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HEALTHY AGING RESEARCH

Prevalence of clinically probable obstructive sleep apnea in American veterans with chronic musculoskeletal pain

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Abstract

Background: Coexistence of obstructive sleep apnea (OSA) and chronic musculoskeletal pain (CMP) is common. Patients experiencing pain have a lower threshold for arousals associated with apnea episodes. Pain treatment with analgesics affects upper airway patency during sleep.

Methods: Eighty-one patients with CMP, and 100 without, were evaluated using the Berlin Questionnaire (BQ), which classifies patients as high or low risk for clinically probable OSA. Confounding variables including demographics (age, gender, BMI), medication use (sedatives, hypnotics, antidepressants), and Epworth sleepiness score (ESS) were compared between groups.

Results: There was no significant difference in gender, use of sedatives and antidepressants, BMI or ESS between cases and controls. There was, however, a significant difference in use of analgesics, and hypnotics. Patients in the control group were significantly older than cases. There was a significant difference in the proportion of high versus low risk BQ values between cases and controls. Logistic regression was performed while adjusting for covariates, which were significantly different between groups (use of analgesics, hypnotics and age). Cases with high-risk BQ scores were not sleepier than controls with high-risk BQ scores.

Conclusions: Patients with CMP have a high prevalence of clinically probable OSA. Sleepiness is not prevalent among patients with probable OSA and CMP. High-risk BQ patients were not sleepier than low risk BQ patients.

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Introduction

In the United States, obstructive sleep apnea (OSA) affects 4% of men and 2% of women between the ages of 30 and 70 years [1]. Evidence from methodologically strong cohort studies indicates that undiagnosed OSA, with or without symptoms, is independently associated with increased likelihood of hypertension, cardiovascular disease, stroke, daytime sleepiness, motor vehicle accidents and diminished quality of life [2]. The prevalence of OSA is high and remains undiagnosed in the general population. It has been found to be under-diagnosed even in patients with conditions associated with high prevalence of OSA, such as obesity and hypertension [3].

Defined as an unpleasant sensory and emotional experience associated with actual or potential tissue

damage [4], pain is a very common complaint. Chronic musculoskeletal pain (CMP) is defined as any muscular pain lasting more than three months. An estimated 39.4 million adults in the US reported persistent pain in 2010 [5]. A 2015 study showed that musculoskeletal pain is common in veterans, and is inversely associated with their functioning and general health status [6]. Pain and OSA both affect sleep quality, and an estimated 55% of chronic pain patients report restless/light sleep after pain onset. Likewise, poor sleep patterns in OSA patients can cause excessive daytime sleepiness and reduces quality of life by causing a wide range of deficits in mood, memory, executive functions and complex tasks [7].

Insomnia is also very common in OSA patients; about half of patients with sleep disorders experience insomnia [8, 9]. The comorbidity between OSA and insomnia is highly prevalent in patients presenting to sleep clinics [9]. Excessive daytime sleepiness is the most common symptom of OSA, but it is also prevalent in patients with and without OSA. Moreover, there is no significant association between daytime sleepiness and OSA. It is also known that self-reported sleepiness is not an objective measure; rather it underestimates the physiological state of sleepiness [9].

Most patients fail to recognize OSA symptoms therefore do not seek help. Moreover, OSA is not frequently diagnosed because physicians' clinical threshold for suspecting OSA is high [10]. The high cost and poor availability of polysomnography (PSG) – the "gold standard" test for the diagnosis of OSA [11] – are also contributing factors for a failure to diagnose this condition in the USA. PSG – usually performed in a sleep laboratory – is valid and reliable, but expensive and impractical for many patients. It is often, therefore, reserved for only the most severely symptomatic patients [12].

A study of 255 consecutive patients who underwent polysomnography for clinically suspected OSA suggested that sleep–wake manifestations of OSA are variable. In this study, 54.9% complained of insomnia; 33.4% reported difficulty in sleep onset, 38.8% reported difficulty in sustaining sleep, and 31.4% reported early morning awakenings [13]. This demonstrates the difficulty in accurately defining and diagnosing OSA in the general population based only on symptoms. Detection of OSA in patients with CMP is particularly important since these patients frequently undergo surgical procedures; untreated OSA can worsen their perioperative management. Studies suggest that 38% of patients remain undiagnosed for moderate-to-severe OSA before their surgeries [14]. Preoperative diagnosis of OSA may help improve post-operative airway and pain management because nocturnal hypoxemia with OSA has been shown to be associated with hypoalgesia and increased potency to opioid analgesia [15].

Previous data suggest that continuous positive airway pressure (CPAP) improves the inflammatory profile of patients with OSA [16]. We speculate that this may positively affect the course and prognosis of disorders causing CMP. Studies to design and answer these questions are required.

Questionnaires such as the Berlin Questionnaire (BQ) and the Epworth Sleepiness Scale (ESS) have been developed and validated to detect OSA in high-risk patients. The BQ identifies patients who are likely to have OSA [17], while the self-administered ESS was developed by Johns [18] to measure the subjective sensation of sleepiness. Sleep disorder clinics may prioritize patients for polysomnography based on the ESS results [19]. However, ESS alone may not be very practical in patients with CMP, since these patients frequently complain of insomnia with OSA. Therefore, to detect patients at risk of OSA, a high index of clinical suspicion is required and BQ may be considered a part of routine clinical evaluation.

The BQ contains 10 questions covering three categories. Based upon BQ results, patients can be classified as high risk (HR) or low risk (LR) for OSA (Appendix A), while ESS score measures sleepiness (Appendix B). Multiple questionnaires, e.g. STOP-Bang, BQ and STOP, are available to screen patients for OSA. These are all comparable, however since BQ is currently used in our primary care clinic, we chose to use BQ [20].

In patients with both OSA and CMP, the pain they experience may not allow them to be sleepy during daytime. We therefore believe that it is easy for the patient and physician to overlook OSA if the patient is not sleepy, or if they have a low ESS score, leading to under-diagnosis in this group. Therefore, in the

present study, we will use the BQ to measure the prevalence of clinically probable OSA in patients with CMP. We also aim to evaluate whether or not the ESS is effective at diagnosing clinically probably OSA in patients with CMP.

Methods

This single-center prospective case-controlled trial was conducted at the Captain James A Lovell Federal Health Care Center (FHCC), Illinois, USA. All patients meeting inclusion criteria were recruited from the Physical Medicine and Rehabilitation (PMR) clinics, while controls were recruited from the Pulmonary Medicine, Primary Care and Rheumatology clinics. Inclusion criteria were: patients > 18 years of age, presenting to PMR clinics, Pulmonary Medicine, Primary care and rheumatology clinics. Patients with diagnosed OSA, mental retardation, legal blindness, pregnancy and minors (i.e. younger than 18 years of age) were excluded from the study.

The study was approved by the Institutional Review Board of Edward Hines Jr. Veterans Administration Medical Center (VAMC), Illinois, USA, and was overseen by the FHCC Independent Data and Safety Monitoring Board. All patients were provided with detailed information and informed consent was obtained in each case.

Consecutive patients presenting to scheduled clinic visits and meeting the inclusion and exclusion criteria were invited to participate in the study. Cases were defined as patients having chronic musculoskeletal pain (CMP) for at least three consecutive months. Controls were defined as patients without CMP. CMP was defined as pain documented in the computerized patient record system (CPRS) for more than three consecutive months, arising from any of the following disorders: chronic low back pain, osteoarthritis, rheumatoid arthritis, gouty arthritis, systemic lupus erythematosus, scleroderma, spinal stenosis, cervical or lumber spondylosis, ankylosing spondylosis, Sjögren syndrome, fibromyalgia, trauma, war, sports, accident, or neoplastic disease involving bones, joints and muscles.

Of the 193 patients asked to participate, 10 declined, and one withdrew from the study. Therefore, total of 182 patients with and without CMP were enrolled over a period of one year (January 1, 2012 until December 31, 2012). Eighty-one patients had CMP (cases, n=81) and 101 patients had no CMP (controls, n=101). All patients were evaluated with ESS and BQ.

Demographic data (age, gender, BMI) were extracted from CPRS, as well as a history of pain and sleep-related medications for each patient, since these are the significant confounding factors affecting sleep. Medications recorded from medical charts included: non-steroidal anti-inflammatory drugs (NSAIDS); oxicam derivatives; aspirin (excluding when prescribed for coronary artery disease treatment or prevention); propionic acid derivatives; acetic acid derivatives; fenamates derivatives and selective COX-2 inhibitors; opioids; hypnotics; sedatives (benzodiazepines, barbiturates, non-benzodiazepines class, antihistamines) and antidepressants; mono-amine oxidase inhibitors (MAOI); selective serotonin receptor inhibitors (SSRI); and tricyclic antidepressants (TCA). Data recorded were reviewed by another researcher in the study to eliminate the chance of errors.

Statistical analysis

A Fisher's exact test was used to determine whether there was any significant difference in categorical variables between cases and controls. An unpaired t-test was performed for continuous variables. Variables that were found to be significantly different between the two groups were included as covariates in the logistic regression model. Logistic regression was used to determine whether there was a significant difference in the proportion of high risk and low risk BQ score values for OSA between cases and controls.

Results

Between cases and controls, no significant difference was found in gender, use of sedatives, use of antidepressants, BMI and ESS levels. There was, however, a significant difference in the use of analgesics between cases and controls ($p < 0.0001$), with only 35.6% of controls and 70.4% of cases using analgesics. Although not significant ($p=0.0590$), there was a difference in the use of hypnotics between

controls (6.9%) and cases (16.1%), in that cases were using more hypnotics. Finally the controls (65.76 ± 15.05) were significantly older than the cases (61.86 ± 11.35) (p=0.0481) (Table 1).

Using logistic regression and adjusting for covariates, there was a significant difference in the proportion of high-risk and low-risk BQ values between cases and controls in terms of use of analgesics, hypnotic's use and age (OR 2.32; confidence interval 1.18–4.57, p=0.0148) (Table 2). In controls, only 48.0% of individuals (48/101) were in the high-risk group, while in the cases, 69.1% of patients (56/81) were in the high-risk group.

Regarding sleepiness, the mean ESS score of our sample was 7.41 + 4.6 SD. Patients with high-risk BQ scores were not sleepier than those with low risk BQ scores (8.86 + 4.89 versus 5.35 + 3.65, p = 2.51). This underscores the lesser applicability of ESS in this particular population. However, when analyzing cases and controls separately, cases were not sleepier compared to the controls (8.13 + 4.49 versus 6.81 + 4.52, p = 0.11). Among cases, patients with high-risk BQ scores were sleepier compared to those with low-risk BQ scores (8.9 + 4.59 versus 6.32 + 3.74, p = 0.03). Among controls, patients with high-risk BQ scores were also sleepier compared to those with low-risk BQ scores (8.7 + 5.2 versus LR 4.9 + 3.5, p = 0.001).

These results indicate that the presence of chronic pain in patients with OSA does not make patients sleepier.

Discussion

OSA is more common in patients than controls across a variety of conditions. Our study also found that clinically probable OSA is higher in veterans with CMP versus veterans without CMP. Clinicians should exercise high clinical suspicion to assess OSA risk in this particular population. We know of no other studies that address this observation in patients with CMP.

We believe the etiology of the high prevalence of probable OSA in this group of patients is multifactorial; a sedentary life style, analgesic medication, muscle relaxants and inflammation may be involved in modulating risk. Patients with CMP tend to be less active [21] and suffer from reduced aerobic fitness compared with the normative population [22]. They also tend to be taking multiple medications, such as opioids. Opioids may affect sleep physiology and can lead to hypercapnia and hypoxia by inducing slow and irregular respiration. Their usage has also been associated with both central and obstructive sleep apnea [23]. Analgesic medications are known to affect pharyngeal muscular tone. In healthy, awake patients, phasic activity of the pharyngeal muscles contracts them immediately before inspiration, helping to resist the negative pressure generated by the diaphragm and keeping the airway from collapsing [24, 25].

Table 1. Comparison of demographic and confounding variables between cases and control

	Control	Case	OR (CI)	p-value
Female gender	6 (5.94%)	10 (12.35%)	0.45 (0.12-1.44)	0.1871
Analgesics	36 (35.64%)	57 (70.37%)	4.25 (2.19-8.45)	<0.0001
Sedatives	11 (10.89%)	11 (13.58%)	1.28 (0.47-3.47)	0.6502
Hypnotics	7 (6.93%)	13 (16.05%)	2.55 (0.89-7.98)	0.0590
Antidepressants	22 (21.78%)	19 (23.46%)	1.1 (0.51-2.34)	0.8589
BMI (mean ± SD)	29.62 ± 6.21	29.18 ± 5.74		0.6199
ESS (mean ± SD)	6.81 ± 5.91	8.13 ± 5.38		0.1198
Age (mean ± SD)	65.76 ± 15.05	61.86 ± 11.35		0.04808

Table 2. Logistic regression showing impact of confounding factors on prevalence of OSA in patients with chronic musculoskeletal pain

	Estimate	Std. error	Odds ratio	LCI	UCI	z value	Pr(>|z|)
Analgesics	1.47	0.34	4.35	2.24	8.47	4.33	< 0.0001
Hypnotics	0.87	0.57	2.38	0.77	7.33	1.51	0.1314
Age	0.00	0.01	1.00	0.97	1.02	-0.31	0.7534
Berlin	0.84	0.35	2.32	1.18	4.57	2.44	0.0148

This phasic pharyngeal contraction is markedly reduced by narcotic pain medications frequently used by patients with CMP, which predisposes patients to develop OSA [26].

Prevalence of OSA is high among subjects with pain, since most factors associated with pain are also associated with OSA as a risk factor. Several small studies found that OSA is frequently present in patients with rheumatic diseases [27, 28]. Laboni et al. studied PSG recordings in systemic lupus erythematosus patients with disabling fatigue. Of the 35 patients studied, 26% met criteria for sleep apnea [29]. Similar to the findings of our study, Reading et al. used the BQ with 164 rheumatoid arthritis (RA) patients and 328 non-RA control patients. Fifty percent of RA patients had high risk for OSA versus only 31% of control patients [30]. Another study, which used the BQ in a mixed general rheumatology clinic population, found that 35.2% of 423 participants were classified as being at high risk for sleep apnea [30].

We propose that upregulation of inflammation may be the key factor in subjects with OSA and pain. Data suggest that inflammatory markers are elevated in patients with OSA [10]. Likewise, elevated levels of proinflammatory cytokines (IFN-γ, IL-1β, IL-2, IL-6, IL-8 and TNF-α) also correlate with elevated pain scores in various neurological and rheumatologic disorders manifesting as chronic pain. One study also suggests that patients with OSA have a higher risk of developing autoimmune diseases [31–35], although another has showed that C-reactive protein, erythrocyte sedimentation rate or neutrophil-to-lymphocyte ratio measurements are not associated with the degree of upper airway obstruction [36].

Based on our findings, and the correlation of pro-inflammatory cytokine levels with pain intensity in patients with CMP, we believe that detection of untreated OSA and its optimal management can positively impact patients' condition and improve inflammatory markers that may result in improvement in chronic pain [16, 37].

Our study also explored the level of sleepiness across the two subject groups, using the ESS. We found that cases with high-risk BQ scores were not, in fact, sleepier compared to controls with high risk BQ scores (8.9 + 4.59 versus 8.59 + 5.23, p = 0.88). This finding suggests that ESS score cannot be relied upon to detect OSA in this particular population. We recommend that clinicians exercise caution when taking ESS scores into account, and consider other tools to assess sleep apnea risk. Clinicians should not overlook OSA in this population on the basis of low ESS scores.

We noted the following weaknesses in our study. Our sample size was small and made up predominantly of male veterans, so caution should be exercised when applying results to female patients. Case-control studies provide weak strength of evidence for detected findings. We did not perform polysomnography (PSG) to diagnose OSA. Instead, we detected patients with high risk of probable OSA using the BQ. Clinicians would agree that PSG is expensive and not practical for screening large groups, therefore BQ should be considered as a tool to screen for patients with likely OSA.

Conclusions

Patients with chronic musculoskeletal pain appear to have a higher prevalence of clinically probable OSA.

To our knowledge, this is the first prospective trial estimating the prevalence of OSA in patients with CMP. We propose a validation study to estimate the sensitivity and specificity of BQ and ESS scores for detecting OSA measured by PSG in this specific population.

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