Original Article

Association Between Asthma and Obstructive Sleep Apnoea

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ABBRIVATIONS USED IN THIS ARTICLE

OSA = Obstructive Sleep Apnoea
PSG = Polysomnography
IL = Interleukin
AHI = Apnoea-Hypopnoea Index
FeNO = Fractional Exhaled Nitric Oxide
hsCRP = High Sensitivity C-Reactive Protein
ACT = Asthma Control Test
PFT = Pulmonary Function Testing
GINA = Global Initiative for Asthma
AASM = American Academy of Sleep Medicine
EEG = Electroencephalography
EOG = Electrooculography
EMG = Electromyography
FVC = Forced Vital Capacity
FEV_1 = Forced Expiratory Volume in First Second
TST = Total Sleep Time
REM = Rapid Eye Movement
SGRQ = St. George's Respiratory Questionnaire
ppb = Parts Per Billion
BMI = Body Mass Index.

Abstract

Background. Asthma and obstructive sleep apnoea (OSA) are the commonest pulmonary diseases worldwide and contribute to significant morbidity and mortality.

Methods. Fifty patients aged 18 years and above with moderate to severe asthma, presented to our out-patient clinic during 2016-2017, were screened for OSA using a self-reported STOP BANG Questionnaire. Of these, 30 were found to be at risk of OSA (STOP BANG score >2) and were included in the study. These 30 patients underwent diagnostic polysomnography (PSG), inflammatory markers interleukin (IL)-4, IL-5, IL-6, IL-13, high sensitivity c-reactive protein, fractional exhaled nitric oxide (FeNO) testing. Their quality-of-life and asthma control was evaluated with St. George Respiratory Questionnaire score and Asthma Control Test, respectively.

Results. After PSG, OSA, apnoea-hypopnoea index (AHI) >5/h was found in 15/30 (50%) cases with moderate and severe asthma (N=15 each). In moderate asthma 6/15 (40%) and in severe asthma 9/15(60%) were diagnosed to have OSA. Asthma patients with OSA fared poorly in asthma control test questionnaire and St. George's Respiratory Questionnaire (P=0.01) in comparison to those without OSA.

Conclusions. Our study indicates high prevalence of OSA among patients of moderate to severe asthma which negatively affects quality of sleep and asthma control that further leads to poor quality-of-life in these patients. Thus, highlighting the need of maintaining high index of suspicion in identifying OSA among patients of moderate to severe asthma.

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Introduction

Asthma and obstructive sleep apnoea (OSA) are amongst common pulmonary diseases worldwide.[1] The prevalence of asthma in general population is about 1%–18% in different countries.[2] In India, about 2.1% of the population is said to be affected by asthma,[3] while, the estimated prevalence of OSA in general population varies. The Wisconsin Sleep Cohort Study reported prevalence of OSA as 4% for men and 2% for women.[4] The existence of these diseases in isolation is well studied but several reports regarding their concurrent occurrence have emerged in last few decades.[5] The simultaneous occurrence of asthma and OSA is also referred to as "alternative overlap syndrome" by some researchers.[6]

Frequency of severe asthma exacerbations was found to be significantly high among the asthma patients with OSA compared with those who did not have OSA.[7]

Also, it has been found that there is a greater prevalence of hypertension and cerebrovascular diseases in severe asthmatics with OSA. This is hypothesised to be the result of OSA-related inflammation which can drive tissue remodelling through increased oxidative stress. In animal models of chronic intermittent hypoxia, OSA was found to cause myocyte hypertrophy, fibrosis and increased apoptosis.[8]

These data suggest worse asthma outcomes and quality-of-life in patients with co-existent OSA, but the results across various studies is variable and there are very few studies done on Indian population. Also, the "alternative overlap" is a lesser studied entity than its counterpart the "overlap syndrome" (chronic obstructive pulmonary disease with OSA). Thereby necessitating the need for further research in this field to understand the bi-directional nature of the disease process. So that in future we will be able to formulate better and individualised management protocols for such patients. Hence, aim of the present study was to ascertain the prevalence of asthma with OSA (alternative overlap syndrome), assess its implications, examine its polysomnographic profile and compare it with the patients of asthma without OSA.

Material and Methods

The study was conducted at the Outpatient Clinics in the Department of Pulmonary Medicine of our Institute after obtaining clearance from the Ethics Committee. Written informed consent was obtained from all the patients.

Fifty patients diagnosed to have moderate to severe asthma during one year (2015-2016) were screened for OSA using a self-reported questionnaire (STOP BANG).[9] Out of these 30 patients were found to be at risk of OSA (STOP BANG score >2) and they were recruited in the study. These patients then underwent detailed clinical and laboratory evaluation followed by in lab (Type 1) diagnostic polysomnography (PSG), serum inflammatory marker (IL-4, IL-5,IL-6,IL-13, hsCRP [high sensitivity c-reactive protein]) and FeNO testing. Their quality-of-life and asthma control were evaluated with SGRQ (St. George Respiratory Questionnaire) score and Asthma Control Test (ACT), respectively. Diagnosis of asthma was confirmed by pulmonary function test (PFT) and its severity was classified as per Global Initiative for Asthma (GINA 2015)[10] guidelines.

Patients who were unable to fill the questionnaire properly, pregnant and lactating females and patients with significant cognitive impairment or poorly controlled psychiatric disorder were excluded.

The sample size calculation was based on reported prevalence of OSA in moderate to severe asthma as mentioned above,[5] by using the formula $[n = z^2p(1-p)/d^2]$, where n is sample size, p is prevalence, z is confidence interval and d is precision, the computed minimum sample size was 24 for asthma. Hence, we planned for a sample size of 30.

All subjects enrolled were evaluated for their clinical symptoms by detailed history including sleep history, general physical examination and systemic respiratory examination. All of the recruited subjects underwent following investigations: haemoglobin, total and differential leukocyte counts, spirometry with reversibility, absolute eosinophil count, chest radiograph (postero-anterior view). Also, electrocardiogram, kidney function test, liver function test, arterial blood gas analysis and other appropriate investigations were done, as and when required.

Patients with asthma recruited for the study underwent (in lab) type 1 diagnostic polysomnography (PSG) according to American Academy of Sleep Medicine (AASM) guidelines, comprising of 7 channels, namely electroencephalography (EEG), electrooculography (EOG), tibialis anterior electromyography (EMG), airflow measured by nasal transducer and thermistor, pulse oximeter and chest and abdominal effort leads.[11] Polysomnographic recordings were scored manually using the EMBLA 2000 by a certified polysomnographic technologist, with physician review. A total sleep time >4 hours was required.

On the basis of AHI, OSA was defined as apnoea-hypopnoea index (AHI) ≥5/hour. As per AASM recommendations, the AHI was calculated by dividing the total number of apnoea plus hypopnoea events by the number of hours of sleep.[11] After PSG, patients were classified as per Chicago criteria, *i.e.* normal (AHI <5/

hour), mild OSA (5-15/hour), moderate OSA (16-30/hour) and severe OSA (>30/hour).[12]

Apnoea was defined as complete cessation of airflow for at least 10 seconds. The event was marked obstructive if during apnoea there was an effort to breathe. Hypopnoea was defined as an abnormal respiratory event with at least a 30% reduction in airflow as compared to baseline lasting at least 10 seconds, and with >4% oxygen desaturation.[11]

Measurement of FeNO levels, serum levels of IL-4, IL-5, IL-6, IL- 13, hsCRP was recorded. The level of asthma symptom was assessed by the ACT and quality-of-life assessment was done through SGRQ score.

Statistical Analysis

Data was entered into Microsoft Office Excel and analysed using Statistical Package for Social Sciences (SPSS, version 17). The descriptive statistics in the form of mean and standard deviations or proportions were used to characterise the study sample. For quantitative data, difference between the means of the two groups was compared by t-test (for normal distribution) or Mann-Whitney test (for non-normal distribution). A P-value of less than 0.05 was considered statistically significant.

Results

Of the 50 patients with moderate to severe asthma who were screened for OSA, 30 patients were found to be at risk of OSA (STOP BANG score >2) and were recruited in the study. Out of the 30 asthmatics who were recruited in the study, there were 14 males. Their age ranged from 36-56 years. After PSG, OSA (AHI ≥5/h) was found in 15 out of 30 cases. Out of 15 OSA cases, 9 had mild OSA (AHI 5-15), 3 with moderate OSA (AHI 15-30) and 3 with severe OSA (AHI >30).

Out of 21 obese cases, 10 (47.6%) were found to have OSA and out of 9 non-obese cases 5 (55.6%) were found to have OSA. The difference was statistically insignificant (P=0.34).

Among 15 cases of asthma with OSA, 9 (60%) were severely asthmatic and 6 (40%) were in moderate category. In non-OSA cases, lesser number of asthma cases were in severe category, *i.e.* 6 out of 15 (40%) and rest were in moderate category. Although this difference was not found to be statistically significant (P=0.711).

The presence of OSA in asthma patients was analysed with respect to the parameters of PFT, *i.e.* forced vital capacity (FVC), (forced expiratory volume in one second (FEV_1) and FEV_1/FVC. No significant difference was found in these PFT parameters between the asthmatics with OSA and without OSA (Table 1).

Table 1. PFT parameters in asthma patients

PFT Parameter	Asthma		P value
	Without OSA (N=15) (Mean±SD)	With OSA (N=15) (Mean±SD)	
FEV_1/FVC	62±12.5	66.16±11.8	0.28
FVC (%)	79.67±22.9	74.2±22.2	0.921
FEV_1 (%)	58±14.6	74.2±16.5	0.963

Polysomnography parameters in relation to the asthma severity were also analysed. There was no significant difference between moderate and severe asthma cases for sleep period, total sleep time (TST) and sleep latency to REM (Table 2). The overall sleep efficiency was poor, *i.e.*<80% (normal >85%)[13] but no statistical significant difference (P=0.31) was found based on the severity of asthma.

Asthma patients with and without OSA were also analysed against several inflammatory markers (IL-4, IL-5, IL-6, IL-13, hsCRP and FeNO). But no statistical significant difference was found in the levels of the markers of inflammation between asthmatics with OSA and without OSA (Table 3).

Table 2. Comparison of PSG parameters between moderate and severe asthma cases

PSG Parameters	Asthma		P value
	Moderate (Mean±SD)	Severe (Mean±SD)	
Sleep period (in minutes)	404.9±77.4	399.7±73.8	0.8
Total sleep time (in minutes)	318.7±73.5	329.7± 99.4	0.7
Sleep latency to REM (in minutes)	127.9± 81.1	134.2±104.9	0.8
Sleep efficiency (%)	77.2±14.1	78.8±16.5	0.7

Table 3. Inflammatory markers and FeNO in asthma patients

Inflammatory markers	Asthma		P value
	Without OSA (Mean±SD)	With OSA (Mean±SD)	
IL-4 (pg/mL)	3.5±2.5	2.5±1.7	0.48
IL-5 (pg/mL)	2.5±1.7	3±2.6	0.39
IL-6 (pg/mL)	33.4±19.1	61.4±15.7	0.52
IL-13 (pg/mL)	7.3±11.2	9.1±12.3	0.21
hsCRP (pg/mL)	91.5±41.5	144±21.6	0.427
FeNO (ppb)	30.4±3.6	23±10	0.86

The analysis of SGRQ score and ACT was done in order to determine impact of OSA on asthma. The statistically significant poor score was found for SGRQ and ACT (P=0.001 and P=0.03, respectively) in asthmatics with OSA (Table 4).

Table 4. SGRQ score and ACT score in asthma patients

Variable	Asthma		P value
	Without OSA (Mean±SD)	With OSA (Mean±SD)	
SGRQ score	38.4±10.4	54.9±10.9	<0.001
ACT score	19.6±2.6	6.4±2.4	0.006

Discussion

The estimates of prevalence of concomitant occurrence of asthma and OSA varies. A prospective study over four-year period has demonstrated that asthma was associated with an increased risk of OSA. In this study new onset OSA occurred in 27% patients of asthma as compared to 17% in the controls. The possible shared direct mechanistic links between OSA and asthma include mechanical effects, intermittent hypoxia, nerve reflex, inflammation, leptin, etc. Indirect mechanistic links include steroid use (oral or inhalational), nasal diseases, smoking, obesity, and gastroesophageal reflux disease.[14]

In the study done by Guven *et al*[15], 74.5% (N=35) of the difficult to treat asthma patients had OSA, in which 11 had mild OSA and 24 had moderate to severe OSA. While Julien *et al*[5], found that prevalence of OSA (AHI ≥5/h) in severe asthma was 50%, 23% in moderate asthma and 12% in controls amongst age-, sex- and BMI-matched individuals who underwent overnight PSG. Yigla *et al*[16] found that OSA occurred in 96% subjects of severe asthma. In our study, 30 out of 50 asthmatics were found to be at risk for OSA (STOP BANG score >2). But after PSG (gold standard) was done in these 30 cases, OSA (AHI ≥5/h) was found in 15 (30%) cases.

Out of 30 patients of asthma who underwent PSG, 21 were obese and 9 non-obese patients. No significant difference was found in the occurrence of OSA among obese and non-obese patients. Hence, high prevalence of OSA was reported irrespective of the obesity status which may indicate that asthma *per se* may be responsible for OSA. Although Peppard *et al*[17] had concluded that, amongst all the risk factors of OSA, increased weight positively correlated with the AHI. They found that the patients who gain 10% of their body weight tend to show an increase of approximately 32% in the AHI and also, 10% reduction in weight resulted in a 26% reduction in the AHI.[17]

On overall evaluation of the severity of asthma in the study participants, there were 15 patients each of moderate and severe asthma. Further, in the non-OSA group, there were less number of severe asthma patients, whereas in OSA group more patients had severe asthma. Thus, we observed a higher occurrence of severe asthma in OSA patients compared to non-OSA patients. Although, statistical significance could not be observed, findings of our study are similar to an earlier study in which authors reported OSA in 23% patients with moderate asthma and 50% cases of severe asthma.[5] Another contributory factor to above findings in our study can be the higher incidence of OSA in the local Asian asthmatic population due to some specific cranio-facial features.[18]

On evaluation the parameters of PFT, no statistically significant difference was found between asthma patients with and without OSA. This may be due to our small sample size and limited time duration of the study. Wang *et al*[19] had demonstrated that OSA leads to a decline in FEV_1 over a five-year period.

On comparing various PSG related parameters between moderate and severe asthma cases, no significant difference was found for sleep period, TST, latency to REM and sleep efficiency between the moderate and severe asthma groups. Although, sleep efficiency was poor (less than 85%) and latency to REM was more than 120 minutes in both the groups. Hence, we conclude that the presence of asthma adversely affects the sleep quality.

There was no statistically significant difference between patients of asthma with OSA and those with asthma alone on evaluating the inflammatory markers (IL-4, IL-5, IL-6, IL-13, hsCRP) and FeNO. It should be noted here that IL-4, IL-5, IL-13 and FeNO are the markers of eosinophilic inflammation. As, eosinophils are implicated in regulation of Th1/Th2 response through synthesis of IL-4 and promotion of IL-4, IL-5 and IL-13 secretion by CD4+ T-cells.[20] Also the value of exhaled FeNO is a predictor of steroid responsiveness even in the absence of induced sputum eosinophils.[21] Thus, our findings further support the findings of an earlier study, that reported occurrence of a non-eosinophilic inflammation in patients of asthma with OSA.[22] Thus, increasing steroids doses may have a potential deleterious effect in the setting of neutrophilic/non-eosinophilic inflammation and that should be cautioned in this setting. Also, steroids in themselves are known to contribute to neutrophilic airway infiltration. Hence, these patients need to be identified separately for better targeted and individualised treatment.

In order to understand the impact of OSA on asthma control and quality-of-life, asthmatics were subjected to

the asthma control test and SGRQ. It was found that asthmatics with OSA scored poorly in both of these sets of questionnaires and the difference between asthmatics with OSA and without OSA was statistically significant. Thus, we conclude that OSA negatively affects asthma control and quality-of-life.

Conclusions

Our study has supported the concept of a causative link between OSA and poor asthma control. However, the present study has methodologic limitations, including lack of appropriate controls and small subject numbers, which limit the impact of the findings. Larger-scale randomised controlled trials are required in order to formulate better and targeted management protocols for such cases.

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