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ORIGINAL ARTICLE

Stroke during sleep and obstructive sleep apnea: there is a link

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Abstract

Objectives The onset of ischemic stroke symptoms has been established to have a diurnal variation, with a sizeable proportion (8–28%) occurring during sleep. Obstructive sleep apnea (OSA) has been established as an important risk factor for ischemic stroke. However, data on the relationship between OSA and wake-up stroke (WUS) has been scarce. The aim of our study is to determine the relationship between OSA and WUS.

Methods This is a case-control study conducted on acute stroke patients who presented to one of two major medical centers in Riyadh of Saudi Arabia. Those who woke up with the symptoms were labeled as WUS, and those whose stroke occurred while awake were labeled as non wake-up stroke (NWUS). The Berlin Questionnaire, which was submitted to either the patient or his/her partner, was used to determine the frequency of OSA in the two groups.

Results One hundred seven patients (60% males) with acute stroke were admitted between March 2016 and March 2017. Of the 40 patients with WUS, 29 (72.5%) had underlying OSA based on the Berlin Questionnaire, whereas only 30 (45%) of the 67 patients with NWUS have underlying OSA. Logistic regression analysis showed OSA is highly prevalent in the patients with WUS (OR = 3.25; 95% CI = 1.397–8.38; $p = 0.0053$).

Conclusion OSA is an important risk factor for ischemic stroke during sleep. Health care providers must be vigilant in inquiring about symptoms suggestive of OSA in every ischemic stroke patient, especially the patient whose stroke occurred during sleep.

Keywords Stroke · Wake-up · Obstructive sleep apnea · Berlin Questionnaire

Introduction

Worldwide, stroke remains as the leading cause of long term disability and among the three leading causes of death in adults [1, 2]. In the last two decades, intravenous tPA and mechanical thrombolysis have been proven effective for acute ischemic stroke [3–5]. However, these treatments must be administered within a few hours from the symptoms onset, rendering the majority of acute ischemic strokes ineligible for such treatments. Thus, stroke prevention, mainly through control of risk factors, remains the foremost effort exerted by the health care workforce.

Obstructive sleep apnea (OSA), which is highly prevalent in the adult population [6], has been established as an important risk factor for ischemic stroke, increasing the risk of stroke by up to threefolds [7–9]. Increased levels of inflammatory biomarkers and higher diastolic blood pressure and serum triglycerides have been demonstrated in patients with OSA [10, 11] and thus postulated as the possible mechanism through which OSA induce ischemic stroke.

The onset of ischemic stroke symptoms has been established to have a diurnal variation, with a sizeable proportion (8–28%) occurring during sleep [12–15]. Yet it is uncertain how sleep induces ischemic stroke. It is also unclear whether OSA is the mechanism through which sleep induces

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ischemic stroke. Hence, we conducted this study to determine whether the main hazard of OSA for ischemic stroke is mainly during sleep.

Methods

Subjects

This is an observational case-control study. Patients who were admitted with acute ischemic stroke, between March 2016 and March 2017, to King Khalid University Hospital (KKUH) or King Fahd Medical City of Riyadh, were recruited to the study. All patients had a brain MRI during hospitalization to confirm the occurrence of acute ischemic stroke. To determine the timing of the stroke onset and its relationship with sleep, the patient or their family member (if the patient is made incapable by the stroke) was asked whether he/she woke up with stroke symptoms. If the patient woke up with stroke symptoms, the stroke was considered to occur during sleep and was labeled as wake-up stroke (WUS). On the other hand, the stroke was labeled as non wake-up stroke (NWUS) if the patient experienced the stroke symptoms while awake. Additionally, the stroke was considered NWUS if the symptoms commenced shortly after bed rise.

Data related to demographic and clinical characteristics, such as age, gender, body mass index (BMI), stroke, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, and tobacco smoking, were collected from the patients' medical records. The study was approved by the Institutional Review Board of King Khalid University Hospital (KKUH) and King Fahd Medical City (KFMC) (KKUH-12/3610/IRB, KFMC-IRB00008644). Additionally, informed consents were taken from the patients themselves or their proxy when patients are not competent.

Identifying OSA: the Berlin Questionnaire

The Berlin Questionnaire [16] has been validated as a sensitive tool to identify individuals at higher risk of having OSA. Also, it has been regularly utilized in clinical research and medical practice as a simple and useful tool for diagnosing patients with OSA [17–20].

We employed the Berlin Questionnaire in our study to assess whether each stroke subject is low or high risk for developing OSA. The Berlin Questionnaire consists of 11 questions grouped in three categories. The first category comprises 5 questions concerning snoring, witnessed apneas, and the frequency of such events. The second category comprises 4 questions addressing daytime sleepiness, with a sub-question about drowsy driving. The third category comprises 2 questions concerning history of high blood pressure (> 140/90 mmHg) and BMI of > 30 kg/m2. Category 1 and 2 were considered positive if there were ≥ 2 positive responses to each category, while category 3 was considered positive with a self-report of high blood pressure and/or a BMI of > 30 kg/m2. Study subjects were considered as being at "high risk" of having OSA if scores were positive for two or more of the three categories. Those patients who scored positively on less than two categories were considered as being at "low risk" of having OSA.

Statistical analysis

Analyses were conducted using statistical software (Stata 12; College Station, Texas). A probability of α error of less than 5% was considered significant for all analyses. Mean and standard deviation were calculated for continuous variables, and Chi-square test was used to compare proportions across categorical variables. Odds ratios were calculated using logistic regression to simultaneously adjust for multiple variables confounding. Cases and controls as binary outcome were defined as WUS or NWUS, while exposure was defined as high-risk OSA.

Results

Demographic characteristics

This sample size was 107 (40 cases and 67 controls). The demographic characteristics of these patients are found in Table 1. Mean age was 63.4 ± 14.4 years with 20% of the sample above age 60. Most of the reviewed cases were males (60%). The mean BMI was 28.7 with a SD of 5.3. Fifty-one percent of the sample was classified as obese (≥ 30.0 BMI). No more that 16% of patients were smokers. None of the characteristics of the sample varied significantly among WUS and NWUS.

Clinical characteristics

Table 2 describes the distribution of clinical characteristics. The median NIHSS was 10 and 11 in the WUS and NWUS respectively. We had a mostly diabetic and hypertensive sample (66.4% and 64.4 respectively). Almost half had dyslipidemia (48.6%) and one-fourth (23%) had a previous stroke that was mostly of the ischemic nature (95.7%).

Most of the clinical characteristics did not show any significant differences across the two groups. The only variable that varied significantly was having a high-risk vs. low-risk OSA (Chi-sq = 7.8; $p = 0.005$).

Table 1 Demographic characteristics of WUS ($N = 40$) and NWUS ($N = 67$) populations (total $N = 107$)

Characteristics	WUS *N* (%)	NWUS *N* (%)	Total *N* (%)	Chi-sq. (*p* value)
Gender				2.07 (0.15)
Males	26 (65)	34 (50.7)	60 (56.1)	
Females	14 (35)	33 (49.3)	47 (43.9)	
Age, years				1.29 (0.73)
≤45	3 (7.5)	6 (8.9)	9 (8.41)	
46–60	17 (42.5)	22 (32.8)	39 (36.4)	
61–75	13 (32.5)	28 (41.8)	41 (38.3)	
≥76	7 (17.5)	11 (16.4)	18 (16.8)	
Body mass index				1.70 (0.64)
< 18.5 (underweight)	1 (2.5)	0 (0)	1 (0.93)	
18.5–24.9 (normal)	9 (22.5)	16 (23.9)	25 (23.4)	
25.0–29.9 (overweight)	11 (27.5)	19 (28.4)	30 (28.0)	
≥30.0 (obese)	19 (47.5)	32 (47.8)	51 (47.7)	
Smoking status				1.28 (0.7)
Non-smokers	33 (82.5)	56 (83.6)	89 (83.2)	
Smokers	7 (17.5)	10 (14.9)	17 (16.0)	

Risk of WUS in relation to obstructive sleep apnea

Results of this case-control analysis indicate that those who have OSA (high risk) are 3.25 times more often to wake up with stroke than those who do not have OSA (low risk). This relation is described in Table 3.

Discussion

Our study showed a high prevalence of OSA among stroke victims (55%), which is consistent with the abundant data in the literature [8, 9]. More importantly, it demonstrated the prevalence to be clustered in the WUS stroke population (OR 3.25) which is indicative that the main hazard of OSA for ischemic stroke is mainly during sleep. Numerous reports have examined the stroke mechanism commonly implicated in patients with OSA. Cardiac emboli have been repeatedly shown to be a common source of stroke in the patients with underlying OSA. In fact, two cardiac lesions have been identified as the culprit for this increase in cardiac source of emboli in this patient population. One is through atrial fibrillation which has already been established as the most common cardiac source of stroke. Cardiac emboli, from atrial fibrillation,

Table 2 Distribution of clinical characteristics among the sample ($N = 107$)

Characteristics	WUS *N* (%)	NWUS *N* (%)	Total *N* (%)	Chi-sq. (*p* value)
Diabetes mellitus	27 (67.5)	44 (65.7)	71 (66.4)	0.037 (0.85)
Hypertension	30 (74.7)	39 (57.5)	69 (64.4)	3.39 (0.065)
Atrial fibrillation	2 (5)	7 (10.4)	9 (8.4)	0.97 (0.33)
Dyslipidemia	16 (4)	36 (53.7)	52 (48.6)	1.89 (0.17)
Obstructive sleep apnea				7.78 (0.005)
Low grade	11 (27.5)	37 (55.2)	48 (44.9)	
High grade	29 (72.5)	30 (44.8)	59 (55.1)	
Previous stroke				0.67 (0.41)
Ischemic	9 (22.5)	13 (19.4)	22 (95.7)	
Hemorrhagic	0 (0)	1 (1.5)	1 (4.3)	
Antiplatelet medication				0.45 (0.5)
Yes	20 (50)	38 (56.7)	58 (54.2)	
No	20 (50)	29 (43.3)	49 (45.8)	

Table 3 The Risk of wake-up stroke examined in relation to obstructive sleep apnea (OSA)

	OSA (high grade)	No OSA (low grade)	Total
WUS	29	11	40
NWUS	30	37	67
Total	59	48	107

have been consistently demonstrated as a frequent source of stroke in the patients with underlying OSA [21]. Patent foramen ovale, through paradoxical emboli, is another common mechanism for cardio-embolic stroke during sleep. Patent foremen ovale is quite prevalent in the general population. However, when it occurs with OSA, it significantly increases the risk of cardiac emboli in the patients whose stroke occurs during sleep [22, 23].

Another probable mechanism for stroke during sleep is small artery disease. It has been asserted as the most common, none cardiac, cause of stroke in OSA. The increased frequency of small artery disease, in this patient population, has been attributed to the endothelial injury induced by both OSA, independently, and hypertension which is highly associated with OSA [24].

The results of our study are consistent with the few published data related to the association between OSA and WUS. For instance, both Siarnik et al. and Hsieh et al. [11, 25] showed a significantly higher prevalence of OSA in the WUS compared with the NWUS population. While Koo et al. [26] found no difference in the prevalence of OSA between the WUS and NWUS groups. However, when gender-stratified analysis was performed, a significantly higher prevalence of OSA was revealed in the WUS of only the male population.

All of the above-mentioned studies utilized the polysomnography procedure, which is considered the gold standard, to identify OSA. Our study is unique in utilizing, instead, the Berlin Questionnaire to detect OSA. This is the main limitation of our study. Nevertheless, there is ample data to suggest that the Berlin Questionnaire is a valid tool that reliably identifies OSA. For example, Netzer et al. [17] showed a high sensitivity and specificity of the Berlin Questionnaire in successfully identifying OSA when compared with polysomnography, 86% and 77% respectively. More importantly, in a study conducted by Saleh et al. [27] to assess the validity and reliability of the Arabic version of the Berlin Questionnaire in identifying OSA, the sensitivity and specificity of the Berlin Questionnaire when compared with polysomnography reached 97% and 90% respectively. The results of our study were similar to the published reports that addressed the same question, but utilized polysomnography instead. This makes our study novel in demonstrating that employing the Berlin Questionnaire that can be completed within few minutes, rather than polysomnography which is expensive, long, and sometimes inconvenient, is sufficient enough to ascertain OSA in the patients whose stroke occurred during sleep.

In summary, our study has verified that OSA is an important risk factor for ischemic stroke in general and for WUS in particular. OSA is treatable through weight loss, sleep hygiene, and C-PAP machine applied during sleep. Unfortunately, OSA remains considerably under diagnosed and undertreated [28]. Yet a simple questionnaire (Berlin Questionnaire) can reliably identify subjects at high risk of having OSA. Hence, extra measures must be exercised to educate both the public and the health care providers on the hazards, symptoms, and risk factors of OSA. More essential, however, is for the health care professionals to screen for OSA (by using the Berlin Questionnaire) whenever encountering any stroke patient, especially the patient whose stroke occurred during sleep.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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