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The Association between Atrial Fibrillation and Stroke in Patients with Obstructive Sleep Apnea: A Population-Based Case-Control Study

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Abstract

Background—Obstructive sleep apnea (OSA) has been shown to be an independent risk factor for ischemic stroke and may increase the risk of atrial fibrillation (AF) by up to four-fold. Given these relationships, it is possible that OSA may provide a link between stroke and AF. A case-control study was conducted to examine the association between AF and stroke in patients with OSA.

Methods—Olmsted county, MN, USA, residents with a new diagnosis of OSA based on polysomnography (PSG) between 2005 and 2010 (N=2980) who suffered a first-time ischemic stroke during the same period were identified as cases. Controls with no history of stroke were randomly chosen from the same database. Univariate and multiple logistic regression analyses were performed with age, gender, body mass index (BMI), smoking, hypertension, hyperlipidemia, diabetes mellitus, apnea-hypopnea index (AHI) and coronary artery disease as co-variables, with the diagnosis of AF as the variable of interest.

Results—A total of 108 subjects were studied. Mean age of cases (n=34) was 73 ±12 years and 53% were men. Among controls (n=74), mean age was 61 ±16 years and 55% were male. On univariate analyses, AF was significantly more common in the cases than among controls (50.0% vs 10.8%, p<0.01). On multivariate regression analyses, the association between AF and stroke

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was significant after controlling for age, BMI, coronary artery disease, hypertension, diabetes mellitus, hyperlipidemia and smoking status (corrected OR: 5.34; 95% CI: 1.79-17.29).

Conclusions—Patients with OSA who had a stroke had higher rates of AF even after accounting for potential confounders.

Keywords

Stroke; OSA; atrial fibrillation; sleep disordered breathing; risk factors; cerebrovascular accident

INTRODUCTION

Stroke is the second most common cause of mortality worldwide and is associated with significant morbidity and health care costs (1). Atrial fibrillation (AF), the most common sustained arrhythmia, is considered to be an important risk factor for stroke in the elderly and its prevalence is expected to increase over the coming few decades(2, 3).

OSA is associated with adverse cardiovascular outcomes including systemic and pulmonary hypertension, coronary artery disease and arrhythmias(4). OSA has been shown to be independently associated with AF (5). Moderate to severe OSA may increase the risk of atrial fibrillation by up to four-fold (6). Patients with untreated OSA have been shown to have a higher recurrence rate of AF after electrical cardioversion or radiofrequency ablation(7, 8).The prevalence of obstructive sleep apnea (OSA) is estimated to be as high as 1 in 5 in the general population and the majority of these cases are undiagnosed(9, 10).

Several studies have shown OSA to be an independent risk factor for stroke (11-15). Also, the risk of mortality is greater in patients following a stroke in patients at high risk of OSA (16). The most common stroke subtype in patients with OSA is ischemic(15). Pathogenetic mechanisms for stroke in patients with OSA are thought to involve hypertension, changes in cerebral tissue oxygenation and cerebral vascular autoregulation, in addition to the promotion of generalized atherosclerosis and dyslipidemia via intermittent hypoxia and expression of inflammatory cytokines (17-20).

Whether AF plays an intermediary role in the relationship between OSA and stroke is unknown. The number of subjects with AF in the studies evaluating stroke occurring in patients with OSA is often low, making it difficult to draw meaningful conclusions.

Given the interactions outlined above, we hypothesized that atrial fibrillation plays an important role in patients with OSA and stroke. We attempted to identify whether atrial fibrillation was more common in patients with OSA who have suffered an ischemic stroke compared to OSA patients who have not had a stroke. We conducted a case-control study of patients who suffered a stroke, nested in a population-based cohort of patients with OSA.

METHODS

Our sample was obtained from a clinical database of Olmsted county residents, from the state of Minnesota. This database, the Rochester Epidemiologic Project, is a medical record linkage system that collates information from all sources of medical care available to residents of Olmsted County(21). These include the Mayo Clinic and the only other hospital in the county, a non-Mayo affiliated community medical center. The Rochester Epidemiologic Project includes the details of medical care provided to all residents of Olmsted County, MN, USA.

From this database we identified those who received a new diagnosis of OSA based on overnight polysomnography (PSG) performed between 1/1/2005 and 10/1/2010. OSA was defined as an AHI ≥ 5 . American Academy of Sleep Medicine criteria were used; apnea was defined as a cessation in airflow with continued respiratory effort for at least 10 seconds and hypopnea was defined as a 30% reduction in airflow for 10 seconds accompanied by a 4% desaturation. Patients with a diagnosis of central sleep apnea (central apnea index ≥ 5 per hour) and where the central apnea/hypopnea index was equal to or greater than 50% of the overall AHI were excluded. This was to ensure that patients with predominantly OSA were included in the study. All cases of incident ischemic stroke during the same timeframe were identified from the same database using ICD-9 codes for possible ischemic stroke, reviewing the comprehensive medical record which includes detailed inpatient, outpatient and emergency department clinical records, all laboratory investigations, death certificate and autopsy data, applying the Rochester Stroke Registry definitions(22). Non-stroke controls were patients with OSA who were randomly chosen from the same database, using a computerized random number sequence generator. Non-stroke status was verified by detailed review of the electronic medical record. This methodology was used to allow for analyses comparing all potential risk factors which could result in an increased risk of stroke in patients with OSA.

Our study was approved by the Institutional Review Board (IRB) and all subjects provided prior research authorization (IRB# 10-002261). Univariate analyses were performed using age, gender, body mass index (BMI, kg/m²), AF, history of ever smoking, hypertension (or the use of antihypertensive medications), hyperlipidemia (or the use of lipid lowering agents), diabetes mellitus (or the use of diabetic medications) and coronary artery disease (CAD) as co-variables. For the analyses, the groups were divided into four based on their BMI (<25, 25-29, 30-34 and ≥ 34 kg/m²). All groups were compared against the group with a BMI <25.

The presence or absence of atrial fibrillation was determined through a manual review of the electronic medical record for each case and control. All hospital admission, discharge and consultation notes, electrocardiograms (ECG), event recorders, and Holter monitors were reviewed. All patients had ECG performed. Atrial fibrillation was defined as a diagnosis of atrial fibrillation or atrial flutter together with confirmation by ECG (showing irregular fibrillatory or regular flutter waves). While the presence or absence of stroke was not explicitly known during this review of the electronic medical record, complete blinding of the investigator to the case/control status was not possible because the list of diagnoses reviewed frequently included stroke.

Age, gender, BMI, history of ever smoking and other medical co-morbidities at the time of PSG were identified by reviewing the detailed medical record. These co-variables were chosen as they were considered to be important risk factors for stroke and were potential confounders. Following this, multiple logistic regression analyses were performed using all the co-factors, and separately with only co-factors where the association with stroke was significant or borderline significant ($p < 0.10$) in the univariate analysis. Statistical analyses were performed using JMP® version 8 (SAS Institute, Cary, NC).

RESULTS

A total of 2980 non-pregnant subjects who were 18 years and older received a diagnosis of OSA during the study period. All subjects who suffered a first time ischemic stroke ($n=34$) during the same time period were identified from this cohort. Seventy four patients with no stroke were randomly chosen from the same database to serve as controls.

The mean age of the cases was 73 ± 12.3 years. The mean age of controls was 61 ± 15.5 years ($p < 0.0001$). Among the cases, 53% were male, and of the controls, 55% were male ($p = 0.81$). The mean AHI for the cases was 22.8 ± 23.1 ; the mean AHI for the controls was 28.47 ± 24.55 ($p = 0.25$). The majority of cases and controls were obese (50% and 56.76% respectively; $p = 0.74$) (also see table 1).

On univariate analyses, AF was much more common in cases as compared to controls ($p < 0.0001$). In our sample, 17 of the 34 (50%) patients who suffered a stroke had AF, compared with 8 of 74 (10.8%) controls. Also, on univariate analyses, age ($p < 0.001$) and a diagnosis of CAD ($p = 0.0061$) were significantly associated with stroke. The association between stroke and hypertension ($p = 0.0548$), as well as stroke and smoking status ($p = 0.0727$) were close to statistical significance. The cases and controls did not differ in terms of the presence of diabetes mellitus and hyperlipidemia ($p = 0.373$ and $p = 0.1232$ respectively). The odds ratios of the associations are listed in table 2.

On multiple logistic regression analyses, after controlling for age, gender, BMI, AHI, smoking status, hypertension, hyperlipidemia, diabetes mellitus and CAD, atrial fibrillation was significantly associated with having a stroke ($p < 0.0001$) in patients with OSA.

On additional analyses accounting only for factors where the association reached statistical significance, or was close to statistical significance in the univariate analyses (i.e. age, atrial fibrillation, smoking status, hypertension and CAD), atrial fibrillation continued to be associated with a diagnosis of stroke. The corrected odds ratio for AF in OSA patients with stroke was 5.34 (95% CI: 1.79-17.29; $p = 0.0025$). Also, older age continued to be associated with stroke in these analyses ($p = 0.0099$).

The results of the multiple logistic regression analyses are further summarized in Table 3.

DISCUSSION

In a population with OSA, those who suffered a first time ischemic stroke had much higher rates of AF than controls who did not have a stroke. The 5.34-fold odds of having atrial fibrillation were significantly higher even after accounting for potential confounders. To our knowledge, this is the first study to directly examine the association between AF and stroke in patients with confirmed OSA.

While AF and OSA have been shown to be important risk factors for ischemic strokes, the literature examining the interaction of OSA with AF and stroke is sparse and equivocal. Some studies examining the relationship between OSA and stroke examined composite outcomes including stroke, TIA, MI or death limiting the ability to examine the effect of AF on the development of stroke in patients with OSA (11, 12). While one study examining the relationship between OSA and ischemic stroke did not find an association between stroke and AF in patients with OSA, it exclusively examined an elderly population (70-100 years) (13). Another study examining the relationship between OSA and stroke only included patients with coronary artery disease (14). In contrast, our study, comprising a larger number of patients with the diagnoses of OSA and stroke and conducted in a community based setting, showed AF to be much more common in this group of patients ($OR = 5.34$) after accounting for confounders, suggesting that AF may be a much stronger risk factor for stroke in those with OSA. This could potentially indicate that patients with OSA and AF need aggressive treatment to mitigate the risk of future stroke.

In a recent study by Redline et al (15), the odds ratio for stroke in patients with OSA decreased slightly in secondary analyses that excluded patients with AF, but did not change the overall results, suggesting that AF did not explain the association between OSA and

stroke entirely. However, the proportion of subjects with AF (2%) in this study was small and the authors hypothesized that paroxysmal AF was possibly a mediating factor. In our study directly examining the association between AF and stroke in patients with OSA, we were able to account for paroxysmal AF as far as possible by evaluating patient notes as well as all ECG and Holter monitors.

Although our study examined and found an increased association of AF with stroke in patients with OSA, it does not establish a causal relationship between OSA and AF. While a clear understanding of the pathophysiology of atrial fibrillation occurring in the context of OSA is lacking, various putative causal mechanisms have been postulated (23). OSA may predispose to the development of AF by causing recurrent swings in intrathoracic pressure during upper airway narrowing that in turn may result in the enlargement of the relatively thin walled atria of the heart. Changes in intrathoracic pressure may also be an important factor involved in remodeling of the pulmonary vein ostia from which electrical discharges are thought to propagate in patients with AF(24). Apneas can cause bradycardia by activation of the diving reflex(25); reduced cardiac refractoriness during bradycardia and the absence of vagolytic effects of normal lung inflation may predispose to electrical discharges within the pulmonary vein ostia(26, 27). Sympathetic activity surges, obesity and systemic inflammation could also play a role in mediating the relationship between OSA and AF (28, 29). There is also the possibility, although less likely, that AF causes OSA with one study reporting a reduction in obstructive events in patients undergoing atrial overdrive pacing for atrial tachyarrhythmias (30).

While the number of cases and controls is relatively small, our study is one of the largest to date in terms of the number of subjects with both OSA and stroke. Since our center serves as the stroke referral center for the region, nearly all patients with stroke from the county were likely to have been included in the population-based stroke cohort. In addition, the non-Mayo affiliated community medical center in Rochester, MN also provides the medical diagnoses for all patients seen at that site into a central medical index as part of the Rochester Epidemiology Project(21). This further increases the likelihood of essentially complete ascertainment of cases with a diagnosis such as stroke. In this study, the diagnosis of sleep apnea was confirmed by attended, in-lab polysomnography and we accounted for the severity of OSA in our analyses. Finally, in all cases and controls the diagnosis of atrial fibrillation/atrial flutter was confirmed by 12-lead ECG. In our study, 17 of 34 patients (50% of cases) had a diagnosis of OSA preceding stroke. Of the remainder, 12 patients (35.3% of cases) had the PSG performed more than 6 months after their stroke occurred; in several of these patients it likely that OSA may have preceded the stroke but was undiagnosed(31).

Other limitations of our study are the use of randomly chosen controls, an acceptable study design, resulted in a control group that was younger than the cases. We accounted for this by performing regression analyses controlling for common confounders including age. Though we chose over two times the number of cases as controls, potentially having an ever larger number could have resulted in more power and allowed for further subgroups analyses while potentially reducing the chances of bias. Also, accounting for multiple common confounders in a small sample could reduce the power to detect some differences. We tried to mitigate this by performing the analyses with all potential confounders, and again with only those factors that were significantly associated with stroke. Atrial fibrillation continued to be significantly associated with stroke in both these analyses.

Our nested case-control study indicates a strong association between atrial fibrillation, stroke and OSA. Our data could suggest that OSA plays an additive causative role in the relationship between AF and stroke. However, temporality, a *sine qua non* for causality, cannot be proven in a case-control study. Nevertheless, such a possibility heightens the

urgency for further prospective studies to help answer important management questions, such as whether OSA should be considered in risk assessments for stroke or prophylactic anticoagulation. Furthermore, interventional trials to determine if the natural history of AF and stroke could be altered by targeted therapy of OSA are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATION LIST

AF	atrial fibrillation
AHI	apnea-hypopnea index
BMI	body mass index, kg/m ²
CAD	coronary artery disease
ECG	electrocardiogram
ICD	International Classification of Diseases
IRB	Institutional Review Board
OSA	obstructive sleep apnea
PSG	polysomnography

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Table 1

Baseline characteristics

Characteristics	Cases (SD or %)	Controls (SD or %)	P Value
Age	73 (±12.3)	61 (±15.5)	<0.0001
Male	18 (53%)	41 (55%)	0.81
AHI	22.83 (±23.10)	28.47 (±24.55)	0.25
BMI < 25	4 (11.76%)	9 (12.16%)	0.74
BMI 25-29	13 (38.24%)	23 (31.08%)	0.74
BMI 30-34	13 (38.24%)	36 (48.65%)	0.74
BMI 35	4 (11.76%)	6 (8.11%)	0.74
Atrial Fibrillation	17 (50%)	8 (10.8%)	<0.0001
Smoking Status	25 (73.5%)	41 (55.5%)	0.0727
Hypertension	25 (73.5%)	40 (54%)	0.0548
Hyperlipidemia	25 (73.5%)	43 (58.1%)	0.1232
Coronary Artery Disease	15 (44.12%)	14 (18.9%)	0.0061
Diabetes Mellitus	9 (26.47%)	14 (18.9%)	0.373

SD = Standard deviation; BMI = Body mass index in kg/m²

Table 2

Univariate analysis

Characteristic	Odds Ratio	Upper Confidence Interval	Lower Confidence Interval
Atrial Fibrillation	8.25	23.4	3.14
Sex	1.10	2.49	0.48
BMI 25-29	1.27	5.44	0.34
BMI 30-34	0.81	3.41	0.22
BMI 35	1.50	8.85	0.26
Smoking Status	2.24	5.66	0.94
Hypertension	2.36	5.98	0.996
Hyperlipidemia	2.00	5.08	0.84
Coronary Artery Disease	3.38	8.38	1.39
Diabetes Mellitus	1.54	3.99	0.57

BMI = Body mass index in kg/m²

Table 3

Multivariate analysis

Characteristic	Corrected Odds Ratio	Upper Confidence Interval	Lower Confidence Interval	p value
Atrial Fibrillation	5.34	17.29	1.79	0.0099
Smoking Status	2.81	9.03	0.98	0.0558
Hypertension	0.81	2.66	0.24	0.7242
Coronary Artery Disease	1.90	5.89	0.61	0.5267