Characteristics of Wake-up Stroke

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Background: Wake-up stroke (WUS) accounts for up to 29.6% of ischemic strokes, but its mechanisms are poorly understood. The purpose of this study is to identify risk factors and characteristics of WUS. *Methods:* Seven-two ischemic strokes were classified as WUS or non-WUS. Collected were demographic information, medical history, cholesterol profile, and stroke characteristics including severity (National Institutes of Health Stroke Scale [NIHSS]) and mechanism (Trial of Org 10172 in Acute Stroke Treatment criteria). Subjects completed questionnaires screening for sleep apnea (Berlin questionnaire) and assessing sleep characteristics. *Results:* There were 72 ischemic strokes, of which 28 WUS (38.9%). WUS and non-WUS patients were similar in regard to stroke risk factors. WUS patients tended to be African American and were significantly younger. WUS was significantly more likely to result from small-vessel disease mechanism (42.9% versus 14.0%; $P = .006$) and tended to be less severe WUS (NIHSS score 3 [1, 4] versus 4 [2, 11]; $P = .13$) than non-WUS. Groups did not differ in regard to scoring positively on the Berlin questionnaire, but WUS sufferers were more likely to snore frequently (90.5% versus 70.0%, $P = .08$). The lipid profile was significantly worse in WUS compared with non-WUS (low-density lipoprotein 124.6 ± 38.4 versus 103.7 ± 36.8; $P = .03$; cholesterol to high-density lipoprotein ratio 5.2 ± 1.6 versus 4.3 ± 1.6; $P = .02$). *Conclusions:* WUS is more likely to result from small-vessel disease mechanism. Poorer cholesterol profile and frequent snoring may contribute to WUS. **Key Words:** Wake-up stroke—small vessel—cholesterol—sleep apnea.
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Introduction

Ischemic stroke displays a circadian pattern of occurrence with morning hours being the most likely time of onset.[1,2] Stroke occurring during sleep or wake-up stroke (WUS) accounts for a significant portion of these morning strokes and 14%-29.6% of all ischemic strokes.[2,3] Because the exact time of stroke onset is obscured in WUS, the use of time-sensitive intravenous thrombolytic therapy is precluded. Given this disconnect, it is of utmost importance to maximize understanding of WUS, including its underlying pathophysiologic mechanisms and clinical features to increase the chances of timely therapy and ultimately a good outcome.

Data regarding the clinical features of WUS are conflicting. Prior studies have reached differing conclusions regarding severity of WUS versus non-WUS, some finding that WUS is more severe and others finding no difference.[2-5] Similarly, there is no consensus on WUS mechanism. Several studies have not found a significant difference in stroke mechanism,[2,6] whereas others have associated lacunar syndromes and small-vessel mechanism with WUS.[4,5,7] Analysis of International Stroke Trial data, including 17,398 ischemic strokes and over 5000 WUS, found that WUS was less likely to include severe anterior circulation syndromes, less severe on presentation but deteriorated to similarly low functional status as non-WUS at 6 months.[3]

Although severity and mechanism of WUS have been investigated, pathophysiologic risk factors that predispose to WUS have not been well studied. Because WUS

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occurs during sleep, it seems likely that disordered sleep could play a mechanistic role in producing WUS. Obstructive sleep apnea (OSA) seems a conspicuous candidate for involvement in WUS as it has consistently proven an independent stroke risk factor.[8] As prior data have suggested that small-vessel disease underlies WUS, diabetes control and cholesterol profile may be other factors that increase risk for WUS. Thus, the aim of the present study is to investigate ischemic WUS occurrence and its potential relationship to sleep disordered breathing while determining clinical features of WUS. We hypothesize that persons with stroke occurring in the sleeping period are more likely to have high risk for OSA and that WUS compared with non-WUS is less severe, more likely of small rather than large-vessel mechanism and associated with measurements of hyperlipidemia and poor blood glucose control.

Methods

Subjects

Acute ischemic stroke patients presenting to University Hospitals Case Medical Center in March and April 2012 and from January to March 2013 were prospectively enrolled. Ischemic stroke was confirmed radiographically by restricted diffusion on brain magnetic resonance imaging, and stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS). Transient ischemic attacks, hemorrhagic stroke, and venous infarct were not included in this analysis. Subjects were also excluded if there were other medical issues that were likely related to stroke mechanism including malignancy, gastrointestinal bleeding, drug use, rheumatologic exacerbation, and central nervous system infection. Participants were carefully asked about whether symptoms of stroke were present on waking up or began during wakefulness. Lack of confirmation of symptoms arising in either sleep or wakefulness constituted exclusion. Participants provided written informed consent, and the study was approved by the Institutional Review Board of University Hospitals Case Medical Center.

Patient and Stroke Characteristics

Data collected included age, sex, race, body mass index (BMI, kg/m^2), total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), hemoglobin A1c, and blood pressure on admission. Comorbidities noted were hypertension, diabetes, hyperlipidemia, atrial fibrillation, and patent foramen ovale. Stroke onset was noted and recorded as WUS if neurologic deficits were present on waking. Participants or participant next of kin completed the Berlin sleep apnea questionnaire, which consists of 10 questions in 3 categories: snoring/apnea, sleepiness, and blood pressure. High sleep apnea risk is present if 2 of 3 categories are scored.[9] Snoring frequency was also used as a surrogate for sleep apnea risk.

Strokes were classified according to the Trial of Org 10172 in Acute Stroke Treatment criteria as small vessel, large vessel, cardioembolic, or cryptogenic.[10] Localization was further classified as arising from anterior or posterior circulation based on magnetic resonance imaging scanning. Stroke volume (volume) was measured using ABC/2 criteria in which diffusion-weighted imaging, the longest lesion axis (A), its perpendicular (B), and the product of slice number and slice thickness (C) are measured. The product of these measures is then divided by 2 (ABC/2).[11]

Statistical Analysis

Descriptive statistics included frequency for categorical variables, mean and standard deviation for continuous variables, and medians with interquartile range for ordinal variables. Characteristics of WUS were compared with non-WUS using χ^2, Student t, and Mann–Whitney testing for categorical, continuous, and ordinal variables, respectively. Logistic and multivariate regression analyses were carried out to model the likelihood of small-vessel disease or low-density lipoprotein, respectively, given parameters of age, sex, BMI, diabetes status, and WUS. All significance levels reported were 2 sided. Analyses were conducted using the R statistical package version 2.15.2 (Auckland, New Zealand).

Results

Demographic Data

There were 72 ischemic stroke patients, 46 men (63.9%), 28 WUS (38.9%), and 44 non-WUS. In the overall sample, age (mean ± SD) was 66.3 ± 14.3 (range 25-97), BMI was 30.8 ± 9.0, and admission NIHSS score (median, IQ range) was 4 (2, 7). WUS patients tended to be African American (53.6% versus 34.1%; $P = .10$) and were significantly younger (61.8 ± 15.4 versus 69.1 ± 13.0; $P = .04$) than non-WUS sufferers. There was no significant difference between the BMI and gender makeup of the groups.

Participant Clinical Characteristics

WUS were similar to non-WUS patients for rates of diabetes, hypertension, hyperlipidemia, and patent foramen ovale (data not shown); atrial fibrillation was significantly more frequent in non-WUS (Table 1). Although there was no difference in sleep apnea risk by Berlin questionnaire, WUS sufferers were more likely to snore frequently (90.5% versus 70.0%, $P = .08$). Hemoglobin A1c and blood pressure were similar. The lipid profile was consistently and significantly worse in persons suffering WUS. In WUS versus non-WUS, total cholesterol was 193.3 ± 37.9 versus 173.6 ± 43.4; $P = .049$; LDL was 124.6 ± 38.4 versus 103.7 ± 36.8; $P = .03$; HDL was 39.7 ± 12.1 versus 44.2 ± 14.8; $P = .17$; and cholesterol to HDL ratio was