Sleep Medicine 15 (2014) 410–414

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

High incidence of stroke in young women with sleep apnea syndrome

Chih-Cheng Chang [a,b], Hsiao-Chi Chuang [a,c], Cheng-Li Lin [d], Fung-Chang Sung [d,e], Yen-Jung Chang [d], Chung Y. Hsu [f,g,*], Ling-Ling Chiang [a,c,*]

[a] Division of Pulmonary Medicine, Department of Internal Medicine, Shuang Ho Hospital, Taipei Medical University, Taipei, Taiwan
[b] Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan
[c] School of Respiratory Therapy, College of Medicine, Taipei Medical University, Taipei, Taiwan
[d] Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan
[e] Department of Public Health, China Medical University, Taichung, Taiwan
[f] Graduate Institute of Clinical Medical Science, China Medical University, Taichung, Taiwan
[g] Department of Neurology, China Medical University Hospital, Taichung, Taiwan

ARTICLE INFO

Article history:
Received 17 October 2013
Received in revised form 13 December 2013
Accepted 19 December 2013
Available online 12 February 2014

Keywords:
Age
Cardiovascular
Sex
Sleep apnea
Sleep-disordered breathing
Stroke

ABSTRACT

Objective: Patients with sleep apnea syndrome (SAS) carry a higher stroke risk. The differential stroke risk between sex and among different age groups has not yet been specifically addressed in previous studies.
Methods: Using a universal insurance claims database, we identified a large cohort of SAS patients from 1997 to 2010 and assessed the sex- and age-specific stroke risk compared with a control cohort matched for age, sex, and index date. Cox regression analyses were performed to assess the hazard ratio (HR) of stroke and the corresponding 95% confidence interval (CI). Stroke-free probabilities were computed using the Kaplan–Meier method and differences between both cohorts were examined using the log-rank test.
Results: We identified 29,961 patients with SAS and a control cohort of 119,844 subjects without SAS. The overall incidence of stroke in the SAS cohort was 37% higher compared to the non-SAS cohort (54.6 per 10,000 individual-years vs 39.8 per 10,000 individual-years). After controlling for sex and comorbidities, the SAS cohort exhibited a 19% higher risk for stroke compared to the control cohort (adjusted HR, 1.19 [95% CI, 1.09–1.30]). Women with SAS ages 35 years or younger had the highest stroke risk compared to older age groups of the same sex and their risk for stroke was relatively higher compared to their male counterparts.
Conclusion: Women aged 35 years or younger with SAS have a higher stroke risk.

1. Introduction

A number of studies have reported on the epidemiology of sleep apnea syndrome (SAS). SAS is a common clinical disorder that consists of obstructive sleep apnea, central sleep apnea, and mixed sleep apnea. SAS is associated with impaired palate-pharyngeal collapse during sleep, including decreased muscle tone of the pharyngeal area and repetitive airway obstruction [1]. Repetitive nocturnal hypoxemia in patients with SAS has been increasingly associated with metabolic and inflammatory diseases [2]. Moreover, these mechanisms have been shown to be associated with the development of cardiovascular disease, suggesting that SAS may potentially contribute to the initiation and progression of cardiovascular disease.

Clinically, SAS is prevalent in patients with preexisting cardiovascular diseases. In the United States, obstructive sleep apnea affects an estimated 15 million adults and is found in a large proportion of patients with hypertension and patients with other cardiovascular disorders [3,4]. Increasing evidence indicates that SAS is a risk factor for stroke. For example, a previous study found that a sleep-clinic population with untreated SAS had a higher rate of fatal and nonfatal cardiovascular events such as ischemic heart disease and stroke compared to healthy subjects [5]. Stroke is the second or third leading cause of death and is the leading cause of adult disability worldwide.

Risk factors for stroke include hypertension, atrial fibrillation, diabetes mellitus, smoking, and obesity. Epidemiologic studies also have shown that SAS may be an independent risk factor for stroke. A cross-sectional study reported a strong association between

* Corresponding authors. Address: Graduate Institute of Clinical Medical Science, China Medical University, Taichung, Taiwan. Tel.: +886 4 22052121x6033 (C.Y. Hsu). Address: School of Respiratory Therapy, College of Medicine, Taipei Medical University, Taipei, Taiwan. Tel.: +886 2 27361661x3519; fax: +886 2 27391143 (L.-L. Chiang).
E-mail addresses: hsuc@mail.cmuh.org.tw (C.Y. Hsu), llchiang@tmu.edu.tw (L.-L. Chiang).

http://dx.doi.org/10.1016/j.sleep.2013.12.011
1389-9457/

moderate to severe SAS and stroke prevalence [6]. Previous studies also have found that the development of SAS is associated with age and sex [7,8]; however, the association of age- and sex-specific differences between stroke and SAS patients remains unclear. In our study, we took advantage of a universal healthcare insurance system, the National Health Insurance in Taiwan, to study a large cohort of patients with SAS to assess the age- and sex-specific vulnerability of developing stroke. Our results showed that younger women aged 35 years or younger had the highest stroke risk compared to any other age group and the men.

2. Materials and methods

2.1. Data sources

The Taiwan National Health Insurance is a single-payer system that integrated 13 public insurance systems in 1995 to serve all Taiwanese residents. This insurance program covers approximately 99% of the 23.7 million residents [9]. The National Health Research Institute has been authorized by the Taiwan Department of Health to manage medical claims data and to establish databases for research use. For our study, we used population-based claims data on 1 million insured individuals from 1996 to 2010. Diagnoses were based on the *International Classification of Diseases, Ninth Revision, Clinical Modification Codes* (ICD-9-CM).

2.2. Study sample

Patients aged 20 years and older with SAS (ICD-9-CM codes 780.51, 780.53, and 780.57) and who were newly diagnosed between 1997 and 2010 were identified from the inpatient claims database. For the diagnoses of sleep apnea, polysomnography was conducted according to the standard criteria [10]. Polysomnographic all-night recordings in the hospital-based sleep laboratory were performed. The average number of episodes of apnea and hypopnea per hour of sleep (apnea-hypopnea index [AHI]) was calculated. The minimum criterion for SAS was AHI $\geqslant$ 5 events per hour. The inpatient diagnosis date of SAS was defined as the index date to determine the follow-up duration. Patients who had a history of stroke (ICD-9-CM codes 430–438) prior to the index date were excluded. For the diagnoses of stroke, computed tomography scans of brain were conducted. The non-SAS cohort consisted of randomly selected participants who were matched to the SAS cohort for age, sex, and index date. The SAS and non-SAS cohorts were selected at a 1–4 ratio to improve the statistical power. Subjects with a history of either stroke or SAS at baseline were excluded.

2.3. Outcome measurements

Both cohorts were followed from the index date until a new diagnosis of stroke was made or until the patients were censored due to a loss of follow-up, death, withdrawal from the insurance system, or the end of 2010—whichever came first. The comorbidities considered in our study included obesity (ICD-9-CM code 278.0), diabetes mellitus (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), hypertension (ICD-9-CM codes 401–405), coronary artery disease (ICD-9-CM codes 410–413, 414.01–414.05, 414.8, and 414.9), congestive heart failure (ICD-9-CM codes 428, 398.91, and 402 $\times$ 1), and atrial fibrillation (ICD-9-CM code 427.31).

2.4. Statistical analysis

Distributions of the demographic characteristics and baseline comorbidities were compared between the SAS and non-SAS cohorts. Categorical variables were compared using the χ^2 test and continuous variables were compared using t tests. The stroke incidence rates were estimated and compared between the SAS and non-SAS cohorts. The SAS cohort to non-SAS cohort incidence rate ratio and the 95% confidence interval (CI) were estimated using Poisson regression analysis. The multivariable Cox proportional hazards regression model was used to assess the hazards ratio (HR) for stroke and the corresponding 95% CI. Stroke-free probabilities were computed using the Kaplan–Meier method and the differences between both cohorts were examined using the log-rank test. All analyses were performed using the SAS statistical software version 9.1 for Windows (SAS Institute Inc., Cary, NC, USA). Two-sided P values less than .05 were considered significant.

3. Results

We identified 29,961 patients with SAS who were matched with 119,844 participants without SAS based on age, sex, and index date (Table 1). No significant difference in sex, age, or follow-up years was found between both cohorts. Both SAS cohorts of men and women showed a significantly higher prevalence rate of selected comorbidities ($P < 0001$), including obesity, diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, atrial fibrillation, and congestive heart failure, compared to the non-SAS cohort.

The incidence and HR of stroke by age among men and women with and without SAS are shown in Table 2. Overall, the SAS cohort had a higher stroke incidence (52.4 per 10,000 individual-years for men and 61.7 per 10,000 individual-years for women) compared to the non-SAS cohort (40.7 per 10,000 individual-years for men and 37.3 per 10,000 individual-years for women), with adjusted HRs between men and women of 1.21 (95% CI, 1.01–1.24; $P < 05$) and 1.44 (95% CI, 1.20–1.72; $P < 05$), respectively. We further assessed the association between SAS and stroke risk stratified by age (Table 2). Among women, the effects of SAS on stroke risk decreased with age (adjusted HR, 4.90 [95% CI, 1.93–12.4] for subgroup aged 20–35 years; adjusted HR, 1.64 [95% CI, 1.01–2.65] for subgroup aged 36–50 years; adjusted HR, 1.38 [95% CI, 1.01–1.89] for subgroup aged 51–65 years). In men aged 36–50 years, we observed an association between SAS and an increased stroke risk (adjusted HR, 1.33 [95% CI, 1.10–1.62]). We further investigated the association of stroke and comorbidities among men and women with SAS (Table 3). No significant association between SAS and comorbidities was observed in men and women with SAS.

Kaplan–Meier analysis was used to estimate the cumulative probabilities of stroke between cohorts of men and women with and without SAS. The SAS cohort had a higher probability of stroke compare to the non-SAS cohort (log-rank test, $P < 001$), particularly among women aged 20 to 35 years as shown in Fig. 1.

4. Discussion

The main finding of our study was that SAS is a risk factor of stroke and exhibits sex- and age-specific differences. The results supporting our conclusion included the overall incidence rate of stroke, which was significantly higher in the SAS cohort compared to the non-SAS cohort. In particular, young women with SAS (ages 20–35 years) had the highest risk for stroke. These findings showed that young women with SAS were the most susceptible group for the development of stroke.

Clinically, sleep apnea in the form of obstructive apnea and central sleep apnea frequently occurs among stroke patients. Previous studies have found that sleep-disordered breathing (SDB) was frequently prevalent among stroke patients [11,12]. Post-stroke patients with moderate SDB had a higher risk for arterial stiffness