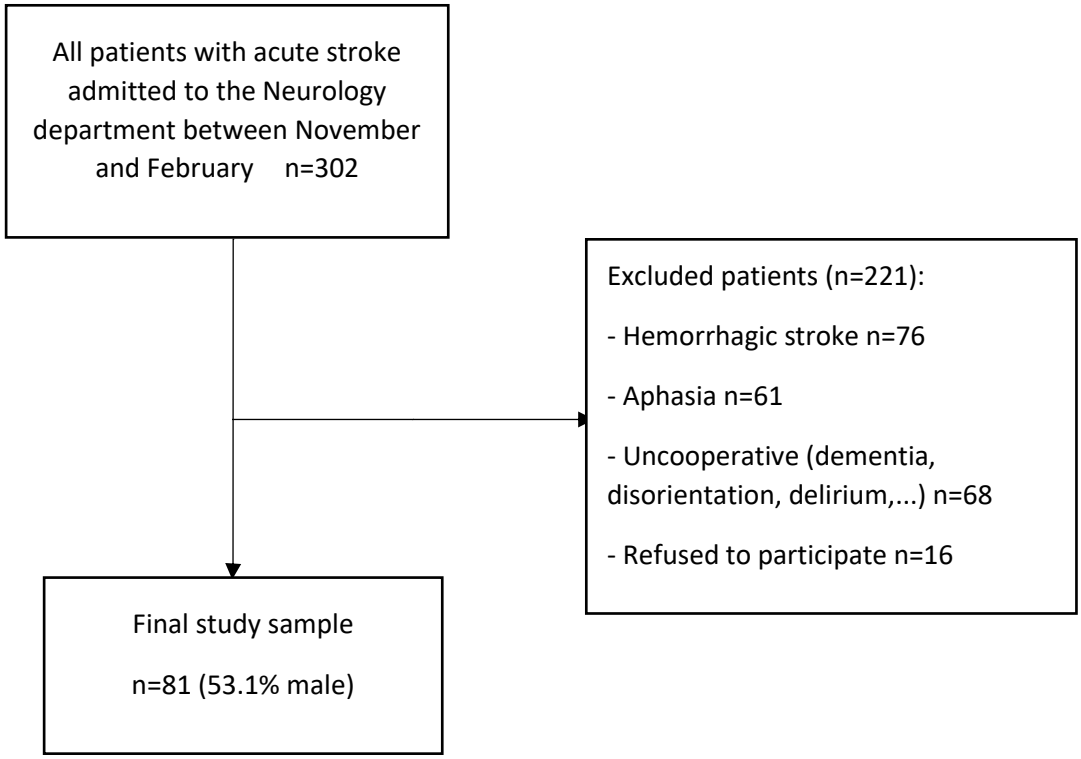

Fig. 1. Flow diagram of study participants

Results

In the studied period 302 patients were admitted with stroke. Of those, 221 were excluded and the remaining 81 are our study population.

In the period selected for the study, 81 patients with ischemic stroke were interviewed, of which, 43 were men and 38 were women. The mean (+SD) age of the studied population was 73.7 ± 12.9 years (range 31-91 years) at the onset of symptoms. Of those 81 patients, 15 (18.5%) suffered WUS.

The mean (+SD) NIHSS score in the studied population was 7.22 ± 4.84. When comparing the two groups, this variable was found to be statistically significant (p=0.008) as WUS patients demonstrated a higher NIHSS value (9.73 ± 4.25) when compared to NWUS patients (6.65 ± 4.81).

Abdominal and cervical perimeter was measured in all patients showing a mean (+SD) of 91.8 ± 11.07 cm and 39.8 ± 3.64 cm, respectively. When comparing the two groups of our study, cervical perimeter was found to be higher in patients with WUS (43.6 ±2.44) than patients with NWUS (39.0 ± 3.32) (Fig.2). Abdominal perimeter was not found to be statistically significant.

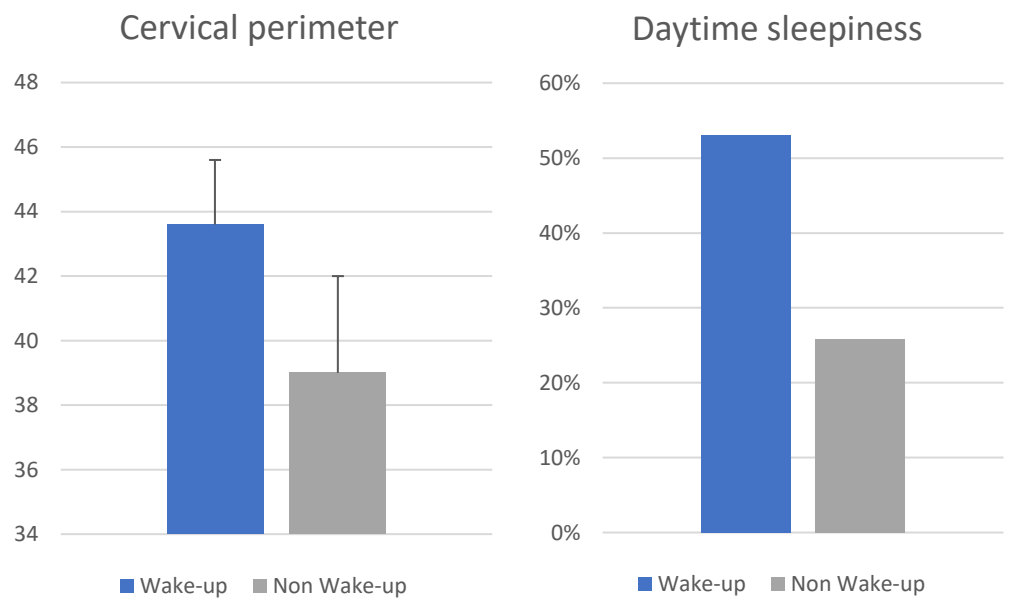

Fig. 2 Compared cervical perimeter and daytime sleepiness mean values (+SD) between WUS and NWUS.

Several clinical characteristics were also evaluated in the study group such as initial systolic blood pressure (SBP), initial diastolic blood pressure (DBP), initial glycemia, BMI, smoking, alcohol consumption, HBP, DM, AF, dyslipidemia, and Congestive Heart Failure (CHF).

A complete summary of demographic and clinical the studied population is reported in Table 1.

Table 1. Clinical and demographic characteristics of the studied population

	Total	Wake up	Non wake up	P Value
Men	43 (53.1%)	7 (46.7%)	36 (54.5%)	0.581
Age	73.7 (12.9)	77.8 (6.19)	72.8 (13.9)	0.019
OXFORDSHIRE				
TACS	16 (19.8%)	3 (20.0%)	13 (19.7%)	0.343
PACS	30 (37.0%)	8 (53.5%)	22 (33.3%)	
LACS	18 (22.2%)	1 (6.7%)	17 (25.8%)	
POCS	17 (21.0%)	3 (20.0%)	14 (21.2%)	
TOAST				
Atherosclerotic	2 (2.5%)	0 (0.0%)	2 (3.0%)	0.327
Cardioembolic	28 (34.6%)	8 (53.3%)	20 (30.0%)	
Small-vessel disease	15 (18.5%)	1 (6.7%)	14 (21.2%)	
Other causes (arteritis, arterial dissection,...)	4 (4.9%)	0 (0.0%)	4 (6.1%)	
Indetermined	32 (39.5%)	6 (40.0%)	32 (39.4%)	
Great-vessel disease	46 (56.8%)	11 (73.3%)	35 (53.0%)	0.152
ASPECTS		10 (2.5)	10 (2)	0.580
NIHSS	7.22 (4.84)	9.73 (4.25)	6.65 (4.81)	0.008
Acute phase therapeutic				
Fibrinolysis	7 (8.6%)	0 (0.0%)	7 (10.6%)	0.187
Thrombectomy	19 (23.5%)	5 (33.3%)	14 (21.2%)	0.317
Initial SBP	157.6 (26.99)	156.2 (31.79)	157.9 (25.98)	0.421
Initial DBP	84.3 (17.05)	86.1 (19.82)	83.9 (16.46)	0.341
initial glycaemia	139.3 (62.19)	148.3 (39.22)	137.0 (66.79)	0.266
Abdominal perimeter	91.8 (11.07)	95.8 (12.89)	90.9 (10.51)	0.06
Cervical perimeter	39.8 (3.64)	43.6 (2.44)	39.0 (3.32)	<0.001
Weight	71.0 (11.29)	70.1 (12.05)	71.1 (11.20)	0.377
Height	163.5 (8.07)	161.7 (7.51)	163.9 (8.19)	0.171
BMI	26.5 (4.08)	26.7 (4.02)	26.5 (4.13)	0.415
Smoking	26 (32.1%)	1 (6.7%)	25 (37.9%)	0.019
Alcohol consumption	50 (61.7%)	10 (66.7%)	40 (60.6%)	0.663
HBP	52 (64.2%)	13 (86.7%)	39 (59.1%)	0.044
DM	21 (25.9%)	6 (40.0%)	15 (22.7%)	0.168
AF	16 (19.8%)	6 (40.0%)	10 (15.2%)	0.029
Dyslipidemia	17 (21.3%)	3 (20.0%)	14 (21.5%)	0.896
CHF	7 (8.6%)	2 (13.3%)	5 (7.6%)	0.474

The total sleep duration of the studied population was evaluated and showed a mean (+SD) of 545 ± 104.4 minutes of sleep during the week and 560 ± 97.5 minutes in the weekend or vacations. Besides that, the latency of sleep, number of nighttime awakenings, notion of repairing sleep and naps were also a part of the patients' interview.

To evaluate the quality of sleep of the study population, nycturia, snoring, respiratory pauses during sleep, paroxysmal nocturnal dyspnea, daytime sleepiness, dry mouth, morning headaches, concentration deficit, orthopnea, vivid dreams and confusional awakenings were also determined.

After comparing the two groups of the study, there was a statistically significant difference between patients with WUS and patients with NWUS (53.3% versus 25.8%, p=0.037) regarding daytime sleepiness (Fig.2)

A complete summary of the characteristics of sleep and sleep disturbances of the studied population is described in Table 2.

Table 2. Characteristics of sleep in the studied population

	Total	Wake up	Non wake up	P Value
Total sleep time per day during the week, min	545 (104.4)	586 (140.2)	535 (93.4)	0.102
Total sleep time per day during weekend/vacations, min	560 (97.5)	588 (132.6)	554 (87.8)	0.179
Sleep latency	35.6 (32.0)	37.7 (38.2)	35.1 (30.7)	0.390
Night time awakenings	1.4 (1.2)	1.4 (1.4)	1.4 (1.2)	0.476
Notion of repairing sleep	54 (66.7%)	10 (66.7%)	44 (66.7%)	1.000
Napping	39 (48.1%)	6 (40.0%)	33 (50.0%)	0.484
Nap duration	75.8 (33.4)	65.0 (35.1)	77.7 (33.2)	0.199
Weekly frequency of napping	5.2 (2.2)	4.2 (2.4)	5.4 (2.1)	0.102
Nycturia	52 (64.2%)	10 (66.7%)	42 (63.6%)	0.825
Roncopathy	25 (30.9%)	2 (13.3%)	23 (34.8%)	0.103
Respiratory pauses during sleep	14 (17.3%)	1 (6.7%)	13 (19.7%)	0.228
Dispneic awakenings	11 (13.6%)	1 (6.7%)	10 (15.2%)	0.387
Daytime sleepiness	25 (30.9%)	8 (53.3%)	17 (25.8%)	0.037
Xerostomia	16 (19.8%)	4 (26.7%)	12 (18.2%)	0.456
Morning headaches	26 (32.1%)	6 (40.0%)	20 (30.3%)	0.468
Concentration deficit	4 (4.9%)	1 (6.7%)	3 (4.5%)	0.732
Orthopnea	7 (8.6%)	0 (0.0%)	7 (10.6%)	0.187
Confusional awakenings	9 (11.1%)	0 (0.0%)	9 (13.6%)	0.129
Vivid dreams	4 (4.9%)	0 (0.0%)	4 (6.1%)	0.328
Epworth Sleep Scale		3 (8)	5 (6)	0.521
STOP-BANG score		4 (1)	3 (2)	0.267
ISI score		4 (13)	2.5 (7.5)	0.774

In univariate analysis, age, NIHSS score, cervical perimeter, smoking, HBP, daytime sleepiness and AF were associated with WUS.

Table 3. Multivariable analysis of independent predictors of wake-up strokes.

	OR	95% CI	p Value
Age	1.006	0.93-1.09	0.886
NIHSS	1.060	0.87-1.29	0.557
Cervical perimeter	1.586	1.21-2.08	<0.001
Smoking	0.101	0.01-1.33	0.082
HBP	3.611	0.45-29.18	0.228
Daytime sleepiness	1.463	0.24-8.81	0.678
AF	2.478	0.37-16.49	0.348

In the multivariable analysis table, we included age, NIHSS score, cervical perimeter, smoking, HBP, daytime sleepiness and AF. After adjustment, the only variable that remained statistically significant was cervical perimeter (table 3).

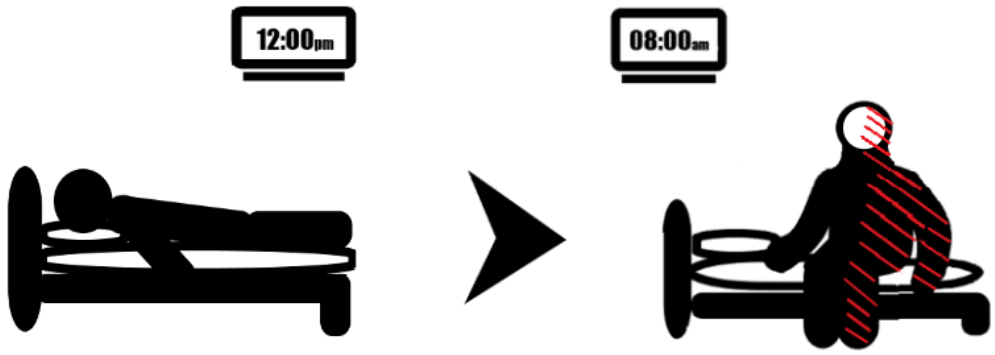

Fig. 3 Illustrative representation of the association between WUS and cervical perimeter

Discussion

The main finding of our study is that patients with WUS are likely to have a higher cervical perimeter and more prestrike daytime sleepiness when compared to patients with NWUS.

As higher cervical perimeter and daytime sleepiness may be clinical signs of sleep-disordered breathing and poor sleep quality, this finding leads us to believe that there might be an underdiagnosis of sleep-disordered breathing diseases such as OSA in patients with WUS.

Both WUS and NWUS score similarly on the STOP-BANG scale, which translates in both groups having similar intermediate likelihood of developing a sleep-disorder breathing. This scale does not predict however the severity of the disorder. Our data suggests that a higher cervical perimeter may be an indicator of more severe apnea-hypopnea index associated with a higher oxygen desaturation index, resulting in a higher prevalence of WUS.

Previous studies have found that the respiratory arrests during sleep are a potential factor for fluctuations in coagulation cascades, hemodynamic responses, blood pressure and in cerebral blood flow leading to chronic inflammation, thus increasing the incidence of stroke(20,21). Besides that, poor sleep quality has been associated with stroke(22). During Non-Rapid-eye movement (NREM) sleep, breathing rate is regular with sparce cases of apnea, and BP and heart rate are declined. On the other hand, during Rapid-eye movement (REM) sleep, the amount of apnea and hypopnea episodes is higher and there are hypertensive spikes in BP. This suggests that, in patients with poor sleep quality or with sleep disorders, there is a higher risk of variations of BP that may be associated with peaks during sleep time(23), and also greater frequency of disturbances of intrathoracic pressure, cardiac arrhythmias and endothelial dysfunction(24).

Since REM sleep occurs predominantly in the last third of the night and it is associated with bursts of sympathetic activity with variations in BP and heart rate, there is a higher risk of vascular events before awakening as compared to the first part of the night (5). This goes in line with our finding that suggests that poor sleep quality may be associated with WUS.

Other studies also found that, when compared to NWUS, WUS patients had higher values of apnea-hypopnea index, desaturation index and diastolic BP(25). At the same time, in response to apnea, cortical arousal occurs repeatedly, producing sympathetic nervous hyperstimulation. These repetitive physiologic stressors create an environment that can trigger WUS, which can justify the association between WUS and sleep disorders like OSA.

In this study, WUS accounted for 18.5% of 81 cases of all ischemic stroke. The overall prevalence of WUS is consistent with previous studies. Comparing with stroke occurring during wakefulness, WUS was associated with older age and higher NIHSS score.

As other studies have reported(24,26), WUS appears to be more severe than NWUS, which was also a finding of our study, since the NIHSS score was significantly higher in WUS patients.

The age of the patients was showed to be statistically different between the two groups as patients with WUS (77.8±6.19) were associated with older age when compared with NWUS patients (72.8±13.9).

There was also no significant difference between ASPECTS from the WUS group and the NWUS, which has been described in previous studies and may indicate that the ischemic changes are similar between the two groups. Roveri et al. compared early ischemic changes on CT between WUS and NWUS patients and stated that overall, there was no significant difference in early CT

changes between wake-up stroke and stroke of known onset within 3 hours(27). Another study also reported no difference after 6h(28).

Otherwise, demographic and clinical findings such as sex, BMI, height, DM, hyperlipidemia and CHF did not differ between the two groups.

Patients with WUS, compared to those with NWUS also presented with higher prevalence of HBP and AF. The finding that WUS is associated with AF is consistent with previous studies which state that the odds of detecting a newly diagnosed AF were 3-fold higher among WUS than among NWUS(29). The association between AF and WUS may be related to the circadian variation of AF that is reported to most frequently occur in the morning hours. For instance, in a large cohort of 3343 patients with new-onset AF, the distribution of paroxysmal AF onset showed a double peak, with a significant increase in the number of episodes in the morning and (to a lesser degree) a second rise in the evening(30)

The association between HBP and WUS is also in line with previous studies and, according to several cross-sectional and longitudinal studies, an increasing body of evidence indicates that nocturnal-dipping status(31) which may happen in patients with hypertension, might lead to arterial wall disorganization and plaque rupture, and it could be associated with the occurrence of WUS. It has been shown that the use of antihypertensive medications may be associated with an exaggerated nocturnal blood pressure dip and, in turn, with the development of ischemic lesions during the night, especially in the territory of stenotic arteries(32) and also due to a reduction in collateral irrigation, as patients with obstructed arteries highly depend on collateral circulation to have an adequate cerebral blood flow, and with these BP decreases, the flow of collateral arteries significantly decreases facilitating the occurrence of these ischemic episodes.

Our study did not find any statistically significant difference regarding the scores of the ESS, STOP-BANG and ISI scales when comparing the two groups. This may be explained by the subjectiveness of these questionnaires and the small sample of our study.

This study had several limitations. First, the sample size was small. The presence of OSA was identified using questionnaires, without a polysomnography assessment, which may underestimate the amount of OSA cases. Besides that, our study excluded stroke patients with severe symptoms who were not able to participate. This exclusion criteria resulted in lower mean NIHSS scores. Finally, the evaluation of sleep characteristics is relative to prestrike period, which may be biased by the patients' memory. Despite these limitations, our study will add to current knowledge of WUS. For future studies we suggest that sleep quality should be better characterized with video-polysomnography, since the great majority of studies used subjective data.

Conclusion

Our study found a significant association between WUS and cervical perimeter and daytime sleepiness, which may indicate that sleep disorders mainly sleep breathing disorders are underdiagnosed in patients with WUS. Knowing the physiopathology of wake-up strokes and possible risk factors is important to improve the prevention strategies as well as the management of these patients, since the difficulty of establishing a specific time of stroke onset limits the available therapeutics for this disease.

Since this is a single-center study, it is of great importance to explore these conclusions in larger populations, using video-polysomnography to better characterize sleep quality. More studies are needed in this field to better understand the relationship between WUS and sleep disorders.

Attachments

Attachment 1 – STOP-BANG Sleep Apnea Questionnaire

OHIO SLEEP MEDICINE INSTITUTE
CENTER OF SLEEP MEDICINE EXCELLENCE™
Main Office | 4975 Bradenton Avenue, Dublin Ohio 43017 | T 614.766.0773 | F 614.766.2599
Branch Office | 7277 Smith's Mill Rd., New Albany 43054 | T 614.775.6177 | F 614.775.6178

Name _____
Height _____ Weight _____
Age _____ Male / Female _____

STOP-BANG Sleep Apnea Questionnaire

Chung F et al Anesthesiology 2008 and BJA 2012

STOP		
Do you SNORE loudly (louder than talking or loud enough to be heard through closed doors)?	Yes	No
Do you often feel TIRED, fatigued, or sleepy during daytime?	Yes	No
Has anyone OBSERVED you stop breathing during your sleep?	Yes	No
Do you have or are you being treated for high blood PRESSURE?	Yes	No

BANG		
BMI more than 35kg/m2?	Yes	No
AGE over 50 years old?	Yes	No
NECK circumference > 16 inches (40cm)?	Yes	No
GENDER: Male?	Yes	No

TOTAL SCORE		

High risk of OSA: Yes 5 - 8

Intermediate risk of OSA: Yes 3 - 4

Low risk of OSA: Yes 0 - 2

sleep wake

Attachment 2 – Epworth Sleep Scale

Epworth Sleepiness Scale

Name: _____ Today's date: _____

Your age (Yrs): _____ Your sex (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = would **never** doze
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each question as best you can.

Situation	**Chance of Dozing (0-3)**
Sitting and reading	
Watching TV	
Sitting, inactive in a public place (e.g. a theatre or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in the traffic	

THANK YOU FOR YOUR COOPERATION

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Insomnia Severity Index

The Insomnia Severity Index has seven questions. The seven answers are added up to get a total score. When you have your total score, look at the 'Guidelines for Scoring/Interpretation' below to see where your sleep difficulty fits.

For each question, please CIRCLE the number that best describes your answer.

Please rate the CURRENT (i.e. LAST 2 WEEKS) SEVERITY of your insomnia problem(s).

Insomnia Problem	None	Mild	Moderate	Severe	Very Severe
1. Difficulty falling asleep	0	1	2	3	4
2. Difficulty staying asleep	0	1	2	3	4
3. Problems waking up too early	0	1	2	3	4

4. How SATISFIED/DISSATISFIED are you with your CURRENT sleep pattern?

Very Satisfied	Satisfied	Moderately Satisfied	Dissatisfied	Very Dissatisfied
0	1	2	3	4

5. How NOTICEABLE to others do you think your sleep problem is in terms of impairing the quality of your life?

Not at all Noticeable	A Little	Somewhat	Much	Very Much Noticeable
0	1	2	3	4

6. How WORRIED/DISTRESSED are you about your current sleep problem?

Not at all Worried	A Little	Somewhat	Much	Very Much Worried
0	1	2	3	4

7. To what extent do you consider your sleep problem to INTERFERE with your daily functioning (e.g. daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood, etc.) CURRENTLY?

Not at all Interfering	A Little	Somewhat	Much	Very Much Interfering
0	1	2	3	4

Guidelines for Scoring/Interpretation:

Add the scores for all seven items (questions 1 + 2 + 3 + 4 + 5 +6 + 7) = _____ your total score

Total score categories:
0–7 = No clinically significant insomnia
8–14 = Subthreshold insomnia
15–21 = Clinical insomnia (moderate severity)
22–28 = Clinical insomnia (severe)

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Attachment 4 – Sleep Questionnaire applied to the study sample

INQUÉRITO

PROJETO: POSSÍVEIS FATORES DA QUALIDADE DO SONO PREDITORES DE ACIDENTES VASCULARES CEREBRAIS DURANTE O SONO

O acidente vascular cerebral (AVC) é atualmente uma das principais causas de morte e de incapacidade funcional em Portugal. Deste grupo fazem parte os AVC detetados imediatamente após o despertar (*Wake-up strokes*), que representam cerca de 20% dos AVC isquémicos. A investigação nesta área é promissora, desconhecendo-se a total relação entre os fatores implicados na qualidade do sono que poderão estar envolvidos numa maior incidência de AVCs que ocorrem durante o sono comparativamente aos que ocorrem em tempo de vigília. Dada a relevância na prevenção da morbilidade e mortalidade associada ao AVC, pretende-se com este estudo determinar possíveis fatores da qualidade do sono preditores de AVCs durante o sono.

É voluntário (é livre de aceitar ou recusar o preenchimento, sem qualquer penalidade ou perda de benefícios e sem comprometer a sua relação com o investigador) e anónimo (a sua identidade não é registada ou publicada).

A preencher pelo médico:

Género: [ ] Feminino [ ] Masculino

Data de nascimento: __ / __ / _____;

Classificação AVC OXFORDSHIRE _____;

Classificação AVC TOAST _____;

Vaso Ocluído _____; **ASPECTS** _____; **NIHSS inicial** _____;

Fibrinólise: [ ] Sim [ ] Não; **Trombectomia:** [ ] Sim [ ] Não; **TICI final** _____;

TA inicial _____; **Glicémia inicial** _____;

Perímetro abdominal _____; **Perímetro cervical** _____; **IMC** _____;

A preencher pelo doente (ou familiar):

Hábitos Tabágicos: _____;

Hábitos Etílicos: _____;

Comorbilidades (HTA, DM, FA, ICC, outro): _____;

Avaliação geral da Qualidade do Sono

Tempo total de sono (min) durante semana: _____;

Tempo total de sono (min) nos fim-de-semanas / férias: _____;

Latência do sono (min): _____;

Número aproximado de acordares noturnos: _____;

Noção de sono reparador: [ ] Sim [ ] Não;

Necessidade de sestas: [ ] Sim [ ] Não, **Se sim, qual a duração (min)** _____ e **frequência (Nº/Semana)** _____;

Avaliação distúrbio respiratório durante o Sono

Nictúria: [ ] Sim [ ] Não;

Roncopatia: [ ] Sim [ ] Não;

Pausas respiratórias detetadas pelo companheiro: [ ] Sim [ ] Não;

Acordares com sensação sufoco: [ ] Sim [ ] Não;

Xerostomia: [ ] Sim [ ] Não;

Cefaleias matinais: [ ] Sim [ ] Não;

Redução capacidade de concentração: [ ] Sim [ ] Não;

Existe dificuldade respiratória em decúbito: [ ] Sim [ ] Não;

Avaliação de possível Síndrome de Pernas Inquietas

Sensação de impaciência com necessidade de mexer os membros inferiores ao deitar: [ ] Sim [ ] Não;

Se sim,

Fatores precipitantes (ex. posição sentada, deitado, lugar de passageiro de viatura): _____;

Fatores de alívio (ex. frio, caminhar): _____;

Frequência semanal: _____;

Duração da sensação (min): _____;

Sensação atinge os membros superiores: [ ] Sim [ ] Não;

Sensação existe no período acordado: [ ] Sim [ ] Não;

Existe história familiar de SPI: [ ] Sim [ ] Não;

Avaliação de possível Parassónia NREM

Existem episódios de acordares confusionais / sonambulismo / terrores nocturnos / sonilóquios: [ ] Sim [ ] Não;

Se sim, qual a frequência semanal: _____;

Avaliação de possível Parassónia REM

Existem episódios de sonhos agitados com conteúdo agressivo: [ ] Sim [ ] Não;

Existe risco de auto ou heteroagressão durante os sonhos agitados: [ ] Sim [ ] Não;

Se sim, qual a frequência semanal: _____;

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Pedro Afonso da Fonseca Barra Oliveira Simões

References

1. The World Health Organization MONICA Project (monitoring trends and determinants in cardiovascular disease): a major international collaboration. WHO MONICA Project Principal Investigators. J Clin Epidemiol. 1988;41(2):105–14.

2. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. Vol. 383, Lancet. 2014.

3. Afonso AD. Programa Nacional para as Doenças Cérebro-Cardiovasculares 2017 Lisboa: Direção-Geral da Saúde. 2017; Available from: www.dgs.pt

4. Bassetti CLA, Randerath W, Vignatelli L, Ferini-Strambi L, Brill AK, Bonsignore MR, et al. EAN/ERS/ESO/ESRS statement on the impact of sleep disorders on risk and outcome of stroke. European Journal of Neurology. 2020 Jul 1;27(7):1117–36.

5. Peter-Derex L, Derex L. Wake-up stroke: From pathophysiology to management. Vol. 48, Sleep Medicine Reviews. W.B. Saunders Ltd; 2019.

6. Huisa BN, Liebeskind DS, Raman R, Hao Q, Meyer BC, Meyer DM, et al. DWI-FLAIR Mismatch in Nocturnal Strokes Patients with Unknown Time of Onset On behalf of the UCLA Stroke Investigators 3. 2012;

7. Hsieh SW, Lai CL, Liu CK, Hsieh CF, Hsu CY. Obstructive sleep apnea linked to wake-up strokes. Journal of Neurology. 2012 Jul;259(7):1433–9.

8. Rubin MN, Barrett KM. What to do With Wake-Up Stroke. Vol. 5, The Neurohospitalist. 2015. p. 161–72.

9. Barreto PR, Diniz DL de O, Lopes JP, Barroso MC, Daniele TM da C, de Bruin PFC, et al. Obstructive Sleep Apnea and Wake-up Stroke – A 12 Months Prospective Longitudinal Study. Journal of Stroke and Cerebrovascular Diseases. 2020 May 1;29(5).

10. Hepburn M, Bollu PC, French B, Sahota P. Sleep Medicine: Stroke and Sleep. Mo Med. 115(6):527–32.

11. Elliott WJ. Circadian Variation in the Timing of Stroke Onset A Meta-analysis [Internet]. 1998. Available from: http://ahajournals.org

12. Mohammad Y, Almutlaq A, Al-Ruwaita A, Aldrees A, Alsubaie A, Al-Hussain F. Stroke during sleep and obstructive sleep apnea: there is a link. Neurological Sciences. 2019 May 1;40(5):1001–5.

13. Baillieul S, Dekkers M, Brill A-K, Schmidt MH, Detante O, Pépin J-L, et al. Sleep apnoea and ischaemic stroke: current knowledge and future directions. Lancet Neurol. 2022;21(1):78–88.

14. Haula TM, Puustinen J, Takala M, Holm A. Wake-up strokes are linked to obstructive sleep apnea and worse early functional outcome. Brain and Behavior. 2021 Aug 1;11(8).

15. Brown DL, Li C, Chervin RD, Case E, Garcia NM, Tower SD, et al. Wake-up stroke is not associated with sleep-disordered breathing in women. Neurology: Clinical Practice. 2018 Feb 1;8(1):8–14.

16. Koo BB, Bravata DM, Tobias LA, Mackey JS, Miech EJ, Matthias MS, et al. Observational study of obstructive sleep apnea in wake-up stroke: The SLEEP TIGHT study. Cerebrovascular Diseases. 2016 Apr 1;41(5–6):233–41.

17. Park J, Yeo M, Kim J, Kim S, Lee S-H, Kwon S, et al. Sleep-disordered breathing and wake-up stroke: a differential association depending on etiologic subtypes. Sleep Med. 2020;76:43–7.

18. Schütz SG, Lisabeth LD, Gibbs R, Shi X, Case E, Chervin RD, et al. Wake-up stroke is not associated with obstructive sleep apnea. Sleep Med. 2021;81:158–62.

19. Zhou L, Yu K, Yang L, Wang H, Xiao Y, Qiu G, et al. Sleep duration, midday napping, and sleep quality and incident stroke: The Dongfeng-Tongji cohort. Neurology. 2020 Jan 28;94(4):e345–56.

20. Hermann DM, Bassetti CL. Sleep-disordered breathing and stroke. Curr Opin Neurol. 2003 Feb;16(1):87–90.

21. Park J, Yeo M, Kim J, Kim S, Lee S-H, Kwon S, et al. Sleep-disordered breathing and wake-up stroke: a differential association depending on etiologic subtypes. Sleep Med. 2020;76:43–7.

22. Li J, Yin J, Luo Y, Ma T, He L, Xie H, et al. Association of healthy sleep pattern with the risk of cardiovascular disease and all-cause mortality among people with diabetes: A prospective cohort study. Diabetes Research and Clinical Practice [Internet]. 2022 Apr;186:109822. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0168822722006349

23. Portaluppi F, Tiseo R, Smolensky MH, Hermida RC, Ayala DE, Fabbian F. Circadian rhythms and cardiovascular health. Vol. 16, Sleep Medicine Reviews. 2012. p. 151–66.

24. Jiménez-Conde J, Ois A, Rodríguez-Campello A, Gomis M, Roquer J. Does sleep protect against ischemic stroke? Less frequent ischemic strokes but more severe ones. Journal of Neurology. 2007 Jun;254(6):782–8.

25. Šiarnik P, Kollár B, Čarnická Z, Šurda P, Klobučníková K, Sýkora M, et al. Association of sleep disordered breathing with wake-up acute ischemic stroke: A full polysomnographic study. Journal of Clinical Sleep Medicine. 2016;12(4):549–54.

26. Kim BJ, Lee SH, Shin CW, Ryu WS, Kim CK, Yoon BW. Ischemic stroke during sleep: Its association with worse early functional outcome. Stroke. 2011 Jul;42(7):1901–6.

27. Roveri L, la Gioia S, Ghidinelli C, Anzalone N, de Filippis C, Comi G. Wake-up stroke within 3 hours of symptom awareness: imaging and clinical features compared to standard recombinant tissue plasminogen activator treated stroke. J Stroke Cerebrovasc Dis. 2013 Aug;22(6):703–8.

28. Huisa BN, Raman R, Ernstrom K, Tafreshi G, Stemer A, Meyer BC, et al. Alberta stroke program early CT score (ASPECTS) in patients with wake-up stroke. Journal of Stroke and Cerebrovascular Diseases. 2010 Nov;19(6):475–9.

29. Riccio PM, Klein FR, Pagani Cassará F, Muñoz Giacomelli F, González Toledo ME, Racosta JM, et al. Newly diagnosed atrial fibrillation linked to wake-up stroke and TIA: hypothetical implications. Neurology. 2013 May 14;80(20):1834–40.

30. Viskin S, Golovner M, Malov N, Fish R, Alroy I, Vila Y, et al. Article No. euhj [Internet]. Vol. 20, European Heart Journal. 1999. Available from: http://www.idealibrary.comon

31. Kario K, Pickering TG, Matsuo T, Hoshide S, Schwartz JE, Shimada K. Stroke Prognosis and Abnormal Nocturnal Blood Pressure Falls in Older Hypertensives [Internet]. 2001. Available from: http://www.hypertensionaha.org

32. Nakamura K, Oita J, Yamaguchi T. Nocturnal blood pressure dip in stroke survivors. A pilot study. Stroke. 1995 Aug;26(8):1373–8.