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HEAD AND NECK

Relationship between the severity of laryngopharyngeal reflux and sleep apnea: using drug-induced sleep endoscopy (DISE)

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Abstract

Objectives The aim of the study is to identify the following associations: (1) severity of obstructive sleep apnea syndrome (OSAS) and laryngopharyngeal reflux (LPR)-related clinical parameters, such as reflux finding score (RFS), reflux symptom index (RSI), and LPR–health-related quality of life (LPR–HRQOL) and (2) complete obstruction on drug-induced sleep endoscopy (DISE) and LPR-related clinical parameters.

Materials and methods Subjects included the OSAS patients without surgery history and all patients perform the polysomnography (PSG) and DISE for their OSAS. Demographics, polysomnographic data, DISE results, and LPR-related parameters were collected prospectively. The patients were divided into age-, sex-, and BMI-matched two groups, according to numbers of complete obstruction on DISE (complete obstruction at 0–1 subsites (unilevel) vs. 2–4 subsites (multilevel). Finally, 19 patients with unilevel complete obstruction and 38 patients with multilevel complete obstruction were compared. The multiple linear regression analysis was employed to determine the predictors of LPR-related quality of life.

Results Among 88 patients, 19 patients demonstrated unilevel complete obstruction, and 69 patients demonstrated multilevel complete obstruction on DISE. There were no significant correlation between OSAS severity and RFS, RSI, and scores of LPR–HRQOL. Multilevel complete obstruction on DISE did not affect the LPR-related clinical parameters ($p > 0.05$). The result of multiple linear regression demonstrated complete obstruction at the epiglottis had a strong influence on the high scores of LPR–HRQOL.

Conclusion LPR is commonly developing disease with OSAS, but the OSAS severity did not affect the LPR-related parameters. The multilevel complete obstruction on DISE was not associated with the LPR-related clinical parameters.

Keywords Drug-induced sleep endoscopy · Laryngopharyngeal reflux · Extra-esophageal reflux syndromes · Obstructive sleep apnea

Introduction

Laryngopharyngeal reflux (LPR) is defined as the backflow of gastric contents to the laryngopharynx and upper aero-digestive tract [1]. LPR is relatively common disease which prevalence was reported up to 10% of patients presenting to an otolaryngologist's office, and 50% of patients with voice disorders had LPR [2]. Besides presenting voice problems, LPR has been considered as a common factor contributing to many extra-esophageal complaints including pulmonary disorder (asthma, cough, pulmonary fibrosis, etc.), dental caries, and even sinusitis and otitis media. Obstructive sleep apnea syndrome (OSAS) is also common complaints to visit ear, nose, and throat (ENT) clinics, and it characterized by repetitive upper airway collapse during sleep, causing sleep fragmentation, oxygen

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desaturation, and daytime sleepiness [3, 4]. Since both OSAS and LPR show similar risk factors such as obesity, male predominance, alcohol usage, and age, many studies had been discussed about possible association of OSAS with LPR [5, 6].

In OSAS patients, coexistence with LPR is very frequent presented as 20–67% [6–9]. Some studies have been tried to reveal the association of these two diseases using simultaneous testing with polysomnography (PSG) and double probed 24-h pH monitoring which has been known for golden standard of LPR diagnosis [7, 10]. However, due to lack of availability and costs, LPR diagnosis is currently based on empiric PPI treatment in many cases. Reflux finding score (RFS) and reflux symptom index (RSI) can also give many information about severity of LPR.

Recently, drug-induced sleep endoscopy (DISE) has been commonly used as a method of three-dimensional evaluation of the upper airway during sleep. Through examination of DISE, we can assess the sleep apnea-related upper airway structure and degree of obstruction. A recent study demonstrated that multilevel complete collapse was associated with severity of OSAS [11].

In this study, we aimed to identify the association with severity of OSAS and LPR-related clinical parameters, such as RFS, RSI, and LPR–health-related quality of life (LPR–HRQOL). Moreover, we tried to elucidate the possible association between complete obstruction on DISE and LPR-related clinical parameters.

Materials and methods

This study was approved by the institutional review board (IRB) of the Kyungpook National University of Hospital ethic committee. We performed a prospective study of the patients who were admitted to a tertiary medical center for the purpose of OSAS diagnosis from April 2014 and July 2015, and all of them were scheduled for diagnostic polysomnography (PSG) and DISE for suspected OSAS. The inclusion criteria for this study included as follows: age > 18 years, apnea–hypopnea index (AHI) > 5 on the PSG. The exclusion criteria included the previous surgical treatment for OSA, history of adenotonsillectomy at childhood, and inability to perform DISE (i.e., pure central apnea and history of allergy on the midazolam). Demographic data, polysomnographic data [AHI, snoring index, arousal index, and lowest oxygen saturation (SpO_2)], and results of the DISE were collected. Before undergoing DISE, a complete endoscopic examination of upper airway was performed, and meanwhile, the RFS of the patients was determined. In addition, all the patients were also queried for LPR symptoms by RSI and questionnaire about LPR–HRQOL.

LPR-related clinical parameters: RFS, RSI, and LPR–HRQOL questionnaire

The RFS is a validated eight-item clinical severity scale used to evaluate the most common laryngoscopic findings related to LPR [1]. The eight items included in the scale are "infraglottic edema, ventricular obliteration, erythema/hyperemia, vocal fold edema, diffuse laryngeal edema, posterior commissure hypertrophy, granuloma/granulation tissue, and thick endolaryngeal mucus". The scale ranges from 0 (no abnormal findings) to a maximum of 26 (worst possible score), and RFS greater than 7 is considered presence of LPR with 95% certainty [1]. The RSI is a self-administered outcome questionnaire for assessing the level of severity of LPR-related symptoms [1]. The questionnaire evaluates the level of symptoms and their severity through a six-point Likert scale, which ranges from 0 (no problem) to 5 (severe problem). The patients were considered to be suggestive of LPR when an RSI score greater than 11.

The LPR–HRQOL has been shown to be a reliable and valid rating scale for evaluating the quality of life (QOL) of LPR patients [12]. It consists of a simple questionnaire of 43 questions in the five categories of "hoarseness, cough, throat clearing, swallowing, and overall impact of acid reflux". The questionnaire consists of basic seven-point Likert scale questions in the first four categories and concludes with a ten-point Likert scale question regarding the overall impact of acid reflux.

DISE and classification of obstructive patterns

The DISE was performed at the outpatient clinic and evaluated by the only one of our author (Heo SJ) for all patients. With the circumstance of silent and dark to facilitate sleep, the nasal mucosa was topically anesthetized and shrunk with 4% lidocaine and 0.1% epinephrine. After anesthetizing the nasal mucosa sufficiently, patients were placed in the supine position with monitoring of arterial oxyhemoglobin saturation using a pulse oximeter. Then, midazolam at a dose of 0.05 mg/kg was administered intravenously to induce sleep. An additional dose of midazolam of up to 12 mg was administered under close oxyhemoglobin saturation monitoring when a sufficient level of sleep could not be achieved. A nasopharyngeal fiberscope (VNL1130, KayPENTAX, NJ, USA) was inserted through the nasal cavity at the onset of snoring or apnea and DISE was performed. The VOTE scoring system (velum, oropharynx, tongue base, and epiglottis) [13] was used to evaluate the obstruction of DISE, and degree of obstruction at each anatomical level as follows: 0, no obstruction;

(1) partial obstruction; and (2) complete obstruction. In this study, we classified the results of DISE scores at each anatomical subsite into two groups according to severity of obstruction (complete obstruction vs. non-complete obstruction). In addition, patients were divided into two groups according to the numbers of anatomical subsites with complete obstruction (1 subsite of complete obstruction; unilevel vs. 2–4 subsites of complete obstruction; and multilevel). These two groups were matched according to age, sex, and body mass index using the propensity score. Finally, 19 unilevel complete obstruction group and 38 multilevel complete obstruction group were investigated.

Statistical analysis

All statistical analyses were performed using the SPSS software (version 20.0; SPSS Inc., Chicago, IL, USA). Categorical data were marked as numbers and percentages, and continuous data were expressed as mean ± standard deviation. The variables with a normal distribution and groups were compared using Student's *t* test, ANOVA. The variables without a normal distribution and groups were analyzed using the Mann–Whitney *U* test. A *p* value less than 0.05 was deemed to indicate statistical significance. We applied multiple linear regression analysis to the all the patients to discover the explanatory variables, adjusting the influence of each independent variable on the dependent variable, rather than as a predictive model.

Results

Totally, 88 patients were included in this study. Table 1 shows the demographics, polysomnographic characteristics, and LPR-related parameters of the study patients. The study population is mainly composed of middle aged men which average age is 46.6 years, and over half of them (55.7%) are overweight (BMI ≥ 25.0). The mean AHI is 33.0 and 77.3% of them (68/88) have moderate-to-severe obstructive sleep apnea. The mean snoring index and arousal index are 203.5 and 36.8. The number of patients who demonstrated complete obstruction at the velum, oropharyngeal lateral wall, tongue base, and epiglottis on DISE was 85 (96.6%), 39 (44.3%), 39 (44.3%), and 16 (18.2%). Among the 88 patients, 69 (78.40%) patients demonstrated more than two subsites of complete obstruction. The distribution of the number of subsites with complete obstruction during DISE was as follows: 0 subsite, 2 of 88 (2.3%); 1 subsite, 17 of 88 (19.3%); 2 subsites, 49 of 88 (55.7%); 3 subsites, 16 of 88 (18.2%); and 4 subsites, 4 of 88 (4.5%). The mean RFS, RSI, and LPR–HRQOL were 6.4, 6.4, and 16.0, respectively.

Thirty-one (35.2%) patients showed significant laryngeal mucosal change (RFS > 7), and 13 patients (14.8%) complained about LPR-related symptoms (RSI > 11). With respect to the relationship between OSAS severity and LPR-related parameters, as described in Table 2, there was no significant correlation between OSAS severity and RFS, RSI, and scores of LPR–HRQOL.

Table 1 Demographics and clinical characteristics of the patients with obstructive sleep apnea

Characteristic	Result	
Age, years	46.6 ± 12.2	(19–68 years)
Sex (male:female)	77:11	
BMI, kg/m^2	25.7 ± 3.5	(18.7–37.0)
Polysomnography data		
Apnea–hypopnea index	33.0 ± 20.0	(6.6–84.0)
(mild:moderate:severe OSA)	20:25:43	
Snoring index	203.5 ± 185.5	(0.0–789.7)
Arousal index	36.8 ± 18.3	(6.3–81.0)
Lowest SpO_2, %	80.6 ± 11.5	(51.0–93.2)
Site of complete obstruction		
Velum	85 (96.6%)	
Oropharynx	39 (44.3%)	
Tongue base	39 (44.3%)	
Epiglottis	16 (18.2%)	
Multilevel (≥ 2) obstruction	69 (78.4%)	
LPR-related parameters		
Reflux finding score	6.4 ± 2.9	
Reflux symptom index	6.4 ± 6.2	
LPR–HRQOL	16.0 ± 26.1	

BMI body mass index, *LPR–HRQOL* LPR–health-related quality of life

Table 3 demonstrates the result of the comparison between unilevel and multilevel complete obstructions on DISE after propensity score matching (age-, sex-, and BMI). The mean AHI was slightly higher in the multilevel obstruction group than unilevel obstruction group with no statistically significant differences ($p = 0.062$). However, the LPR-related parameters, RSI, RFS, and total scores of LPR–HRQOL demonstrated no statistical significant differences.

Table 4 demonstrates the multiple linear regression analysis with the total scores of LPR–HRQOL as the dependent variable. The factor which made the greatest contribution to the LPR–HRQOL was the complete obstruction of the epiglottis ($p = 0.012$). However, other factors did not demonstrate significant relation to the LPR–HRQOL.

Discussion

Due to sharing the same risk factors and coexisting in many patients, an association between the OSAS and LPR has been suggested in the past studies. In a recent large cohort

Table 2 Relationship of obstructive sleep apnea and laryngopharyngeal reflux (LPR)-related clinical parameters, such as RFS, RSI, and LPR–health-related quality of life (LPR–HRQOL)

	Severity of OSA			*p* value
	Mild OSA ($n=20$)	Moderate OSA ($n=25$)	Severe OSA ($n=43$)	
Age	48.1 ± 12.9	43.4 ± 13.0	47.8 ± 11.2	0.301
BMI	25.3 ± 3.2	24.3 ± 2.4	26.7 ± 3.9	0.019
Reflux finding score	6.6 ± 3.3	6.1 ± 2.6	6.6 ± 2.9	0.820
Reflux symptom index	8.1 ± 7.9	5.8 ± 5.1	5.9 ± 5.8	0.380
LPR–HRQOL				
Voice	9.1 ± 14.6	3.4 ± 5.7	3.3 ± 7.5	0.055
Cough	2.5 ± 4.2	2.6 ± 5.1	1.5 ± 3.0	0.471
Throat clearing	4.6 ± 9.3	1.4 ± 2.3	2.0 ± 4.4	0.126
Swallowing	2.9 ± 5.8	1.4 ± 3.2	2.6 ± 4.8	0.502
Total reflux	4.9 ± 10.2	3.1 ± 8.1	5.4 ± 9.9	0.610

Table 3 Frequency of complete obstruction on drug-induced sleep endoscopy (DISE) and laryngopharyngeal reflux (LPR)-related parameters among age-, sex-, and BMI-matched 57 patients

	Unilevel complete obstruction ($n=19$)	Multilevel complete obstruction ($n=38$)	*p* value
Age	47.3 (24, 67)	46.6 (23, 65)	0.923
Sex (Male:Female)	18:1	36:2	1.000
BMI	24.6 ± 2.1	24.5 ± 2.6	0.907
Apnea–hypopnea index	26.7 ± 9.6	33.9 ± 18.7	0.062
Reflux finding score	6.1 (1, 11)	6.6 (1, 14)	0.720
Reflux symptom index	4.8 (0, 20)	5.3 (0, 17)	0.237
LPR–HRQOL	12.2 (0, 52)	11.3 (0, 88)	0.887

Table 4 Multiple linear regression analysis with the total score of health-related LPR questionnaire (LPR–HRQOL) as the dependent variable ($n=88$)

LPR–HRQOL	β	SE	95% CI	*p* value
Constant	12.778	2.988	6.838, 18.718	< 0.001
Age	− 0.035			0.739
Sex	0.021			0.843
BMI	0.152			0.146
Apnea–hypopnea index	− 0.075			0.475
Drug-induced sleep endoscopy (Complete obstruction)				
Velum	0.105			0.318
Oropharynx	− 0.001			0.995
Tongue base	0.124			0.247
Epiglottis	17.910	7.008	3.979, 31.840	0.012*
Multilevel	0.012			0.910

*Indicates statistical significance

study, 38.9% of OSAS patients, and the prevalence of gastroesophageal reflux disease (GERD) was considerably increased compared to the general population [14]. Our result was similar to the previous study that the prevalence of LPR which estimated by RFS was 35.2%. Moreover, the result accorded with the previous study that severity of OSAS and presence of GERD did not show the significant relationship. In a recent study, the authors revealed that severe OSAS patients have significantly higher nocturnal reflux by performing 24-h double-channel pH monitoring, not related to daytime reflux [15].

The close relationship between OSAS and LPR can be explained by one hypothesis that the increased respiratory effort during sleep leads to highly negative intrathoracic pressure, and it causes a vacuum-like effect inducing acid reflux. The acid reflux contributes to progression of upper airway obstruction [16]. The acid reflux develops the inflammation of the laryngopharyngeal mucosa, and inflammation directly causes tissue edema and upper airway narrowing. In addition, chronic inflammation and chemical irritation of the laryngopharyngeal mucosa generate sensory deficits and disrupt reflexes important in maintaining upper airway patency [16]. Based on these hypotheses, we hypothesized that the anatomical obstruction during sleep apnea which evaluated by DISE might influence the LPR-related parameters. DISE has proven valuable tool in diagnosing the presence and location of obstruction [13, 17, 18] by reproducing physiologic sleep. There have been few studies [11, 19], reported the correlation between AHI and obstruction site during DISE; however, there were no consistent results. One study [11]

reported that multilevel complete collapse was associated with higher AHI, whether another study [19] reported that there was no correlation between numbers of complete obstruction on DISE and AHI. This discrepancy can be explained with differences of patient selection, protocol, and obstruction definition. In our study, the increased numbers of complete obstruction on DISE seemed to have an influence on the high level of AHI with no statistical significance.

In the relationship between LPR-related parameters, RFS can be used to quantify the severity of laryngeal inflammation. While a study reported about negative correlation between AHI- and LPR-related parameters expressed by RFS [17], other study reported the positive correlation [20]. Our study also showed no significant relationship between severity of AHI and RFS. In addition, RSI and total scores of LPR–HRQOL were not associated with AHI. According to our hypothesis, multilevel complete obstruction on DISE might be associated with LPR-related parameters, but the results showed no significant findings. In the questionnaire of LPR–HRQOL, we can find the positive result that the complete obstruction at the epiglottis tends to have poor LPR-related life quality. This finding is agreed with other large cohort study which demonstrated a significant association between increased AHI and epiglottic obstruction [21].

This study has some limitations to consider. First of all, the 24-h pH monitoring is the golden standard to diagnose the presence of LPR, but we did not use it. The pH monitoring is invasive, expensive test, and also poorly tolerated. For those reasons, RFS, RSI, and questionnaire of LPR are commonly used to diagnose the presence of LPR in clinical setting with empirical proton pump inhibitor test. In our study, one physician (Kim H) scored the RFS, and it helps to increase the interrater reliability. Second, our study population is relatively smaller than a large cohort study. A larger study is also required to evaluate the DISE result as a useful clinical indicator of the LPR in patients with OSAS. Third, we have made decisions related to DISE, such as dividing the group with complete obstruction or not, and counting the numbers of complete obstruction on DISE. However, there is no definite standard in the literature; therefore, these limitations are currently inherent.

Nevertheless, this study has a strong point that this was the first attempt to identify the relationship between the LPR-related clinical parameters and anatomical obstruction findings during DISE. Nowadays, many sleep clinics perform the DISE and obstruction findings during DISE can be helpful to understand the physiologic mechanism of LPR with OSAS.

Some studies reported that nasal continuous positive airway pressure (CPAP) may help to reduce the reflux symptom and intensity [22]. It may be interesting to investigate the effect of post-CPAP or post-sleep surgery which makes changes of upper airway using DISE. Further study would be expected to identify the post-surgery effect on DISE.

Conclusions

LPR is commonly developing disease with OSAS, but the OSAS severity did not affect the LPR-related parameters such as RSI, RFS, and LPR–HRQOL. Multilevel complete obstruction on DISE seemed to be associated with high AHI; however, it was not associated with LPR-related clinical parameters. Meanwhile, the complete obstruction at the epiglottis may be associated with the poor LPR-related quality of life. Further large study would be expected to determine the relationship between LPR and anatomical obstruction findings on DISE.

Compliance with ethical standards

This work was supported by Biomedical Research Institute grant, Kyungpook National University Hospital (2014).

Conflict of interest Author Kim H has received research grants from Biomedical Research Institute grant, Kyungpook National University Hospital (2014).

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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