Polysomnographic variables in Alternate overlap syndrome: data from sleep heart health study

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ABSTRACT

Objective: To evaluate influence of asthma on polysomnographic variables of patients with obstructive sleep apnea (OSA).

Methods: A longitudinal retrospective study using data collected from the Sleep Heart Health Study (SHHS).

Results: All 2822 patients included had OSA, 2599 were non-asthmatic whereas 223 were asthmatic. Average BMI for non-asthmatics was 28.8 kg/m² whereas asthmatics had 29.5 kg/m². Median pack-years of smoking was 1.42 vs. 1.98 in non-asthmatic and asthmatic groups, respectively. Sex distribution, age (in years), BMI, FEV₁, FVC, AHI ≥ 4% (all apneas, hypopneas with ≥4% oxygen desaturation or arousal per hour of sleep), RDI ≥ 3% (overall respiratory disturbance index at ≥3% oxygen desaturation or arousal), sleep latency, percentage of sleep time in apnea/hypopnea and Epworth sleep scale score were all statistically significant. Non-asthmatics had greater AHI (12.63/hr) compared to asthmatics (11.34/hour), RDI in non-asthmatics and asthmatics was (23.07 vs 20.53; p = 0.009). Sleep latency was found to be longer in asthmatics 19.8 minutes vs. 16 minutes (p = 0.006). Epworth sleepiness scale score was high in asthmatics (9 vs. 8, p = 0.002).

Conclusion: OSA was found more severe in non-asthmatic subgroup, but asthmatics had statistically significant higher Epworth sleepiness scale score and sleep latency. Clinicians should be vigilant and keep low threshold to rule out OSA particularly on patients with difficult to control asthma, smoker, GERD, obese and nasal disease.

1. Introduction

The estimated global asthma burden is 235 million individuals, contributing to 180,000 yearly mortality and the prevalence has been increasing [1]. Asthma spares no race, age, socioeconomic status, geographic or ethnicity but its burden is specifically high in the urban areas [2]. Airway obstructive diseases, like asthma and chronic obstructive pulmonary disease (COPD), have a common basis of local and systemic inflammation. Also, they have been classically associated with nocturnal mortality and morbidity [3,4]. Interestingly, nocturnal asthma and obstructive sleep apnea (OSA) share similar features, and this has led to multiple studies on asthma relating to nocturnal sleep and OSA [5–7]. A clear association between OSA and asthma has not been established yet but has been on speculation for decades as seen in one classic study done by Shu Chan C. et al. [8]. Correlation between poor asthma-related symptoms and sleep-disordered breathing (S) have been described in the literature [9]. OSA in COPD patients is termed ‘Overlap syndrome’ which is common in literature, but there is a relative lack of study of OSA and asthma. Emerging evidence of an association between OSA and asthma have led some scholars to coin the term sole syndrome ‘Alternate overlap syndrome.’

2. Patients and methods

2.1. Study design

We conducted a longitudinal retrospective study using data collected from the Sleep Heart Health Study (SHHS) [10–13].

2.2. Data source

Data were compiled from the SHHS which is a large multi-center cohort study implemented by the National Heart Lung & Blood Institute to determine the cardiovascular and other consequences of SDB. It tested whether sleep-related breathing was associated with an increased risk of coronary heart disease, stroke, all-cause mortality, and hypertension. The

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SHHS1 dataset represents data from the baseline and first follow-up visit, collected on 6,441 individuals between 1995 and 1998. All patients in this database are de-identified to protect their privacy. Therefore, informed consent was waived to conduct our study.

2.3. Patient selection

In the SHHS1 dataset, 6,441 participants aged 40 years and older were enrolled between November 1st, 1995 and January 31st, 1998 to take part in SHHS Visit 1. We identified participants diagnosed with OSA, defined as an apnea-hypopnea index (AHI) ≥ 5 based on polysomnographic data [10–12]. We then divided the participants into two cohorts based on a history of asthma. Patients with missing data were then excluded from this study. This left a total of 2,861 records for final analysis.

2.4. Statistical analyses

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS), version 25.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were provided for all study variables. Continuous variables were not normally distributed and presented as median and IQ range. Categorical variables were presented as count and percentage. Statistical tests of significance (Mann-Whitney U test for continuous variables and Chi-Square test or Fischer’s Exact test for categorical variables) were conducted to assess differences between the cohorts. A two-tailed p-value ≤0.05 was regarded as statistically significant.

3. Results

Baseline demographic, clinical, spirometry and polysomnographic characteristics of the study population are summarized in Table 1.

The total number of patients included in the study was 2,822. All enrolled patients had OSA, defined as AHI ≥ 5 with ≥ 4% desaturation or arousals per hour of sleep. Of all the included patients, only 223 were asthmatics whereas 2,599 were non-asthmatics. The male-to-female ratio was 1.46 with the median age of

| Table 1. Baseline demographic, clinical, spirometry and polysomnographic characteristics of the study population. |
|---|---|---|---|---|---|---|
| Characteristics | Count (Percent) | Median (IQ range) | Total (n = 2599) | Non-Asthmatics (n = 223) | Asthmatics (n = 232) | p Value |
| Gender | | | | | | |
| Male | 1675 (59.4) | 1564 (56.2) | 111 (49.8) | 0.003* |
| Female | 1147 (40.6) | 1035 (39.8) | 112 (50.2) |
| Age (Years) | 66 (56–74) | 66 (58–74) | 64 (54–71) | 0.001* |
| Race | | | | | | 0.925 |
| Black | 228 (8.1) | 209 (8.0) | 19 (8.5) |
| White | 2429 (86.1) | 2339 (86.1) | 190 (82.5) |
| Others | 165 (5.8) | 151 (5.8) | 14 (6.3) |
| BMI (kg/m²) | 28.8 (25.8–32.3) | 28.8 (25.8–32.2) | 29.5 (26.5–33.7) | 0.013* |
| Comorbidities | | | | | | |
| Diabetes | 252 (9.3) | 2712 | 226 (9.0) | 26 (12.4) | 0.073 |
| Hypertension | 1383 (49.0) | 2822 | 1280 (49.2) | 103 (46.2) | 0.210 |
| Previous MI | 59 (15.0) | 393 | 51 (15.2) | 8 (13.8) | 0.493 |
| Stroke | 22 (5.6) | 392 | 18 (5.4) | 4 (6.9) | 0.415 |
| Smoking (pack-years) | 1.47 (0–25) | 2686 | 1.42 (0–25) | 1.98 (0–24) | 0.809 |
| Spirometric Parameters | | | | | | |
| FEV₁ | 2.66 (2.11–3.27) | 2721 | 2.68 (2.14–3.29) | 2.44 (1.87–3.09) | < 0.001* |
| FVC | 3.53 (2.78–4.31) | 2678 | 3.54 (2.79–4.32) | 3.42 (2.72–4.21) | 0.046* |
| PSG Parameters | | | | | | |
| AHÍ ≥ 4% | 12.52 (7.86–21.14) | 2822 | 12.63 (7.92–21.26) | 11.34 (7.27–19.65) | 0.015* |
| Anusol index | 20 (14.63–27.65) | 2738 | 20.1 (14.7–27.77) | 18.93 (14.0–26.18) | 0.131 |
| Average SaO₂ during NREM sleep | 94.18 (92.94–95.30) | 2822 | 94.2 (92.94–95.32) | 93.89 (92.71–95.13) | 0.162 |
| Average SaO₂ during REM sleep | 93.89 (92.23–95.15) | 2738 | 93.94 (92.23–95.16) | 93.6 (92.26–94.93) | 0.272 |
| Minimum SaO₂ in non-REM sleep | 86 (83–88) | 2732 | 86 (83–88) | 86 (82–88) | 0.995 |
| Minimum SaO₂ in REM sleep | 85 (81–88) | 2719 | 85 (81–88) | 84 (81–88) | 0.378 |
| RDI ≥ 3% | 22.89 (16.42–34.38) | 2738 | 23.07 (16.52–34.67) | 20.53 (15.04–30.94) | 0.009* |
| Time in REM sleep | 77 (57–94) | 1288 | 77 (57–94) | 78 (56.5–97.0) | 0.780 |
| Percent of sleep time with SaO₂ < 85% | 0.019 (0–0.310) | 2818 | 0.018 (0–0.318) | 0.039 (0–0.276) | 0.449 |
| Percent of sleep time with SaO₂ < 90% | 1.236 (0.255–4.955) | 2818 | 1.212 (0.253–4.974) | 1.397 (0.352–4.825) | 0.452 |
| Percent of time in Apnea | 2.66 (0.8–6.87) | 2822 | 2.80 (0.84–7.03) | 1.66 (0.49–8.43) | < 0.001* |
| Percent of time in Hypopnea | 20.29 (15.4–26.43) | 2822 | 20.38 (15.61–26.52) | 19.07 (13.49–26.14) | 0.011* |
| REM Latency | 74 (55–106.5) | 2552 | 74 (54.5–106) | 76 (58.5–106) | 0.452 |
| Sleep efficiency | 82.79 (75.06–88.01) | 1652 | 82.85 (75.17–88.08) | 82.46 (73.84–87.92) | 0.679 |
| Sleep latency | 16.5 (9.5–28) | 1652 | 16.0 (9.5–28.0) | 19.8 (12.6–31.4) | 0.008* |
| Epworth Sleepiness Scale score (Sleep Heart Health Study Visit One (SHHS1)) | 8 (5–11) | 2731 | 8 (5–11) | 9 (5–12) | 0.002* |

IQ range, interquartile range; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; FeV₁, forced expiratory volume in one second; FVC, forced vital capacity; PSG, polysomnography; AHÍ, apnea-hypopnea index; RDI, respiratory disturbance index; REM, rapid eye movement; SaO₂, Oxygen saturation.
66 years (58–74 years). The majority included cases were whites (86%), whereas black and other races only represented 8.1% and 5.8%, respectively. Median BMI was higher for asthmatics when compared to non-asthmatics (29.5 vs. 28.8 Kg/m², respectively). Median pack-years of smoking was 1.42 in non-asthmatics vs. 1.98 in asthmatics. Sex distribution, age (in years), BMI, history of COPD, FEV₁, FVC, AH1 ≥ 4% (all apneas, hypopneas with ≥ 4% oxygen desaturation or arousal per hour of sleep), RDI ≥ 3% (overall respiratory distribution index at ≥ 3% oxygen desaturation or arousal), percent sleep time in apnea, sleep latency, percentage of sleep time in Apnea/Hypopnea and Epworth sleep scale score were all statistically significant. Non-asthmatics had greater AH1 (12.63/hour) as compared to asthmatics (11.34/hour, p = 0.015). RDI was significantly higher in non-asthmatics when compared to asthmatics (23.07 vs. 20.53; p = 0.009). Sleep latency was found to be longer in asthmatics (19.8 minutes vs. 16 minutes, p = 0.008). Epworth sleepiness scale score was significantly higher in asthmatics (9 vs. 8, p = 0.001). Percent of sleep time with saturation less than 85% and 90% were both more in asthmatics than non-asthmatics, (0.039 vs. 0.018 and 1.397 vs 1.212, respectively).

4. Discussion

OSA and asthma are both highly prevalent conditions. Epidemiologic data show the prevalence of OSA as high as 70% among asthmatics [14,15]. Asthma and OSA share several risk factors together like obesity, smoking, gastroesophageal reflux, sinonasal disease and systemic inflammation [16]. OSA and asthma exhibit very similar obstructive characteristics and also both have diurnal and nocturnal variations [17]. Current guidelines recommend testing for OSA in overweight and or obese patients with poorly controlled asthma. Since its introduction by Sullivan in 1981, CPAP has been the main line of treatment for OSA [18]. Growing evidence suggests bidirectional effects of OSA with asthma and better outcomes of asthma treated with CPAP in patients with concomitant OSA [14,19–21].

Effects of asthma on OSA involves mechanical factors (increased airway resistance during REM sleep due to reduction in Functional Residual capacity and End Expiratory Lung Volume leading to upper airway collapse and worsening of apneas), Smoking (directly increasing airway edema and resistance), Corticosteroids use (causing airway myopathy, obesity and airway fat deposition) and increased nasal resistance due to rhinitis or polyps. Similarly, recent animal and human studies have shown OSA could influence lower airway inflammation and remodeling [22]. Effects of OSA on asthma includes increasing vagal tone during apneic episodes triggering muscarinic receptors induced bronchoconstriction, intermittent hypoxic oxidative stress causing endothelial dysfunction, increased inflammation, Vascular Endothelial Growth Factor (VEGF-hypoxia-sensitive glycoprotein which may contribute to bronchial inflammation), Leptin-related airway changes (pro-inflammatory effects), Sleep fragmentation (causing increased cholinergic outflow during REM sleep), GERD (asthma triggered form micro-aspirations and respiratory mucosal injury and reflex bronchospasm) and cardiac dysfunction (OSA leads to cardiac dysfunction and CHF itself has been known to worsen asthma) [23–26]. The majority of patients with asthma have rhinitis and nasal obstruction which causes changes in airway velocity and resistance promoting upper airway collapse and thus symptoms of SDB [27]. OSA is an under-recognized condition, and failure to diagnose OSA may result in initiating standard treatment of asthma in OSA-asthma overlap syndrome. Nasal disease and corticosteroids use in such cases could probably promote OSA based on the mechanisms mentioned above. This leads to a vicious cycle of difficult to control symptoms. OSA, on the other hand, in itself is also an independent risk factor for asthma exacerbation [28–30]. Hypothetical mechanisms by which sleep fragmentation may worsen asthma control include left ventricular dysfunction, impaired immunological function, and weight gain [27]. Also, the prevalence of SDB increases with increasing asthma severity [31]. There appears to be a bidirectional synergistic effect between asthma and OSA [16]. However, there are some conflicting reports regarding the use of CPAP in patients with concomitant asthma and OSA (Alternate overlap syndrome). Ballard et al. found that the functional residual capacity of the asthmatics fell during sleep, which might partly contribute to the nocturnal increase in airway resistance and induce airway collapse which might contribute to SDB symptoms [32,33]. Some studies have reported symptomatic improvement, asthma control, decreased nocturnal attacks and alleviation of FEV₁ decline by CPAP in asthmatics with OSA [8,20,34–36]. While other studies, for instance, Lafond C. et al. demonstrated that in newly diagnosed OSA patients with mild to moderate asthma had no improvements in airway responsiveness or FEV₁ with nocturnal CPAP [37]. Similarly, Devoassoux G. et al. suggested a long-term follow up for CPAP induced airway hyper-responsiveness in OSA patients [38]. Frequent use of steroids in asthma might further worsen OSA by mechanisms explained above. Increased airway collapsibility secondary to steroid-induced airway myopathy can potentially contribute to this scenario [39]. Exact mechanisms are yet to be elucidated. Two widely recognized pathophysiological hypotheses are...
systemic inflammation in obesity and mechanical effects of obesity on lung and airway function. Neither of them fully clarifies the pathogenesis and unlikely that single mechanism will explain all.

As noticed in the general population, in our study, asthma was more prevalent in the females [40]. Relatively higher pack-years of smoking was seen in asthmatics than non-asthmatics which is also consistent with data demonstrating a higher risk of OSA and asthma with increasing pack-years. Asthmatic subgroup consisted of a relatively younger population and had higher BMI as compared to the non-asthmatic subgroup. This demonstrates increasing trends towards smoking and unhealthy lifestyles among the younger generation. As BMI increases (particularly in morbidly obese individuals) there is evidence of a reduction in expiratory flow and a decrease in FEV₁ and FVC which could be seen in our study especially in asthmatic subgroup [41]. FEV₁ has been noted to be significantly lower in the asthmatic group which is expected, as asthma and obesity both contribute independently to a reduction of FEV₁. It remains to be answered if there is additive or synergistic or no difference in decline if the two factors act together. Similar to meta-analysis by De-Lei Kong et al., our study has demonstrated asthma patients with OSA have higher BMI than non-asthmatic OSA patients, (28.8 vs. 29.5, \( p = 0.013 \)) [19]. Despite the factors mentioned above, more severe OSA was observed in the non-asthma group, AHI (12.63 vs. 11.34, \( p = 0.015 \)). The severity of the OSA in asthmatics demonstrated in this study was probably due to the gender and age factor. Non-asthmatic population consisted of greater number of male patients (60.2% vs 49.8%) and also consisted of an older population compared to asthmatic population (mean age 66 years vs. 64 years). Older age and male gender both are established risk factors of OSA which reflected in AHI and RDI; probably resulting in significant severe OSA in the non asthmatic population. The difference of the population in both subgroups might have contributed in the difference noticed. Furthermore, sleep latency was seen significantly longer in asthmatics (19.8 vs. 16 min, \( p = 0.008 \)), and the Epworth score was also significantly higher in the asthmatic subgroup (9 vs. 8, \( p = 0.02 \)). This reflects data from cross-sectional and experimental studies which link OSA with worse clinical outcomes in patients with asthma, across the healthcare continuum [22]. Kwon et al. have labeled inhalers as ‘doubled aged sword’ while Teodorescu et al. have demonstrated a linear dose-dependent increase in OSA risk and habitual snoring with inhaled corticosteroids [42,43]. Fluticasone inhalers in asthmatics have shown variable effects on OSA depending upon the baseline characteristics of the patient [44]. Much work remains to understand the implications of asthma treatment on OSA. Asthma-OSA overlap could potentially be managed as a separate entity where care is tailored to the individual patient.

5. Conclusion

There is an urgent need for early and periodic detection of OSA in asthma. Clinicians should also keep a low threshold to rule out OSA particularly on elderly obese male patients with difficult to control asthma. Immediate and long-term implications of asthma treatment on the OSA remains unclear but current consensus is to manage both diseases simultaneously. A further prospective randomized control trial is needed to understand the effects of asthma on OSA.

6. Limitations

This study is subject to the limitations inherent in its retrospective cross-sectional design. The study population majority was white and patients aged 40 or older were only included. Unwilling patients, healthy patients and patients whose social, physical or mental conditions preclude a home polysomnogram were not included. History of asthma was reported by a doctor of medicine. Disparities among the subgroup number of patients were included. Data obtained from the SHHS visit one and was not followed up with the visit 2.

Disclosure statement

No potential conflict of interest was reported by the authors.

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