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Original Article

Sleep disorders increase the risk of burning mouth syndrome: a retrospective population-based cohort study

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ABSTRACT

Background: Sleep disorders (SD), including apnea and nonapnea, and burning mouth syndrome (BMS) have been mutually associated with systemic diseases. Based on our research, the association between BMS and SD has not been elucidated. We determined whether SD patients have an increased risk of BMS.
Methods: We used information from health insurance claims obtained from the Taiwanese National Health Insurance (NHI) program. We identified patients newly diagnosed with sleep apnea syndrome between 1998 and 2001 as the apnea SD cohort, and newly diagnosed patients with nonapnea SD as the nonapnea SD cohort. The non-SD cohort was 1:2 frequency matched the case group according to sex, age, and index year. We analyzed the risks of BMS by using Cox proportional hazards regression models.
Results: Compared with the non-SD cohort, both of the apnea SD (adjusted HR = 2.56, 95% CI = 1.30–5.05) and nonapnea SD (adjusted HR = 2.89, 95% CI = 2.51–3.34) were associated with a significantly higher risk of BMS. The hazard ratio (HR) increased with increased age in the apnea SD cohort and in the nonapnea SD cohort compared with patients younger than 40 years of age. Female apnea SD patients (IRR = 4.63, 95% CI = 3.82–5.61) had a higher risk of developing BMS than did male patients (IRR = 1.76, 95% CI = 1.39–2.24).
Conclusions: Based on our research, SD might increase the risk of BMS.

1. Introduction

Sleep disorders (SD) have affected approximately 4–6 million people in Taiwan according to a survey by the Taiwan Society of Sleep Medicine (TSSM) [1]. Sleep is a critical factor for maintaining mental and physical health [2]. Lack of sleep and sleep deprivation threatens a person's health. The primary effects of sleep deprivation include physical effects, such as sleepiness, chronic fatigue syndrome, hypertension, cognitive disorder (eg, deteriorated attention and motivation, diminished concentration and intellectual capacity, and increased risk of accidents during working and driving), and mental health problems [3]. SD impairs the ability to think, manage stress, and maintain a healthy immune system and emotions. Complete sleep deprivation has been fatal in certain animal study models [4]. It is implicated that sleep is a crucial and essential factor of quality of life. Recent studies have shown an association between the immune system and SD [5–7]. The mechanisms by which SD affect health are unclear. However, certain recent studies indicated that SD might also affect or aggravate chronic pain and pain sensation by producing a hyperalgesic state in healthy people, which influences pain perception [8]. The relationship between SD and pain is very complex and the possible mechanism might be sleep and pain are both processed via the high pathway of the central nervous system (CNS) and through a pain–sleep interaction mechanism [9]. Clinically, pain can directly affect the sleep quality and quantity of patients with pain related to their underlying medical diseases, such as fibromyalgia, rheumatoid arthritis, and cancers [10,11] and psychiatric disorders such as anxiety and depression [9,12].

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Burning mouth syndrome (BMS) is an idiopathic, chronic pain condition that affects large populations in modern society, characterized by a burning, stinging, and itching sensation of oral mucosa in the absence of any organic disease [13,14]. BMS is also defined by the International Association for the Study of Pain [15] as a burning pain in the oral mucous membrane and tongue, with normal signs and laboratory data lasting 4–6 months [16,17]. Butlin and Oppentheim first described it as glossodynia [18]; however, it is currently referred to as glossopyrosis, oral dysesthesia, sore tongue, stomatodynia, stomatopyrosis, and most commonly as BMS. The BMS mechanism is not fully elucidated at present, but the neuropathic mechanism for BMS is currently acceptable [19]. Studies have revealed trigeminal nerve alterations in both hyper- and hyposensitivity as well as fiber neuropathy [19–21]. BMS is also associated with a high prevalence of psychiatric symptoms or mental disorders [22,23]. Therefore, the pathogenesis mechanism remains to be determined. Previous studies have reported sleep dysfunction as a risk factor of patients with BMS [12,24]. However, no large population-based study has outlined the relationship between BMS and SD in Taiwan. Thus, we investigated whether SD, which includes nonapnea SD and apnea SD (or obstructive sleep apnea disorder), increases the risk of BMS. The original database was derived from the Taiwanese National Health Insurance (NHI) system in Taiwan. The results presented in this paper were derived from a retrospective cohort study to assess the possibility of a lower risk of BMS with clinical management of apnea and nonapnea SD.

2. Materials and methods

2.1. Data sources

In March 1995, the Taiwanese government implemented the National Health Insurance (NHI) program, which provides universal health insurance coverage to 99% of the population of Taiwan. The National Health Research Institutes (NHRI) compiles all inpatient and outpatient medical-benefit claims in the NHI program and releases the database for research purposes. The National Health Insurance Research Database (NHIRD) contains medical information, including inpatient and outpatient care facilities, drug prescriptions, insurant sex, date of birth, date of visit or hospitalization, and diagnoses coded in the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) format. Previous studies have described the details of the NHIRD. We analyzed the one million beneficiaries randomly selected from all insurants from 1996 to 2000, which has been demonstrated to be representative of the entire population. The study conformed to STROBE Guidelines. The NHRID encrypts the patients' personal information for privacy protection and provides researchers with anonymous identification numbers associated with the relevant claim information, which includes the patient's sex, date of birth, registry of medical services, and medication prescriptions. Patient consent is not required for accessing the NHIRD. This study was approved by the Institutional Review Board of China Medical University in Central Taiwan (CMU-REC-101-012).

2.2. Study participants

For the case cohorts, we identified patients newly diagnosed with sleep apnea syndrome (ICD-9-CM 780.51, 780.53, and 780.57) between 1998 and 2001 as the apnea-SD cohort, and patients newly diagnosed with nonapnea SD (ICD-9-CM 307.4 and 780.5, except 780.51, 780.53, and 780.57) as the nonapnea-SD cohort. Patients were excluded if they were younger than 20 years of age or were diagnosed with BMS (ICD-9-CM 781.1, 529.0, and 529.6) before the index date. In total, 47,941 patients with SD comprised the case group. The same exclusion criteria were also applied to the non-SD control. The non-SD cohort was 1:2 frequency matched to the case group by sex, age, and index year (n = 95 882). We excluded patients with medication history of angiotensin-converting enzyme (ACE) inhibitors. Finally, there were a total of 39,349 subjects in the SD cohort and 86,299 subjects in the non-SD cohort.

2.3. Outcome measurement and comorbidities

The index date for each participant was the first SD diagnosis date. We identified the study endpoint as the first diagnosis of BMS from outpatient claims or hospitalization records from 1998 to 2010. All of the study participants were followed from the index date to endpoint occurrence, withdrawal from the database, or the end of 2010, whichever date came first.

We also incorporated inpatient and outpatient diagnosis records to ascertain the baseline comorbidities, including diabetes (ICD-9-CM 250), hypertension (ICD-9-CM 401–405), hyperlipidemia (ICD-9-CM 272), dementia (ICD-9-CM 290.0–290.4, and 331.0), parkinsonism (ICD-9-CM 332), trigeminal neuralgia (ICD-9-CM 350.1), temporomandibular joint disorder (ICD-9-CM 524.6), anxiety (ICD-9-CM 300.00), and depression (ICD-9-CM 296.2–296.3, 300.4, 311).

2.4. Statistical analysis

We compared the baseline characteristics between apnea SD, nonapnea SD, and non-SD controls by using the chi-square test. The age- and sex-specific incidence densities (IDs) were determined under the Poisson assumption. Cox proportional hazards regression models were performed with adjustment for age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, dementia, parkinsonism, trigeminal neuralgia, temporomandibular joint disorders, anxiety and depression. For estimating the cumulative incidence of BMS in SD patients and non-SD patients, we performed a survival analysis by using the Kaplan–Meier method, with significance based on the log-rank test. All statistical analyses were performed using SAS (Version 9.2; SAS Institute, Cary, NC, USA). Statistical significance was determined by a data type I error of 0.05.

3. Results

Table 1 presents the baseline characteristics of the patients in the three groups. The distribution of age varied somewhat different, but significant. Approximately half of the study participants were 41–65 years of age. The mean ages of the SD cohort and non-SD cohort were 49.8 (±15.6) and 50.6 (±15.8) years, respectively. In the apnea SD cohort, most patients were men (62.0%), which inverted in the nonapnea SD cohort (36.0%). Patients in the nonapnea SD cohort were likely to have diabetes (5.64%, $P < 0.001$), dementia (0.39%, $P < 0.001$), parkinsonism (1.01%, $P < 0.001$), anxiety (3.99%, $P < 0.001$), and depression (6.17%, $P < 0.001$), whereas the apnea SD cohort patients were likely to have hypertension (27.4%, $P < 0.0001$), hyperlipidemia (21.5%, $P < 0.0001$), trigeminal neuralgia (0.27%, $P < 0.0001$), and temporomandibular joint disorders (0.54%, $P < 0.0001$).

Compared with the non-SD cohort, the apnea SD (IRR = 2.84, 95% CI = 2.45–3.30; adjusted HR = 2.56, 95% CI = 1.30–5.05) and nonapnea SD (IRR = 3.07, 95% CI = 2.95–3.19; adjusted HR = 2.89, 95% CI = 2.51–3.34) were associated with a significantly higher risk of BMS (Table 2). Figure 1 presents the cumulative incidence of BMS compared with the apnea SD cohort and the nonapnea SD cohort. The risk of BMS was significantly higher for patients both in the apnea SD cohort (log-rank $P = 0.001$) and the nonapnea SD cohort (log-rank $P < 0.001$) than for participants without SD.

Female apnea SD patients (IRR = 4.63, 95% CI = 3.82–5.61) had a higher risk of developing BMS than did male patients (IRR = 1.76,