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Original Article

Sleep disordered breathing in patients with primary Sjögren's syndrome: A group controlled study

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ABSTRACT

Objective: Patients with primary Sjögren's syndrome (pSS) have higher fatigue levels and also suffer from excessive day time sleepiness. The underlying mechanisms for this are not fully understood. Knowing that these patients have higher salivary surface tension, we postulated that sleep disordered breathing (SDB) would be more common and would be a contributor to these symptoms amongst pSS patients. We investigated the prevalence of SDB in pSS patients and its relationship to their symptoms of fatigue and excessive daytime sleepiness.

Methods: This was an observational study of 28 pSS patients (mean ± SEM age, 58.7 ± 1.9) and 18 healthy subjects (mean ± SEM age, 55.8 ± 3.4) matched for age, sex, and BMI. All the participants underwent an overnight polysomnography. The two groups were compared for fatigue, sleepiness, anxiety, and depression scores, and for the frequency of obstructive apneas and hypopneas during sleep. Correlation analyses were used to explore relationships between sleep study variables and excess sleepiness and fatigue.

Results: Fatigue, sleepiness, anxiety and depression symptoms, and sleep onset latency were significantly greater in pSS patients than controls. pSS patients had twice the frequency of obstructive apneas and hypopneas compared with control subjects (median[IQR],18.6/h [10.4–40.1] vs. 9.9/h [6.5–23.4]; $p = 0.032$) and OSA defined as an apnea–hypopnea index >15 events/h of sleep was more prevalent amongst pSS patients than controls (64% vs. 28%; $p = 0.033$). While no significant correlations were found between parameters of sleep disordered breathing and sleepiness scores or fatigue scores in the pSS group, CPAP treatment in a small subset of the pSS who were more severely affected by OSA suggested significant symptomatic benefit.

Conclusion: OSA appears to be increased in pSS and may be a useful therapeutic target to improve the quality of life of these patients.

1. Introduction

Primary Sjögren's syndrome (pSS) is a multi system autoimmune disorder characterised by lymphocytic infiltration and exocrine failure of salivary and lacrimal glands, resulting in the classical symptoms of the disease including xerostomia (dry mouth) and keratoconjuctivitis sicca (dry eyes) [1]. In addition, other extraglandular features have also been associated with the disease, including interstitial nephritis, renal tubular acidosis, peripheral neuropathy and palpable purpurae [2]. Other less common extraglandular features can occur, e.g., lymphocytic interstitial pneumonitis, cutaneous vasculitis, autonomic dysfunction, and increased risk of non-hodgkin's lymphoma.

Patients with pSS have increased salivary and upper airway lining surface tension [3], and there is some evidence that increased surface tension forces are involved in the pathophysiology of obstructive sleep apnea (OSA) [4,5]. OSA is a sleep-related breathing disorder characterised by repetitive airway obstruction and arousal during sleep and is an established cause of daytime

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hypersomnolence. Patients with pSS also report frequent sleep disturbances and excessive daytime sleepiness [6,7]. Up to 70% of pSS patients report higher fatigue levels compared to non-pSS control subjects [1,7]. pSS patients show more sleepiness during the day and suffer from fatigue and nap more frequently than healthy controls and rheumatoid arthritis patients [6]. Another study has demonstrated excessive daytime sleepiness in female patients with pSS, as measured by the Epworth Sleepiness Scale (ESS) [8], when compared to control patients with osteoarthritis [9]. There are a number of other possible explanations, in addition to OSA, for increased sleepiness and fatigue in pSS. For example, a recent study showed a possible overlap between fatigue and fibromyalgia in pSS [10].Other factors that may be important include mood disturbance, medication side effects, and sleep restriction. Sleep restriction in pSS could be related to awakening to drink water to relieve dry mouth, nocturia [9] or nocturnal musculoskeletal pain. In addition, patients with pSS have been shown to have an increased frequency of restless legs symptoms, which are often associated with periodic limb movements of sleep, which can cause daytime sleepiness [6].

We postulated that OSA would be more prevalent in patients with pSS compared to healthy age and weight-matched controls and that excessive daytime sleepiness and fatigue in patients with pSS could possibly be due to a disorder of sleep and be related to the severity of OSA.

2. Methods

2.1. Participants

Female patients with pSS were recruited from a cohort of rheumatology clinic patients approached consecutively from the clinic list to be a part of the study. All patients fulfilled the American-European Classification Criteria for Sjogren's syndrome [11]. Group matching was performed on the basis of gender, age, and body mass index (BMI), resulting in the selection of eighteen non-pSS controls, who were recruited through local advertisements and friends of index cases. Controls were healthy and had none of the symptoms of Sjögren's syndrome. Participants in both groups had not been previously screened for sleep disorders. Participants had no history of significant respiratory, craniofacial, or cardiovascular disorders or recent respiratory tract infections (<1 month ago).

2.2. Study protocol

The study was approved by the Repatriation General Hospital Research and Ethics Committee. All participants provided informed written consent. The study protocol consisted of a preliminary visit during which baseline data were obtained, followed by the main experimental visit during which formal overnight polysomnography (PSG) was undertaken.

2.2.1. Preliminary visit

Subjects presented to the laboratory for a brief preliminary visit during which written consent was obtained and the subjects met with research personnel and were familiarised with the testing equipment and procedures. Demographic data and other pertinent information were obtained, including menopausal status, BMI, and other relevant medical history. Subjective daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS), which has been validated as a simple and reliable method for the measurement of persistent daytime sleepiness in adults [8,12]. An ESS value >10 was taken to indicate clinically significant daytime sleepiness. Fatigue was assessed using the Facit-F fatigue score [13]. Higher Facit-F scores are inversely proportional to the severity of fatigue. Participants also completed the Hospital Anxiety and Depression Scale (HADS), a validated screening tool for mood disturbance in adult populations [14]. HADS scores of one to seven are regarded as normal, scores of 8–10 as mildly elevated, and scores of >11 indicative of probable clinically significant anxiety or depression [15].

2.2.2. Overnight polysomnography

Subjects presented to the sleep laboratory at 20:30 h on the night of their study having abstained from alcohol, caffeine, and strenuous exercise for 12 h. A standard PSG protocol was followed to record two-channel EEG (C3–A2; C4–A1), left and right EOG, left and right EMGs, leg movements, ECG, and SaO_2 according to internationally-agreed criteria [16]. After set up, subjects were allowed to read or watch television until their usual bed time. Sleep architecture, including the frequency of arousals, was scored by a single, experienced sleep technician in the standard fashion [17,18] and sleep apneas and hypopneas were scored using the 1999 American Academy of Sleep Association standards and definitions [19]. An apnea was defined by a decrease in the amplitude of the nasal pressure signal of >90% from the baseline lasting for at least 10 s. Hypopneas were scored if there was a reduction of >50% in the amplitude of nasal trace or a reduction of <50% lasting $\geqslant$10 s with an oxygen desaturation of >3% or an arousal and the event duration was >10 s. The apnea–hypopnea index (AHI) was computed by dividing the total number of disordered breathing events by the total time asleep in hours. We used an AHI cut-off of $\geqslant$15/h to define a diagnosis of OSA [20]. We defined Obstructive sleep apnea syndrome (OSAS) as the presence of AHI $\geqslant$15/h along with ESS of >10. The pSS patients with the AHI values greater than 40/h were offered CPAP treatment and their responses to treatment followed over time.

2.3. Statistical analysis

Data were assessed for normality using Lilliefors adjusted Kolmogorov–Smirnov tests. Normally distributed data are presented as mean ± standard error of the mean (SEM), and were compared between pSS vs. control groups using independent samples Student's *t*-tests (PASW Statistics 18, IBM SPSS statistics, NY, USA). Non-normally distributed data are presented as median (interquartile range) and were compared between groups using independent samples Mann–Whitney *U* tests. The prevalence of OSA and OSAS were compared between groups using Fisher's exact test. Spearman's correlation analyses were used to explore the contribution of clinical and sleep study variables to excess sleepiness and fatigue. These included PSG variables such as AHI and arousal index (AI) and patient characteristics such as age, obesity, and HADS score.

3. Results

3.1. Baseline characteristics

A total of 46 middle-aged females were recruited to the study, 28 of whom were formally diagnosed with pSS, and 18 of whom were healthy controls. Complete data were collected from all participants, but fatigue scores are missing from six controls. The two groups were very similar in terms of their age and BMI, as per the study protocol; however, pSS patients had significantly increased daytime sleepiness, fatigue, anxiety, and depression, but not MWT scores, compared to the control group (Table 1).

As a group, pSS patients had a mild degree of daytime sleepiness and experienced higher fatigue compared with the controls. Though pSS patients had significantly higher anxiety and depression scores