Eur Arch Otorhinolaryngol (2012) 269:2575–2580
DOI 10.1007/s00405-012-2062-z

MISCELLANEOUS

Management of patients with coexisting obstructive sleep apnea and laryngopharyngeal reflux disease

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Received: 1 January 2012 / Accepted: 22 May 2012 / Published online: 17 June 2012

Abstract Obstructive sleep apnea syndrome (OSAS) and Laryngopharyngeal reflux disease (LPR) are both common health problems causing severe morbidity. Since they have similar risk factors, the prevalence of LPR among patients with OSAS is higher compared with general population. However, there exist only a few studies showing the potential causal relation between LPR and OSAS. The aim of this study was to evaluate the coexistence between OSAS and LPR and to determine whether the therapy of OSAS alters LPR parameters and vice versa. In this study, 44 patients underwent double probed 24 h pH monitoring simultaneously with polysomnography due to the complaints of obstructive sleep apnea and reflux. Twenty of those 44 patients were diagnosed with both OSAS and LPR. Among those patients, 10 patients with mild to moderate OSAS were given only LPR treatment for 3 months. The remaining 10 patients who had severe OSAS underwent CPAP treatment for 3 months. After the end of treatment, all patients were reevaluated with double probed 24 h pH monitoring simultaneously with PSG. Moreover, the patients were evaluated subjectively by Epworth Sleepiness Scale (ESS), snoring Visual Analogue Scale (VAS), Reflux Symptom Index (RSI), and Reflux Finding Score (RFS). The results of this study revealed that OSAS and LPR coexist frequently. LPR treatment did not improve the polysomnographic parameters, but significantly reduced ESS and snoring VAS ($p = 0.02$ and $p = 0.007$, respectively). Although the CPAP treatment significantly improved subjective parameters of reflux, such as RSI and RFS ($p = 0.016$ for both), there was no significant improvement in objective parameters of 24-h pH monitoring. We concluded that since there is a high frequency of coexistence between LPR and OSAS, all patients with OSAS should also be queried for LPR symptoms. In addition, more in-depth and comprehensive research is required to elucidate the association between OSAS and LPR.

Keywords Obstructive sleep apnea syndrome · Laryngopharyngeal reflux · Continuous positive airway pressure · Polysomnography · Double probed 24 h pH monitoring

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Introduction

Obstructive sleep apnea syndrome (OSAS) is characterized by long-lasting hypoxia, sleep fragmentation, and daytime symptoms caused by repetitive episodes of obstruction at one or more levels of upper airway, during sleep [1, 2]. This syndrome affects nearly 2–5 % of the population [1, 3, 4].

OSAS is known to be highly associated with cardiovascular morbidity and mortality. Many systemic diseases

such as left ventricular dysfunction, myocardial infarction, hypertension, congestive heart failure, cerebrovascular incidents, and pulmonary hypertension are all demonstrated to have relation with this syndrome [5–7]. Thus, effective treatment of OSAS is mandatory, to reduce symptoms and consequences of OSAS.

Laryngopharyngeal reflux (LPR) is a disease which displays mainly the extraesophageal symptoms and signs of gastroesophageal reflux (GER) like hoarseness, dry cough, irritation at throat, and globus pharyngeus [8]. The symptoms occur due to leakage of gastric content from upper esophageal sphincter and consequent damage to laryngopharyngeal mucosa. The incidence of LPR is so high that nearly 10 % of patients admitted to otolaryngology outpatient clinics had complaints of LPR [9]. Since both OSAS and LPR show similar risk factors such as obesity, male predominance, alcohol usage, and age, possible associations of OSAS with LPR had been the subject of different studies [10, 11]. In OSAS patients, coexistence with LPR is very frequent with a high percentage of 20–67 [5, 11–14].

A few possible mechanisms which explained the coexistence of OSAS and LPR were suggested previously [10, 14]. In those previous studies, association of these two diseases was searched by simultaneous testing with polysomnography (PSG) and double probed 24 h pH monitoring which are main diagnostic tools for OSAS and LPR, respectively [5, 15].

Since 1981, continuous positive airway pressure (CPAP) devices have been considered as the gold standard for the treatment of OSAS [16]. Meanwhile, for the treatment of LPR, behavioral and dietary regulations beside medications including proton pump inhibitors, antiacids, and H_2 blockers play important roles. Since these two diseases have strong associations then one may consider the possible benefits from therapy in between them. There are some studies which showed that application of CPAP in OSAS patients decreased the symptoms of GER and also treatment of GER with medications had positive impacts on the severity of OSAS findings [5, 11, 17–20], but unfortunately a similar association between LPR and OSAS had not been discussed enough previously. Although both GER and LPR occur due to gastric content leakage, their symptomatology, clinical findings and treatment policies are mostly different [21–23]. But in only few studies in the literature, the coexistence of OSAS and LPR was surveyed objectively by 24-h pH monitoring and PSG [5, 15].

The aim of this presented study was to evaluate the coexistence of two common and highly morbid diseases; OSAS and LPR and to determine the effects of LPR treatment on OSAS findings and the effects of CPAP treatment on LPR findings.

Materials and methods

This study was conducted at the Departments of Otolaryngology, Chest Diseases and Gastroenterology, Uludag University Medical School between March 2007 and March 2009. The study protocol was approved by the Ethics Committee of Uludag University Medical School with an approval number of 2006-25/6. Signed informed consent was taken from all participant patients.

The study protocol included two-staged evaluation. In the first stage the patients who were admitted to the department of Chest Diseases with OSAS complaints were also queried for LPR symptoms. To determine the severity of subjective symptoms regarding OSAS, Epworth sleepiness scale (ESS) and snoring visual analogue scale (VAS) (out of 10 points) were used. To assess the severity of reflux symptoms and to compare the response to treatment of LPR, reflux symptom index (RSI) containing nine items was used [24]. A complete endoscopic examination of upper airway was performed and meanwhile the reflux finding scores (RFS) of patients were determined [25]. Forty-four patients who had complaints of LPR and OSAS and a body mass index (BMI) <30 underwent PSG testing on the same night of 24-h pH monitoring. The 24-h pH measurement was performed at the department of Gastroenterology by double probed MMS Orion® device. Under endoscopic guidance, pharyngeal probe was placed at postcricoid region and second probe just 15 cm below to this point in the morning. The patients whose pH monitoring findings filled the diagnostic criteria of LPR described by Postma et al. [26] were considered as LPR-positive cases. Later on the night of the same day, the patient was taken to sleep laboratory for PSG testing.

The PSG testing was performed using Compumedix sleep pursuit system, P series (Australia) at the department of Chest Diseases. Polysomnography recording consisting of two electroencephalography (EEG)(C3/A2 and O2/A1), two electrooculogram (EOG), one submental electromyogram (EMG), and one electrocardiogram (EKG) started immediately after the patient fell asleep. Respiratory monitoring was performed using a computerized system which recorded oronasal air flow by an oronasal thermistor, oxygen saturation of hemoglobin by a pulse oximeter, and chest wall movement by a Respiratory Inductive Plethysmograph (RIP) belt and body position. Nasal airflow was analyzed carefully to assess ventilation during sleep. Apnea was defined as a complete cessation of airflow for a minimum of 10 s. On the other hand, a decrease of 50 % or more in thermistor signal for at least 10 s associated with an arousal or 3 % fall in basal oxygen saturation was characterized as hypopnea [2]. The apnea-hypopnea index (AHI) was calculated by dividing the number of apneas and hypopneas by number of sleep hours. The patients who had

more than five obstructive apneas greater than 10 s per hour in their PSG and had associated symptoms were considered as OSAS-positive cases according to American Association of Sleep Medicine (ASSM) criterias [2].

Twenty-Five of these 44 patients who were positive for both OSAS and LPR enrolled in the second-stage study group. Since three of these 25 patients refused to use CPAP and other two patients were non compliant to reflux treatment protocols, the analyses were done with 20 patients. In the second stage, these 20 patients were divided into equal number of two groups according to AHI scores as AHI: 5–30 (mild or moderate OSAS) and AHI >30 (severe OSAS). To first group of 10 patients with mild or moderate OSAS, proton pump inhibitors (lansoprazole) 30mg × 2/day and Alginic acid 4 × 20 ml/day were administered for 3 months of duration and they were also counseled for dietary regulation. To patients with severe OSAS in second group, CPAP was the preferred treatment modality. After 3 months, all patients were reevaluated with simultaneous PSG and 24 h pH monitoring as described before. The association between apnea–hypopnea cycles and reflux attacks was assessed during these tests.

For subjective evaluation of success of treatment, ESS, snoring VAS, RSI, and RFS were compared with pretreatment counterparts. The efficacy of treatment modalities was assessed objectively by AHI, arousal index, lowest and mean oxygen saturation, duration of oxygen saturation <90 % in PSG and percentage of total reflux, total reflux time, number of reflux drop episodes, and period index in the 24-h pH monitoring. The reflux drop number indicated as, episodes at which pH value dropped more than 1 but not below 4. Period index referred to number of episodes at which pH fell down below 4 in daily period. The control PSG testing was performed under CPAP in patients included in CPAP group.

Statistical analysis was carried out using SPSS v.13.0 for Windows (SPSS inc.Chicago, USA). The data were analyzed with Shapiro–Wilk test to ascertain if the distribution followed the normal curve. Comparison of dependent groups was analyzed with Wilcoxon sign rank test and Mann–Whitney *U* test was used to compare the independent groups. The comparison of categorical data was done with Pearson Chi-squared test and Fisher's exact test, and correlations between variables were analyzed with Spearman's rank correlation coefficient. A '*p*' value which was less than 0.05 was considered to be statistically significant.

Results

The distribution of 44 patients in first stage revealed coexistence of OSAS and LPR in 25 patients (57 %). LPR findings were also positive in 89.2 % of OSAS (+) patients. Furthermore, in 61 % of LPR (+) patients OSAS was present (Table 1). The second stage of the study was conducted with 20 patients including 14 females and 6 males. The ages of these patients varied between 30 and 62 years (mean age 49.6 ± 10.9). There was no difference between two treatment groups according to sex and age ($p = 1$) and all patients had BMI <30.

Table 1 The distribution of all patients showing coexistence of OSAS and LPR

	LPR (+)	LPR (−)	Total
OSAS (+)	25	3	28
OSAS (−)	16	0	16
Total	41	3	44

OSAS Obstructive sleep apnea syndrome, *LPR* Laryngopharyngeal reflux

In first group including 10 patients with mild or moderate OSAS, medical treatment of LPR did not cause any significant difference in PSG findings. The mean AHI score was increased to 14.6 ± 13.8 from 10.1 ± 4.8 ($p = 0.44$) and minimum oxygen saturation was decreased to 84.5 ± 16.1 from 86.7 ± 5.2 ($p = 0.65$). However, the subjective parameters such as ESS and snoring VAS revealed significant improvement after medical treatment (Table 2). The objective parameters of 24 h pH monitoring in first group all showed a nonsignificant improvement after 3 months of medical treatment. There was statistically significant improvement in both subjective parameters of LPR (RSI and RFS) in this group (Table 3).

In the second group including 10 patients with severe OSAS, the evaluation of objective and subjective parameters under CPAP revealed significant improvement in mean AHI, ESS, and snoring VAS after 3 months of treatment ($p = 0.005$ for all) (Table 4). For same group, the assessment of the efficacy of CPAP treatment on LPR showed non-significant deterioration of objective parameters in 24 h pH monitoring; nevertheless, those subjective findings in RSI and RFS showed significant improvement ($p < 0.016$ for both) (Table 5).

There were 15 reflux attacks detected during 40 PSG tests throughout the study, but only eight of these attacks occurred simultaneously with apnea-hypopnea episodes. Sixteen of reflux attacks were observed during daytime while PSG testing was not performed. Beside these findings, there was no significant correlation between AHI score and RSI or RFS ($p > 0.05$). Before treatment, there was a significant inverse correlation between AHI and total reflux percentage ($r = 0.447$, $p = 0.048$). A similar inverse correlation was also significant between AHI and total reflux duration ($r = 0.623$, $p = 0.003$). Meanwhile after treatment, significant positive correlation was

Table 2 The change of OSAS parameters in patients with AHI: 5–30 who underwent LPR treatment

	Before LPR treatment	After LPR treatment	*p* value
Objective findings			
AHI	10.1 ± 4.8	14.6 ± 13.8	0.44
Arousal index	12.9 ± 6.7	19.9 ± 10.4	0.07
Lowest O_2 sat.	86.7 ± 5.2	84.5 ± 16.1	0.65
Mean O_2 sat.	95.5 ± 2.1	95.1 ± 1.7	0.47
O_2 <90 % duration	11.5 ± 14.9	7.6 ± 8.1	0.75
Subjective findings			
ESS	8.1 ± 4.5	5.3 ± 3.9	0.02*
Snoring VAS	7.2 ± 1.8	4.6 ± 1.7	0.007*

AHI Apnea hypopnea index, *ESS* Epworth sleepiness scale

* shows statistical significance

Table 3 The change of LPR parameters in patients with AHI: 5–30 who underwent LPR treatment

	Before LPR treatment	After LPR treatment	*p* value
Objective findings			
Total reflux	7.6 ± 17.4	1.6 ± 1.8	0.270
Total reflux time	88.5 ± 233.9	40.2 ± 43.3	0.359
pH drop number	163.6 ± 64.7	157.8 ± 180.3	0.799
Period index	13.9 ± 3.9	9.2 ± 12.1	0.260
Subjective findings			
RSI	12.7 ± 7.1	5.8 ± 4.0	0.005*
RFS	2.9 ± 1.8	0.9 ± 0.3	0.011*

RSI Reflux symptom index, *RFS* Reflux finding score

* shows statistical significance

Table 4 The change of OSAS parameters in patients with AHI >30 who underwent CPAP treatment

	Before CPAP	Under CPAP	*p* value
Objective findings			
AHI	54.9 ± 19.06	5.9 ± 3.9	0.005*
Subjective findings			
ESS	15.2 ± 4.2	7.9 ± 3	0.005*
Snoring VAS	9.2 ± 0.7	5 ± 1	0.005*

AHI Apnea hypopnea index, *ESS* Epworth sleepiness scale

* shows statistical significance

calculated only between AHI and pH drop number ($r = 0.455$, $p = 0.044$), but other parameters of pH monitoring did not show any significant correlation with AHI.

Table 5 The change of LPR parameters in patients with AHI >30 who underwent CPAP treatment

	Before CPAP	Under CPAP	*p* value
Objective findings			
Total reflux	0.9 ± 0.7	7.4 ± 20.2	0.558
Total reflux time	5.5 ± 7.9	137.3 ± 287.4	0.123
pH drop number	223.2 ± 93.2	159.2 ± 93.4	0.314
Period index	6.8 ± 10.7	11.68 ± 17.2	1
Subjective findings			
RSI	10 ± 6.6	4.7 ± 2.6	0.016*
RFS	4.1 ± 2.5	1.7 ± 0.4	0.016*

RSI Reflux symptom index, *RFS* Reflux finding score

* shows statistical significance

Discussion

OSAS and LPR are two common diseases causing morbidity. Since they coexist frequently in the population, some studies suggested that these diseases have similar etiological risk factors. The mechanisms which explained this coexistence was choking sensation and arousals during sleep due to microaspiration of gastric acid and the second mechanism was inflammatory edema which induces upper airway obstruction and neural damage. This neural damage eventually deteriorates laryngeal dilatator reflex mechanisms and cause apnea. One other mechanism was a central nervous system stimulus which resulted from esophageal dilatation and disturbance of acid clearance. This neural stimulus was considered to induce arousals during sleep [10, 14].

Today for objective evaluation of LPR, 24 h pH monitoring is still the gold standard diagnostic tool. Some authors indicated that even only one laryngopharyngeal reflux attack detected should be considered as positive result [9, 23]. But other studies showed that one reflux attack could be seen in 50 % of normal population and compatibility of serial pH monitoring with similar results was only 55 % [23, 27]. In their study, Hanson et al. [28] revealed that in symptomatic patients, the sensitivity of pH monitoring in detecting pathology was 50 %. Currently, double probed pH monitoring including pharyngeal probe that we already used in our study is still the gold standard diagnostic tool.

Wise et al. [11] indicated that coexistence of OSAS and LPR was 60.7 % in their study. Nevertheless, in that study, a correlation between objective findings of PSG and parameters of pH monitoring could not be determined. A similar study of Ozturk et al. [14] which evaluated the association of these two common diseases with simultaneous pH monitoring and PSG revealed that in 62.2 % of

OSAS patients, LPR was also positive. On the contrary, Jecker et al. [15] in their study found that there was no difference in the frequency of LPR between OSAS patients and healthy group. In our study, 89.2 % of OSAS patients, LPR was again positive and also the coexistence of OSAS and LPR was found to be 57 %. These common findings of many studies indicated that these two diseases frequently coexist and hence they might have the common risk factors. Although OSAS and LPR frequently coexist, we could not mention an association between their severities since findings of pH monitoring did not show positive correlation with AHI.

Any possible association of apnea-hypopnea episodes with reflux attacks could only be determined by simultaneous pH monitoring and PSG. The study of Ozturk et al. [14] revealed this association up to 70 % of LPR attacks occurred during apnea-hypopnea episodes. Ing et al. [10] in their study pointed out that the association of GER attacks with apnea-hypopnea episodes and arousals was 53.4 and 43.8 %, respectively. Whereas in a study of Kerr et al. [29] a significant association was demonstrated between reflux attacks and arousals, a similar association was not present between attacks and apnea episodes. In the study of Steward [20], 50 % of arousals were found to be related with apnea-hypopnea. In our study, majority of reflux attacks were observed during daytime and almost half of overnight attacks were associated with apnea-hypopnea. All these findings suggest a long-term interaction between OSAS and LPR rather than a simultaneous development.

Since arousals are adversely related to quality of sleep and deep sleep duration, as mentioned in previous studies in patients with LPR or GER, sleep disturbances were highly observed [10, 20, 30, 31]. If so we expected to observe reduction in arousal index; nevertheless, in our study LPR treatment did not show any positive influence on arousal index. Furthermore, ESS which was another subjective parameter of sleep quality revealed significant improvement. Thereby we concluded that medical treatment of LPR provided an additional benefit for relief of subjective symptoms.

In their study Senior et al. [32] showed 25 % reduction in mean AHI with a success of 30 % in all patients (AHI decrement as 50 %) after LPR treatment. On the contrary, Steward [20] pointed that in his study which included 27 patients with sleep disordered breathing, there were decrements in ESS, sleep partner assessment of snoring and reflux awakening them from sleep only. However, no significant improvement was noted in snoring quantification, apnea, or AHI in that study. In other study of Ing et al. [10] after medical treatment with H2 blockers, they observed reduction in arousal index but no change in AHI. Suurna et al. [33] indicated improvement in ESS and decrement in arousals with PSG after completion of proton pump inhibitor treatment for 4 weeks. In our study there was no improvement in parameters of PSG after LPR treatment, but in subjective findings of OSAS such as snoring VAS and ESS, changes were significant. In only 30 % of patients AHI declined to 50 % which showed clinical success in common literature. We could not achieve an improvement in arousal index which was assumed to associate with ESS, contrary to the findings of common literature.

Another objective of this present study was to evaluate the influence of CPAP on LPR findings. There were different theories which explained positive influence of CPAP on lower esophageal sphincter pressure [17, 34, 35]. In their study Kerr et al. [36] used CPAP treatment to six patients with GER, and showed that CPAP had antireflux mechanism by influencing on middle and inferior constrictor pressures. And also this study revealed significant improvements in parameters of pH monitoring. In another study of Kerr et al. [29] they demonstrated significant decrease in GER frequency and duration in patient with OSAS and GER. The efficacy of 1-week CPAP treatment in patients with OSAS and concomitant GER was evaluated in the study of Tawk et al. [17]. They showed a significant reduction in acid contact duration with 24 h pH monitoring after CPAP treatment. In their other study Ing et al. [10] showed that CPAP usage in GER patients with or without OSAS, reflux number and reflux durations were significantly reduced. All these aforementioned studies were mainly aimed to assess the association between OSAS and GER. Since GER and LPR are two different clinical entities which might share common risk factors, we searched for coexistence of only OSAS and LPR and the effects of treatment in between them. For this reason, we preferred to evaluate data obtained from upper probe located at the level of postcricoid region. In our study there were significant improvements in subjective findings of RSI and RFS, but the objective parameters of pH monitoring did not show any significant change after CPAP treatment. This might be explained by inadequacy of CPAP to prevent reflux attacks during daytime.

Unfortunately, absence of blind study with control group and low number of patients may be the shortcomings of this presented study.

Conclusion

Since OSAS and LPR coexist frequently, all patients with OSAS should also be evaluated for LPR. However, the association between these two diseases remains unclear due to very complicated relation between them. Although there i some evidence that reveals positive impacts of LPR treatment on OSAS and vice versa, those findings have not been proved objectively. In the highlights of this study, we

concluded that more in-depth and comprehensive research is required to elucidate the association between OSAS and LPR and to develop accurate diagnosis and rationalized treatment policy covering each pathology.

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