Are Chronic Cough and Laryngopharyngeal Reflux More Common in Obstructive Sleep Apnea Patients?

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**Objectives/Hypothesis:** To assess if there is a significant difference in the prevalence and severity of chronic cough symptoms in obstructive sleep apnea (OSA) patients versus non-OSA patients and examine this relationship in regard to laryngopharyngeal reflux (LPR) symptoms.

**Study Design:** Prospective cohort study.

**Methods:** Patients referred to Northwestern Medicine Sleep Lab for home sleep testing were enrolled. Patients filled out the Leicester Cough Questionnaire (LCQ) and Reflux Symptom Index (RSI) before completing sleep testing. Home sleep testing results were reviewed, and patients were separated into non-OSA and OSA groups by standard Apnea-Hypopnea Index (AHI) criteria. Demographic characteristics and questionnaire scores of the two groups were compared. The relationship between OSA severity, as determined by AHI, and LCQ and RSI scores was assessed.

**Results:** Of the 52 patients enrolled, 33 patients met criteria for OSA and 19 patients did not. Comparing patients without OSA versus those with OSA, there was a significant difference in mean LCQ score (129.9 vs. 120.0, respectively; \( P = 0.02 \)), implying worse cough symptoms among OSA patients, and mean RSI score (3.2 vs. 11.2, respectively; \( P = 0.0013 \)), implying worse upper-airway reflux symptoms among OSA patients. There was a significant correlation between LCQ score and AHI \((r = 0.39, P = 0.0061)\) and between RSI score and AHI \((r = 0.37, P = 0.0078)\).

**Conclusions:** OSA patients demonstrate worse chronic cough and LPR-related quality of life versus non-OSA patients. Furthermore, the severity of these quality-of-life measures was correlated with the severity of the AHI. Chronic cough and particularly the pharyngeal LPR symptoms may be associated with the presence and severity of OSA.

**Key Words:** Obstructive sleep apnea, cough, laryngopharyngeal reflux.

**Level of Evidence:** 2

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**INTRODUCTION**

Obstructive sleep apnea (OSA) affects approximately 15% of the US adult population.\(^1\) Untreated OSA is classically associated with cardiovascular disease,\(^2\) motor vehicle accidents,\(^3\) and decreased quality of life (QOL).\(^4\) Despite this, a significant fraction of OSA patients remain undiagnosed.\(^5\) Maintaining a high level of suspicion for this chronic disease thus remains important for providers. This is especially important for otolaryngologists, as approximately one-third of sleep-disorder patients present initially to them for management, usually for OSA.\(^6\)

Similar to OSA, chronic cough and laryngopharyngeal reflux (LPR) are common and burdensome diseases. Chronic cough is one of the most common complaints in ambulatory practice, more frequently seen than pediatric fevers or earaches.\(^7-9\) Likewise, it is estimated that LPR patients make up 10% of otolaryngology outpatient clinic visits.\(^9\) Although LPR can cause mild symptoms, including chronic cough, chronic untreated disease can contribute to severe upper-airway disease including subglottic stenosis, laryngospasm, and malignant disease of the head and neck.\(^10\) Chronic-cough patients have independently been found to have significantly impaired QOL versus normal controls.\(^11\)

Several studies have noted coexistence between OSA and chronic cough or LPR. However, these studies have shown conflicting results,\(^12\) have been small and retrospective,\(^13,14\) or relied on extrapolation from treatment effects via continuous positive airway pressure (CPAP)\(^15,16\) or surgery\(^17\) without addressing initial prevalence. There is no prospective study examining the link between OSA and the severity of symptoms of chronic cough and LPR. Thus, the goal of this study is to test the hypothesis that patients with OSA have increased severity of chronic cough and LPR symptoms and to assess the relationship between disease-specific QOL measures and
OSA severity. This information would argue for more aggressive diagnostic sleep evaluation of patients with unexplained chronic cough or reflux symptoms and better elucidate the pathophysiology of these conditions.

MATERIALS AND METHODS

Patient Population

Adult patients aged 18 years or older referred to the Northwestern Memorial Hospital sleep laboratory for home sleep testing for diagnosis of OSA were recruited prospectively between July and December 2017. Patients were excluded from this study if they had a previous diagnosis of OSA or other sleep disorders or a history of chronic pulmonary disease, LPR, or chronic cough. Patient history was reviewed to ensure patients had never been treated with CPAP or sleep surgery to ensure they had no history of treated OSA. All patients provided written informed consent to be enrolled in this study. The Northwestern University Institutional Review Board reviewed this protocol and approved this study.

Study Design

All participants completed the Leicester Cough Questionnaire (LCQ), Reflux Symptom Index (RSI), Epworth Sleepiness Scale (ESS), and Pittsburgh Sleep Quality Index (PSQI). The LCQ is a 19-item, patient-reported, validated measure of chronic cough symptom severity and impact on QOL (score range, 19–133, with higher scores indicating better health-related QOL). The RSI is a nine-item patient-reported measure validated to measure LPR symptom severity (score range, 0–45, with higher scores indicating increased severity of component symptoms). The ESS is an eight-item patient-reported measure assessing daily life sleep propensity (score range, 0–24, with high scores indicating higher daytime sleepiness). The PSQI is a self-reported questionnaire composed of 19 items evaluating sleep quality of the previous month. Answers from the items are used to assign a score of 0 to 3 to each of seven component scores, and the components are added to form the global score (range, 0–21, with high scores indicating more severe sleep difficulties). Patients then underwent home sleep testing to diagnose OSA. Demographic characteristics including sex, age, and body mass index (BMI) were obtained from the medical records of each patient. Portable polysomnograms were interpreted by board-certified members of the Division of Sleep Medicine. Final results of home sleep tests were obtained 2 weeks after the study date and were entered for data analysis. Presence of OSA was defined as AHI > 5 per hour based on American Academy of Sleep Medicine (AASM) criteria.

Statistical Analysis

Microsoft Excel (Microsoft, Redmond, WA) was used for descriptive statistics and summary tables; χ² tests and t tests were used to compare OSA and non-OSA groups. Pearson correlation coefficients were used to examine the correlation between AHI and LCQ score, as well as between AHI and RSI score. A P value of < .05 was considered statistically significant. All statistical analysis was performed in Stata (StataCorp LP, College Station, TX).

RESULTS

Demographic information for the study population is summarized in Table I. This study included 52 patients (61.5% male and 38.5% female) with a mean age of 44.1 years (range, 20–82 years).

On review of home sleep testing results, 33 (63.5%) patients were diagnosed with OSA. Although mean BMI scores were higher in OSA patients, it did not achieve statistical significance. There were no significant differences between OSA and non-OSA patients, respectively, in levels of sleepiness by ESS (6.89 vs. 6.42; P = .69) or in subjective sleep quality by PSQI (8.57 vs. 9.21; P = .61).

Patients with OSA had significantly lower mean LCQ scores than did non-OSA patients (Table II), reflecting an increased burden from chronic cough (120.0 vs. 129.9; P < .02). Mean RSI scores were significantly higher among patients with OSA (11.2 vs. 3.2; P = .0013). There were significant correlations between questionnaire scores and AHI, as well as between AHI and RSI score. A P value of < .05 was considered statistically significant. All statistical analysis was performed in Stata (StataCorp LP, College Station, TX).
scores and AHI. Lower LCQ score ($r = -0.39; P = .0061$) was significantly correlated with higher AHI (Fig. 1). Additionally, higher RSI score ($r = 0.37; P = .0078$) was also significantly correlated with increasing AHI (Fig. 2). A breakdown of the RSI question scores comparing OSA versus non-OSA patients is provided in Table III.

**DISCUSSION**

OSA is a prevalent and burdensome disease. Several prior studies have postulated a high prevalence of coexisting chronic cough and LPR in small, retrospective reviews. Further, treatment of OSA with CPAP or surgery has been found to mitigate chronic cough and LPR in selected groups. There is a need for a large, controlled study examining this relationship more closely.

This study enrolled patients suspected of having OSA sent for home sleep testing at Northwestern Medicine by their primary-care or specialty-care physicians. Participants completed validated surveys for chronic cough (LCQ) and LPR (RSI), before completing home sleep studies. Our results showed that participants who became diagnosed with OSA had significantly higher rates of QOL complaints from chronic cough and LPR. Strengthening this association, there was a significant correlation between AHI and worse LCQ and RSI scores. It is also striking that certain LPR symptoms were better symptomatic predictors of the presence of OSA than more traditionally used sleep measures like the PSQI and ESS in this series.

It is worth noting that cough is a symptom of LPR, and two of the RSI’s nine questions focus on this complaint. Our study hoped to assess if OSA significantly affects QOL complaints from cough and/or other LPR complaints. To better examine other LPR symptoms, we performed a subanalysis of our RSI results to examine differences in OSA versus non-OSA patients (Table III). We found significant differences between OSA and non-OSA patients related to the following questions: clearing your throat (1.79 vs. 0.32; $P = .00015$); excess throat mucus or postnasal drip (2.03 vs. 0.47; $P = .00036$); coughing after you ate or after lying down (1.09 vs. 0.32; $P = .03$); breathing difficulties or choking episodes (1.03 vs. 0.16; $P = .02$); troublesome or annoying cough (0.88 vs. 0.16; $P = .01$); and sensations of something sticking in your throat (1.33 vs. 0.05; $P = .002$). So, although cough complaints are likely an aspect of patients’ LPR burden,
there are several other significant symptoms. Interestingly, the symptoms most related to OSA are more pharyngeal complaints versus cough or traditional esophageal reflux sensations (burning, indigestion, dysphagia); no other report has examined OSA and specific domains of the RSI or specific LPR-related symptoms. This novel association deserves further research to determine more definitively which LPR symptoms OSA contributes to and why.

The underlying pathophysiology for how OSA could create an environment facilitating chronic cough and LPR is still under investigation. However, several well-researched pathways have been proposed, with the likelihood being that there are multifactorial explanations. It is widely agreed that OSA creates an environment of negative intrathoracic pressure during obstructive events; this can overcome lower esophageal sphincter tone, allowing exposure of the upper airway to gastric contents.25 Mechanical trauma and vibration-induced injury from snoring and forceful breathing events cause direct tissue injury in laryngeal tissues.26,27 Repetitive obstructive episodes cause ischemia-reperfusion injury to the airway.28,29 all the while OSA patients have increased systemic inflammatory mediators predisposing the soft tissues to free-radical development.30 These same theories have been proposed recently for two small cohort samples finding higher levels of sinonasal complaints in OSA patients,31,32 though no study has definitively linked OSA and higher rates of sinusitis. It is worth mentioning that a separate study of our cohort found no difference in sinusitis QOL scores (by Sino-Nasal Outcome Test) between OSA and non-OSA patients. Theoretically, chronic cough and LPR could contribute to upper-airway inflammation and sensory neuropathy, but this is likely a minor point and no prior studies have been done showing this relationship.

Obesity has also been proposed as having an independent impact on chronic cough and LPR via separate inflammatory pathways related to leptin and adipose physiology.33 Increased body mass also leads to increased parapharyngeal, tongue, and hypopharyngeal fat deposition, narrowing the airway and causing nightly episodes of negative intrathoracic pressure to overcome obstruction, as mentioned above.34 It is worth noting that there was no significant difference in BMI between OSA and non-OSA patients in this study, although this may reflect the relatively small sample size of our study.

Approximately one-third of patients with OSA present initially to an otolaryngologist for their care.6 Given its public health and socioeconomic ramifications, it is imperative for ENTs and other providers to maintain a high index of suspicion for this disorder. Further, subjective markers of sleepiness and sleep quality, like the ESS and PSQI, have been shown to have poor utility as screening tests for OSA and poor correlation with polysomnographic measures.35 Our own data reflect this, with no significant difference between ESS or PSQI scores for OSA versus non-OSA groups.

Our study highlights significant associations between having OSA and having chronic cough or LPR symptoms. This builds upon small, retrospective, and anecdotal studies suggesting diagnostic workup for patients with these complaints. Further, the QOL impact from cough and LPR in OSA patients is high in our study—providers seeing OSA patients should be vigilant in inquiring about and managing these disorders. For all patients with OSA being seen by otolaryngologists, we recommend eliciting history of chronic cough or LPR complaints. For those with concerning symptoms, measures like the RSI and LCQ can be used to elicit QOL burden from these complaints to help guide treatment. Management can begin with treating the patient’s OSA (via CPAP or surgery, if indicated) and measuring the patient’s empiric response. For continued symptoms, treatment aimed at improving chronic cough36 and LPR symptoms37 should be instituted in a stepwise manner.

There are several limitations to our study. Perhaps the most difficult to address is the lack of uniform criteria for diagnosing chronic cough or LPR—usually these disease states depend upon a nonacute history, general constellation of symptoms, and an otherwise negative workup. Because of this, we focused on overall symptom scores and QOL measures related to these disorders. We relied upon the LCQ and RSI surveys to assess for presence and QOL impact from chronic cough and LPR. Although both are validated and well-studied, neither of these measures have the sensitivity or specificity to diagnose these chronic conditions. Nevertheless, our results are in line with prior studies and our study adds to the evidence that OSA may be an important factor in chronic cough and LPR. Understanding this association may lead to better relief for patients with these conditions.

### Table III: RSI Scores According to OSA Status

<table>
<thead>
<tr>
<th>Symptom</th>
<th>All Participants, N = 52</th>
<th>Non-OSA, n = 19</th>
<th>OSA, n = 33</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoarseness or problem with your voice</td>
<td>0.75 (1.28)</td>
<td>0.63 (1.46)</td>
<td>0.81 (1.18)</td>
<td>.62</td>
</tr>
<tr>
<td>Clearing your throat</td>
<td>1.25 (1.43)</td>
<td>0.32 (0.67)</td>
<td>1.79 (1.47)</td>
<td>.00015</td>
</tr>
<tr>
<td>Excess throat mucus or postnasal drip</td>
<td>1.46 (1.59)</td>
<td>0.47 (1.02)</td>
<td>2.03 (1.59)</td>
<td>.00036</td>
</tr>
<tr>
<td>Difficulty swallowing liquid or pills</td>
<td>0.54 (1.07)</td>
<td>0.16 (0.37)</td>
<td>0.76 (1.28)</td>
<td>.052</td>
</tr>
<tr>
<td>Coughing after you ate or after lying down</td>
<td>0.81 (1.28)</td>
<td>0.32 (0.67)</td>
<td>1.09 (1.47)</td>
<td>.03</td>
</tr>
<tr>
<td>Breathing difficulties or choking episodes</td>
<td>0.71 (1.33)</td>
<td>0.16 (0.37)</td>
<td>1.03 (1.57)</td>
<td>.02</td>
</tr>
<tr>
<td>Troublesome or annoying cough</td>
<td>0.62 (1.01)</td>
<td>0.16 (0.37)</td>
<td>0.88 (1.17)</td>
<td>.01</td>
</tr>
<tr>
<td>Sensation of something sticking in your throat</td>
<td>0.87 (1.51)</td>
<td>0.05 (0.22)</td>
<td>1.33 (1.73)</td>
<td>.002</td>
</tr>
<tr>
<td>Heartburn, chest pain, indigestion, stomach acid coming up</td>
<td>1.27 (1.40)</td>
<td>0.89 (0.81)</td>
<td>1.48 (1.62)</td>
<td>.15</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD) (mean events in the last month). OSA = obstructive sleep apnea; RSI = Reflux Symptom Index; SD = standard deviation.
utilizes an objective measure, such as endoscopic findings or 24-hour pH monitoring, and patients may not have had clinical diagnoses of either condition. Several confounders can contribute to chronic cough and LPR; we mention obesity above, but history of heavy alcohol use (more than one drink a day) or smoking history could also contribute. In our cohort, rates of heavy alcohol use or smoking history were not significantly different (Table I). Treatments of OSA, especially with CPAP and surgery, could theoretically alter airway tissue and affect cough and reflux complaints, but we carefully selected our patient population to exclude patients who had undergone prior treatment for OSA.

We utilized results from home sleep testing to assess for presence and severity of OSA instead of in-laboratory polysomnography, the gold standard for OSA diagnosis. The home sleep test is a well-validated alternative to in-laboratory testing; however, there could be minor differences between them.38 There are numerous reports supporting home sleep testing for diagnosis of OSA in patients with high pretest probability.39–41 We chose to examine patients with a suspicion of OSA versus normal controls to make this as clinically relevant to otolaryngologists as possible; most OSA patients presenting to an otolaryngologist have significant snoring complaints or were referred based on suspicion for sleep apnea. We aimed to see if this group of patients has significantly more burden from chronic cough and LPR based on the presence, or not, of OSA—we believe this study supports that they do. This study stands as the only prospective study examining rates and severity of chronic cough and LPR in OSA patients and provides useful information moving forward.

CONCLUSION

We found that OSA patients have significantly higher burden of chronic cough and LPR complaints. Chronic cough and LPR symptoms may be associated with the presence and severity of OSA. This information argues for diagnostic workup of OSA in patients with persistence of these complaints, as well as aggressive management of cough and LPR in OSA patients.

BIBLIOGRAPHY


