

Association Between Obstructive Sleep Apnea and Sudden Sensorineural Hearing Loss

A Population-Based Case-Control Study

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Objective: To examine the putative association between obstructive sleep apnea (OSA) and sudden sensorineural hearing loss (SSNHL) using a nationwide population-based data set. Obstructive sleep apnea has been associated with generalized inflammation and neuroendocrine, cardiovascular, and other systemic biophysiological phenomena. However, to our knowledge, no investigations have been conducted using large data sets to examine the association between OSA and auditory disorders.

Design: Case-control study.

Participants: We identified 3192 patients diagnosed with SSNHL from the Taiwan Longitudinal Health Insurance Database as the study group and randomly extracted the data of 15 960 subjects matched by sex, age and year of first SSNHL diagnosis as controls.

Main Outcome Measures: Cases of OSA were identified by having been diagnosed as OSA prior to the index date of SSNHL diagnosis. Conditional logistic re-

gression matched on age group and sex was used to assess the possible association between SSNHL and OSA among the sampled patients.

Results: Of 19 152 patients, 1.2% had OSA diagnoses prior to the index date; OSA was diagnosed in 1.7% of the SSNHL group and 1.2% of the controls. After adjusting for sociodemographic characteristics and comorbid medical disorders, we found that male patients with SSNHL were more likely to have prior OSA than controls (odds ratio, 1.48; 95% CI, 1.02-2.16) ($P=.04$). No such association was found among female patients.

Conclusions: Male patients with SSNHL had a higher proportion of prior OSA than non-SSNHL-diagnosed controls; no such association was found among female patients. Further study will be needed to confirm our findings, explore the underlying pathomechanisms, and investigate the difference between sexes.

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OBSTRUCTIVE SLEEP APNEA (OSA) is a very common disorder affecting 24% of men and 9% of women by the time they reach middle age.¹ It is characterized by repetitive episodes of apnea and/or hypopnea and various degrees of hypoxia caused by upper airway collapse during sleep. Obstructive sleep apnea carries potentially serious consequences: excessive daytime sleepiness, neurocognitive deterioration, endocrine and metabolic derangements, and cardiovascular disease including stroke.²⁻⁴ In addition, OSA is an independent risk factor for cardiovascular-related and all-cause mortality.^{4,5} Obstructive sleep apnea is also associated with asthma exacerbation,⁶ ocular disorders,⁷ erectile and sexual dysfunction,⁸ and overactive bladder.⁹ Although the pathogenesis of OSA is not fully understood, intense systemic inflammation is present. Obstructive sleep apnea has therefore been

suggested to be a systemic rather than a localized disease.¹⁰

Few previous reports have examined potential associations between OSA and auditory disorders. In a cross-sectional study of 224 hospital volunteers, Hwang et al¹¹ found that OSA was associated with impaired central auditory function in older subjects. They hypothesized that OSA directly contributes to the development of age-related hearing impairment through cerebral vascular insufficiency and that this effect is enhanced synergistically by central obesity and metabolic derangements related to OSA. In a case-control study of small sample size, Fisher et al¹² reported that patients who developed sudden hearing loss had OSA more frequently than others. They attributed the relationship to cerebrovascular risk factors common to cerebral infarction and sudden hearing loss but could not establish a causal relationship owing to the cross-sectional design and small sample size of their study. Large

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Table 1. Demographic Characteristics of 19 152 Patients With Sudden Sensorineural Hearing Loss and Comparison Group Patients in Taiwan in the Years 2001 Through 2008^a

Variable	Patients With Sudden Sensorineural Hearing Loss (n = 3192)	Comparison Cohort (n = 15 960)	P Value
Sex			
Male	1720 (53.9)	8600 (53.9)]. >.99
Female	1472 (46.1)	7360 (46.1)	
Age, y			
<30	450 (14.1)	2250 (14.1)]. >.99
30-39	490 (15.3)	2450 (15.3)	
40-49	679 (21.3)	3395 (21.3)	
50-59	621 (19.4)	3105 (19.4)	
60-69	554 (17.4)	2770 (17.4)	
>69	398 (12.5)	1990 (12.5)	
Monthly income, NT\$			
≤15 840	1186 (37.2)	6140 (38.5)]. .01
15 841-25 000	1251 (39.2)	6430 (40.3)	
≥25 001	755 (23.6)	3390 (21.2)	
Hyperlipidemia	582 (18.2)	2185 (13.7)	<.001
Diabetes	521 (16.3)	1825 (11.4)	<.001
Hypertension	1021 (32.0)	4095 (25.7)	<.001
Coronary heart disease	453 (14.2)	1745 (10.9)	<.001
Obesity	46 (1.4)	170 (1.1)	.07
Geographic region			
Northern	1484 (46.5)	7590 (47.6)]. <.001
Central	875 (27.4)	3735 (23.4)	
Eastern	761 (23.8)	4265 (26.7)	
Southern	72 (2.3)	370 (2.3)	
Urbanization level			
1	902 (28.3)	4800 (30.1)]. .02
2	995 (31.2)	4500 (28.2)	
3	535 (16.8)	2805 (17.6)	
4	428 (13.4)	2180 (13.6)	
5	332 (10.4)	1675 (10.5)	

^aUnless otherwise indicated, data are given as number (percentage) of study subjects.

epidemiologic investigations into the association between OSA and auditory disorders are lacking. Therefore, the goal of this study was to explore the putative association between OSA and sudden sensorineural hearing loss (SSNHL) using a large, nationwide population-based data set in Taiwan.

METHODS

DATABASE

This study used data from the Longitudinal Health Insurance Database 2000 (LHID2000), which contains all the original claims data for 1 000 000 individuals randomly sampled from the 2000 Registry of Beneficiaries of the Taiwan National Health Insurance (NHI) program. The Taiwan National Health Research Institutes created the LHID2000, a subset of the full body of data, and provided it to researchers so that statistical analyses could be performed without special computing resources (the full database contains records on 25.68 million people enrolled in the NHI, making it infeasible to perform such an analysis using a personal computer). The Taiwan National Health Research Institutes confirms that there was no significant difference in sex distribution between the LHID2000 and the full

data set. The LHID2000 contains records for all the medical services provided to these 1 000 000 individuals since the inauguration of the NHI. It therefore provides a large and information-rich resource from which to examine the association between SSNHL and OSA.

As the LHID2000 consists of deidentified secondary data released to the public for research purposes, this study was exempt from full review by the Taipei Medical University institutional review board.

STUDY SAMPLE

This study was designed as a matched case-control study. We first identified all patients who had visited ambulatory care centers (including outpatient departments of hospitals or clinics) or were hospitalized with a new diagnosis of sudden hearing loss (*International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 388.2*) between January 1, 2001, and December 31, 2008 (n = 3405). The date of the first diagnosis for each case was assigned as its index date. To increase the likelihood of selecting only new cases, we excluded 13 patients who were diagnosed as having SSNHL prior to January 2001. In addition, we excluded patients from the analysis who were younger than 18 years (n = 200). Ultimately, our case group included 3192 patients with SSNHL.

We extracted the control group from the remaining subjects in the Registry of Beneficiaries of the LHID2000. We selected 15 960 controls (5 for every SSNHL case), matched with the cases by age group (<30, 30-39, 40-49, 50-59, 60-69, and >69 years), sex, and year of the index date. We confirmed that none of the selected controls had ever received a diagnosis of SSNHL since the initiation of the NHI in 1995.

Cases of OSA were identified based on a diagnosis of OSA (*ICD-9-CM codes 327.23, 780.51, 780.53, or 780.57*) after receiving polysomnography. We included patients in this group only when OSA was diagnosed prior to the index date.

STATISTICAL ANALYSIS

We used SAS software (SAS System for Windows, version 8.2, SAS Institute Inc) for statistical analyses. Descriptive statistics and the χ^2 test for independence were used to describe and compare the differences between patients with and without SSNHL in terms of monthly income (New Taiwan [NT] \$0-NT\$15 840; NT\$15 841-NT\$25 000; or \geq NT\$25 001), geographic location (northern, central, eastern, or southern Taiwan), urbanization level of the patients' residence (1-5 scale, 1 representing the most urbanized and 5, the least urbanized), selected comorbid medical disorders (hypertension, diabetes, coronary heart disease, and/or hyperlipidemia), and obesity. We selected these comorbidities because prior studies have documented their possible association with SSNHL.^{13,14} All the selected comorbidities were defined on the basis of data obtained before the index date. Finally, conditional logistic regression conditioned on age group and sex was used to assess the association of SSNHL with OSA among the sampled patients. Significance was set at 2-tailed $P \leq .05$.

RESULTS

In total, 3192 patients with newly diagnosed SSNHL were identified and matched to 15 960 controls. The mean (SD) age was 49.2 (16.6) years, with men comprising 53.9% of the sampled patients (**Table 1**). After matching for age group, sex, and year of index date, patients with SSNHL were found to be more likely than controls to have

Table 2. Crude ORs for OSA Among the Sampled Patients

Presence of OSA	Study Subjects ^a					
	Total	Male		Female		Comparison Cohort
	Patients With SSNHL	Comparison Cohort	Patients With SSNHL	Comparison Cohort	Patients With SSNHL	
Yes	55 (1.7)	185 (1.2)	38 (2.2)	125 (1.5)	17 (1.2)	60 (0.8)
No	3137 (98.3)	15 775 (99.8)	1682 (97.8)	8475 (98.5)	1455 (98.8)	7300 (99.2)
OR (95% CI)	1.50 (1.11-2.03) ^b	1 [Reference]	1.53 (1.06-2.22) ^c	1 [Reference]	1.42 (0.83-2.44)	1 [Reference]

Abbreviations: CI, confidence interval; OR, odds ratio; OSA, obstructive sleep apnea; SSNHL, sudden sensorineural hearing loss.

^aUnless otherwise indicated, data are number (percentage) of study subjects. The ORs were calculated by conditional logistic regression, which was conditioned on sex and age group.

^b $P < .01$.

^c $P < .05$.

Table 3. Adjusted Odds Ratios for Obstructive Sleep Apnea for Patients With SSNHL And Comparison Patients In Taiwan

Characteristic	SSNHL, Odds Ratio (95% CI)		
	Total	Male	Female
Prior obstructive sleep apnea			
Yes	1.42 (1.05-1.93) ^c	1.48 (1.02-2.16) ^c	1.31 (0.76-2.27)
No	1 [Reference]	1 [Reference]	1 [Reference]
Monthly income, NT\$			
≤15 840	1 [Reference]	1 [Reference]	1 [Reference]
15 841-25 000	1.16 (0.81-1.67)	2.23 (1.35-3.69) ^b	0.56 (0.34-0.93) ^c
≥25 001	1.67 (1.14-2.46) ^a	3.29 (1.96-5.52) ^a	0.41 (0.18-0.93) ^c
Hyperlipidemia	1.94 (1.40-2.69) ^a	2.07 (1.37-3.10) ^a	1.57 (0.88-2.82)
Diabetes	1.49 (1.30-1.71) ^b	1.27 (1.14-1.54) ^b	1.02 (0.53-1.96)
Hypertension	1.33 (0.96-1.84)	1.48 (0.99-2.20)	1.07 (0.60-1.89)
Coronary heart disease	1.76 (1.24-2.51) ^b	2.54 (1.67-3.86) ^a	0.63 (0.29-1.38)
Obesity	0.59 (0.14-2.43)	0.40 (0.05-3.00)	0.73 (0.10-5.42)
Geographic region			
Northern	1 [Reference]	1 [Reference]	1 [Reference]
Central	0.98 (0.70-1.38)	0.73 (0.47-1.13)	1.63 (0.91-2.93)
Eastern	0.48 (0.32-0.70) ^a	0.45 (0.28-0.71) ^a	0.55 (0.27-1.10)
Southern	1.00 (0.38-2.64)	1.61 (0.58-4.46)	NA
Urbanization level			
1	1 [Reference]	1 [Reference]	1 [Reference]
2	1.08 (0.77-1.50)	1.02 (0.68-1.52)	1.07 (0.58-1.97)
3	1.15 (0.79-1.69)	1.26 (0.82-1.96)	0.74 (0.33-1.64)
4	0.75 (0.45-1.24)	0.68 ^c (0.17-0.82)	1.44 (0.68-3.05)
5	0.66 (0.36-1.21)	0.56 (0.26-1.18)	0.72 (0.25-2.09)

Abbreviations: CI, confidence interval; NA, not applicable; SSNHL, sudden sensorineural hearing loss.

^a $P < .001$.

^b $P < .01$.

^c $P < .05$.

the following comorbidities: hyperlipidemia (18.2% vs 13.7%) ($P < .001$), diabetes (16.3% vs 11.4%) ($P < .001$), hypertension (32.0% vs 25.7%) ($P < .001$), and coronary heart disease (14.2% vs 10.9%) ($P < .001$). In addition, patients with SSNHL were more likely to be obese ($P < .001$), to have monthly incomes of NT\$25 001 or higher ($P = .01$), and to reside in the central part of Taiwan ($P < .001$) compared with non-SSNHL controls.

Of the 19 152 patients, 240 patients had been diagnosed as having OSA prior to the index date (1.2%); 55 were from the case group (1.7% of the patients with SSNHL); and 185 were from the control group (1.2% of non-SSNHL patients) (**Table 2**). Table 2 also shows that there was a statistically significant difference in OSA diagnosis prior to index date between patients with and

without SSNHL. A higher proportion of OSA was found among patients with SSNHL compared with controls (odds ratio [OR], 1.50; 95% CI, 1.11-2.03) ($P = .01$).

We further analyzed the OR of OSA after stratifying the sampled patients by sex. Our findings revealed that male patients with SSNHL were more likely than controls to have OSA prior to the index date (OR, 1.53; 95% CI, 1.06-2.22) ($P = .02$), whereas no statistical difference was found between female patients with SSNHL and controls for prior OSA (OR, 1.42; 95% CI, 0.83-2.44) ($P = .20$).

Table 3 lists the adjusted ORs for OSA among the sampled patients. After adjusting for patients' monthly income, geographic location, urbanization level, hypertension, diabetes, coronary heart disease, and hyperlip-

idemia and obesity, we found that patients with SSNHL were more likely than controls to have prior OSA (OR, 1.42; 95% CI, 1.05-1.93) ($P=.03$). Similarly, after adjusting for the aforementioned covariates, we found that male patients with SSNHL had a higher proportion of prior OSA than controls (OR, 1.48; 95% CI, 1.02-2.16) ($P=.04$). There was no statistical difference in the proportion of prior OSA between female patients with SSNHL and controls. Furthermore, diabetes, coronary heart disease, and hyperlipidemia were all found to be independent risk factors for SSNHL.

COMMENT

To our knowledge, this is the first study to investigate the epidemiologic association between OSA and SSNHL adjusted for patient sociodemographic characteristics and comorbid medical disorders. A statistically significant higher proportion of prior OSA was found among patients with SSNHL compared with controls. A growing body of evidence suggests that OSA is associated with a number of cardiovascular and metabolic consequences, including coronary heart disease, hypertension, diabetes, and hyperlipidemia.^{4,15-17} In addition, it has been suggested that cardiovascular disease and cardiovascular risk factors are associated with the risk of developing SSNHL.^{13,14} Thus, a possible explanation for the association between OSA and SSNHL is that OSA indirectly contributes to the development of SSNHL via the effects of cardiovascular disease and cardiovascular risk factors. But since our analysis included adjustment for coronary heart disease, hypertension, diabetes, hyperlipidemia, and obesity, our results suggest that cardiovascular disease and cardiovascular risk factors are not the only mechanisms contributing to the association between OSA and SSNHL.

The actual mechanisms contributing to the association between OSA and SSNHL are unclear. Previous studies have proposed underlying causes for SSNHL, including viral infection, vascular occlusion, breaks in labyrinthine membranes, immunomediated mechanisms, and stress response.^{18,19} The cochlea is especially sensitive to circulatory alterations because it is supplied by a single terminal artery and lacks adequate collateral blood supply.¹⁹ Obstructive sleep apnea may lead to cerebral vascular insufficiency resulting in hypoxia, acute hemodynamic change, and decreased cerebral blood flow during episodes of apnea.² In addition, elevated sympathetic nerve activity secondary to the reflex effects of hypoxia and hypercapnia as well as oscillations in blood pressure occurring during episodes of apnea may result in adverse cerebrovascular events and hence ischemic injury to the cochlea.²⁰

The link between OSA and cardiovascular and metabolic consequences may be mediated by the oxidative stress induced by chronic intermittent hypoxia, a key feature of OSA.^{21,22} There is a body of evidence suggesting that the repetitive episodes of hypoxia and reoxygenation following apnea induce the formation of superfluous reactive oxygen species (ROS) and increased oxidative stress, which in turn activate inflammatory and immune responses leading to cardiovascular and meta-

bolic complications.²³⁻²⁵ Oxidative stress and ROS have been implicated in the transcriptional activation of nuclear factor κ B (NF- κ B), which leads to the activation of the proinflammatory response. This response sets off a cascade of cytokines and chemokines that contribute to endothelial dysfunction and vascular damage, which while being known to precipitate the occurrence of sudden vascular events, such as a myocardial infarctions or strokes, may also contribute to the development of SSNHL.^{26,27} Moreover, abundant NF- κ B and the presence of cytokine receptors in cochlear tissue implies that the cochlea is vulnerable to disruption by systemic and local sources of cytokines and that abnormal activation of NF- κ B may play an important role in linking OSA to SSNHL.^{18,28}

The finding that male but not female patients with SSNHL were more likely to have prior OSA than controls demands further thought and study. One of the possible explanations is the underrecognition and underdiagnosis of OSA in women. Low awareness of OSA in women by physicians, variations in presenting symptoms, and the underreporting of classic symptoms of OSA such as snoring in women may all contribute to the underdiagnosis of OSA in women.^{29,30} Several studies have demonstrated a higher apnea-hypopnea index (AHI, an index of OSA severity) in men than in women.³¹⁻³³ Shahr et al³² reported that prevalent cardiovascular disease is associated with the AHI and the proportion of hypoxemia experienced during periods of sleep.³² It is reasonable to hypothesize that milder OSA in women protects them from the risk of SSNHL owing to less severe hypoxia and vascular insufficiency.

A particular strength of this study is the use of a nationwide population-based data set that provides sufficient sample size and statistical power to explore the association between OSA and SSNHL. Nevertheless, some insufficiencies in our study should be addressed. First, OSA and SSNHL diagnoses, which rely on insurance claims data reported by physicians and hospitals, may be less accurate than diagnoses made according to standardized criteria. However, to avoid mistaken diagnoses, we selected only patients who had a diagnosis of OSA after receiving polysomnography. The NHI in Taiwan routinely samples medical charts and assesses them for accuracy in medical coding and validity of claims. It has been reported that the NHI Research Database has acceptable validity for epidemiologic investigations.³⁴ Second, the severity of OSA and SSNHL cannot be determined in our database. Third, additional theoretically relevant confounding variables such as smoking, alcohol consumption, and body mass index,^{3,35,36} could not be included in our analysis because they were not included in our data set. Further study is needed to clarify the effects of these factors.

In conclusion, our study supports an association between OSA and SSNHL in male but not in female patients. The mechanism underlying the association is not clear but may include oxidative stress, vascular insufficiency, and the contribution of cardiovascular risk factors. Further studies describing OSA severity and sex-specific differences in smoking, alcohol consumption, and obesity are needed to confirm the association found in

the present study and to enrich our understanding of its implications.

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