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Original Article

Impact of obstructive sleep apnea on severe asthma exacerbations

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ABSTRACT

Background: Patients with asthma have a higher incidence of obstructive sleep apnea (OSA). However, the association between OSA and the exacerbation of severe asthma remains unclear. In this study, we aimed to investigate the prevalence of OSA in a cross-sectional study of asthma patients and to prospectively examine the significance of the effect of OSA on severe asthma exacerbations.
Methods: One hundred and forty-six patients with asthma and 157 matched-controlled individuals were enrolled in this study. The patients with asthma were prospectively studied for one year, and exacerbation episodes were identified based on the patients' medical histories. Lung function and the percentages of eosinophils in induced sputum samples were determined, and the frequencies of severe asthma exacerbations during the previous year were evaluated in the group of patients with asthma.
Results: The rates of OSA were 19.2% (28/146) among the patients with asthma and 9.6% (15/157) among the control individuals ($p = 0.016$). The frequency of severe asthma exacerbations was significantly higher among the asthma patients with OSA compared with those who did not have OSA ($p < 0.001$). The apnea–hypopnea index (AHI) correlated significantly with the number of severe asthma exacerbations ($r = 0.507$, 95% confidence interval [CI] 0.357–0.637, $p < 0.001$). Logistic regression analyses determined that the AHI was significantly associated with the occurrence of severe asthma exacerbations (odds ratio 1.322, 95% CI 1.148–1.523, $p < 0.001$).
Conclusions: Patients with asthma had a high prevalence of OSA, which was an important factor associated with severe asthma exacerbations.

1. Introduction

Asthma is a common chronic disease of the respiratory system that involves complex interactions among airflow obstruction, airway hyper-responsiveness, and inflammation. It is estimated that about 300 million people of all ages suffer from asthma [1] and, in 2011, more than half of these asthma patients experienced asthma attacks [2]. Severe asthma exacerbations increase the usage of health care resources and families' social and economic burdens. These attacks are associated with reductions in assessed quality of life and are potentially life-threatening [3,4]. Reducing the risk of exacerbations is a crucial/highly necessary treatment goal within asthma management guidelines. Therefore, identifying the risk factors for exacerbations could lead to appropriate early interventions and greatly benefit patients. While the findings from previous studies have identified that previous asthma exacerbations, the use of bronchodilator therapy, reduced pulmonary function, chronic sinusitis, gastroesophageal reflux disease, and the need for larger amounts of controller therapy are among the risk factors for asthma exacerbations [5–10], comorbid conditions have received far less attention.

Findings from studies suggest a bidirectional relationship between obstructive sleep apnea (OSA) and asthma. The findings from epidemiological studies have demonstrated that patients with asthma have a higher prevalence of OSA [11,12]. A population-based cohort study discovered that the overall incidence of OSA was 2.51 times greater in the cohort of patients with asthma than in the comparison cohort [11]. The findings from a population-based prospective epidemiological study demonstrated that asthma was associated with both new-onset OSA and OSA with habitual sleepiness [12]. Likewise, patients with OSA have been reported to display many of the symptoms associated with asthma. Alharbi et al. reported that patients with OSA had a high prevalence of asthma (35.1%) [13]. The findings from a 14-year prospective study also suggested a pathogenic role for asthma in sleep-disordered breathing [14]. Accumulating evidence suggests that OSA contributes to poor asthma

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control [10,15–17], while continuous positive airway pressure treatment can improve the quality of asthma patients' lives [17].

However, it remains unclear whether OSA affects severe exacerbations in patients with asthma. Understanding the impact of OSA on severe asthma exacerbations is a necessary element in the efforts to reduce the burden of both OSA and asthma. Therefore, we performed a prospective cross-sectional study to investigate the prevalence of OSA among patients with asthma as well as the associations between OSA indices and severe asthma exacerbations.

2. Methods

2.1. Ethical approval and informed consent

The study's protocols and the patient consent documents were approved by the ethics committee at Xiangyang Hospital, Hubei University of Medicine and Renmin Hospital, Wuhan University. All of the participants were able and willing to provide informed consent and to complete our study.

2.2. Subjects

Subjects aged 18–65 years who had asthma, which was defined as a minimum 12% increase in the post-bronchodilator forced expiratory volume in 1 s (FEV1) and >200 mL of the FEV1, or a positive methacholine challenge test reaction, were recruited from in-patients who had been discharged from the hospital and returned for routine follow-up visits. The study also included subjects who were out-patients with physician-diagnosed asthma, were being treated with inhaled glucocorticoids (400 mg of fluticasone or its equivalent), and had not changed their controller therapy for at least eight weeks before they were enrolled to participate in the study at Xiangyang Hospital and Renmin Hospital. Healthy matched-controlled subjects were recruited from health centers based on their ages, body mass indices (BMIs), and sex. Subjects were excluded if they had comorbidities that included respiratory disorders other than asthma, active gastro-esophageal reflux disease, or histories of malignant diseases within five years of the study commencing, if they had an FEV1 that was <50% of the predicted value, had initiated and withdrawn asthma medications during the follow-up period, had used systemic corticosteroids daily, or had used long-term oxygen therapy.

We collected data about the patients' medical histories, and about their physical examinations, asthma control assessments, and spirometry tests that were undertaken at each clinic visit between January 2012 and December 2015. In total, 146 patients with asthma and 157 control individuals met the study's entry criteria and completed this study.

2.3. Definition of a severe asthma exacerbation

A severe asthma exacerbation was defined as asthma symptoms that required an urgent health care visit, a visit to a physician's office, systemic corticosteroids, or an increase from the stable maintenance dose for at least three days or hospitalization [18]. The numbers of severe asthma exacerbations that occurred between January 2012 and December 2015 were recorded, and we determined the severe acute exacerbation frequencies within the preceding year.

2.4. Obstructive sleep apnea evaluation

All of the subjects underwent full-night PSG at the sleep laboratories at Xiangyang Hospital using a digital system (Compumedics E-series EEG/PSG Recording System, Abbotsford, Victoria, Australia). As recommended by the American Academy of Sleep Medicine (AASM), the following factors were assessed simultaneously and continuously: airflow via a thermocouple and nasal pressure, electroencephalograms, electro-oculograms, electrocardiograms, electromyograms of the chin and leg muscles, thoracic and abdominal respiratory efforts using inductance plethysmography, snoring, body positions, oxyhemoglobin saturation (SpO2), and the pulse rates. The findings were scored using the criteria outlined in the 2007 AASM Manual for Scoring Sleep and Associated Events, version 1 [19]. Hypopnea was defined as an event with a ≥30% decline in the baseline amplitude of the nasal pressure for ≥10 s accompanied by a ≥ 4% decrease in the SpO2 based on the pre-event baseline value. Data describing the apnea–hypopnea index (AHI), the mean oxygen saturation level, and the percentage of the time that the oxygen saturation was <90% (T_{Sat90}) were recorded.

2.5. Sputum induction and processing

In accordance with the European Respiratory Society's recommendations [20], the subjects with asthma were pre-treated with salbutamol (200 mg) that was inhaled using a metered-dose inhaler, then, 10 min later, saline (3%) was nebulized for 20 min for sputum induction. Each sample collected was processed immediately as described next. The contaminating saliva was separated from the sample, then, 0.1% dithiothreitol was added to the sputum at a ratio of 1:4. The mixture was then placed in a shaking water bath at 37 °C for 20 min, and it was homogenized. The sample was further diluted with an equal volume of phosphate buffered saline. After filtering the suspension through gauze to remove any mucus and centrifugation, the differential cell count was determined and at least 400 non-squamous cells were counted that had been stained using the May Grunwald Giemsa method. Only samples with cell viabilities of >50% and squamous cell contamination of <20% were considered adequate. The slides were read by two independent investigators.

2.6. Statistical analysis

All of the statistical analyses were performed using IBM® SPSS® version 19.0 (IBM Corporation, Armonk, NY, USA.). The data are presented as the means ± standard deviations or as the medians (interquartile ranges [IQRs]), based on whether the variables were normally distributed or non-normally distributed. Descriptive statistics were used to characterize the subjects within the asthma groups and control groups. The differences between groups were analyzed using Student's *t* test for the parametric variables and the Mann–Whitney test for the non-parametric variables. Spearman's rank correlation test was used when appropriate. Logistic regression analysis was used to determine whether individual factors were associated with asthma exacerbations. The relationship between the groups was evaluated using the χ^2 test. A value of $p < 0.05$ was considered statistically significant.

3. Results

One hundred and forty-six patients with asthma and 157 control individuals completed this study. Table 1 shows the subjects' baseline characteristics. There were no significant differences between the groups in relation to age, sex, the FEV_1, the forced vital capacity (FVC), the AHI, the BMI, the mean oxygen saturation level, the minimum oxygen saturation level, and the T_{Sat90}.

Forty-three patients were diagnosed with OSA using PSG, comprising 28 patients with asthma and 15 control individuals (Table 2). OSA was significantly more prevalent among the patients with asthma than among the control subjects, and the relative risk was 2.25 (95% confidence interval [CI] 1.15–4.40, $p = 0.016$) (Table 2).