Turk J Gastroenterol 2004; 15(2): 77-81

Laryngopharyngeal reflux in laryngeal cancer

Larenks kanserinde larengofarengeal reflü

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Background/aims: *Gastropharyngeal or laryngopharyngeal reflux is considered as a factor in various diseases of the larynx and pharynx. The most important consequence of the reflux into the larynx is laryngeal cancer.* ***Methods:*** *In this prospective study the incidence of gastropharyngeal and laryngopharyngeal reflux in 22 patients with untreated laryngeal cancer was investigated with 24-hour, double probe pH measurements. A group of 25 patients with heartburn and dyspepsia complaints in whom esophagogastroscopy revealed no pathology and for whom 24-hour pH measurement was indicated served as a control group.* ***Results:*** *Two of the 22 patients never smoked and two others had quit smoking 16 and 25 years previously. All four of these patients revealed gastropharyngeal reflux. In total, 14 of the laryngeal cancer patients (63.6%) revealed gastropharyngeal reflux. The rate of gastroesophageal reflux was close among the two groups (50% in the cancer group vs 32% in the control group, p>0.05), but the laryngopharyngeal reflux rate was much higher in the cancer group (63.6% of the cancer patients vs 20% in the control group, p: 0.003). Among the reflux-positive patients and the controls, gastroesophageal reflux rate was higher in the supine position in cancer patients (12.10% vs 6.25, p: 0.02). In the upright position, control cases revealed higher rates of gastroesophageal reflux than the cancer patients. Laryngopharyngeal reflux rates were slightly higher in laryngeal cancer patients than the controls in both upright (9.29% vs 7.67%, p: 0.6) and supine positions (4.83% vs 3.50%, p: 0.6).* ***Conclusions:*** *Laryngeal cancer patients and patients with heartburn complaints all have a high rate of gastroesophageal reflux. But cancer patients reveal a higher rate of laryngopharyngeal reflux than the symptomatic patients with normal laryngeal findings.*

Keywords: Laryngopharyngeal reflux, laryngeal cancer

Amaç: *Gastrofarengeal veya larengofarengeal reflünün, larenks veya farenksin çeşitli hastalıklarında etken olduğu düşünülmektedir. Larenkse reflünün en önemli sonucunun larenks kanseri olduğu ileri sürülmektedir. Bu çalışmada larenks kanserli olgularda distale ve proksimale patolojik reflü sıklığının araştırılması amaçlanmıştır.* ***Yöntem:*** *Yeni tanı almış 22 larenks kanserli olguda, gastroözofageal ve larengofarengeal reflü, 24 saatlik pH monitorizasyonu ile prospektif olarak araştırılmıştır. Kontrol grubu olarak retrosternal yanma ve dispepsi yakınması ile başvuran ancak özofagogastroduodenoskopileri normal olan 25 olgu alınmıştır. Bu olgulara da 24 saatlik pH monitorizasyonu uygulanmıştır.* ***Bulgular:*** *Larenks kanserli 22 olgunun 2'si daha önceden sigara kullanmamış, 2 olguda 16 ve 25 yıl önce sigarayı bırakmışlardı. Bu 4 olgunun tümünde gastrofarengeal reflü tespit edilmiştir. Larenks kanserli olguların 14'ünde (%63.6) gastrofarengeal reflü saptanmıştır. Gastroözofageal reflü oranı her iki grup arasında benzer iken (kanser grubunda %50, kontrol grubunda %32, p>0.05), larengofarengeal reflü oranı kanser grubunda daha yüksek bulunmuştur (kanser olgularında %63.6, kontrol grubunda %20, p:0.003). Gastroözofageal reflü, larenks kanserli olgularda yatar pozisyonda daha belirgin (%12.10, % 6.25, p<0.05) bulunmuştur. Kontrol olgularında ayakta pozisyonda, gastroözofageal reflü oranı kanser olgularından daha fazla idi. Larengofarengeal reflü oranları, larenks kanserli olgularda hem ayakta (%9.29, %7.67, p:0.6) hem de yatar pozisyonda (%4.83, %3.50) kontrol grubuna göre hafif derecede yüksek bulunmuştur.* ***Sonuç:*** *Larenks kanserli olgularda ve kontrol grubunda gastroözofageal reflü oranları benzerdir. Ancak larenks kanserli olgularda proksimale reflü kontrol grubundan anlamlı derecede fazla bulunmuştur. Sigara kullanmayan olgularda da proksimale reflü tespit edilmesi larenks kanseri etyolojisinde reflünün de rolü olabileceğini düşündürmektedir.*

Anahtar kelimeler: Larengofarengeal reflü, larenks kanseri

INTRODUCTION

Gastropharyngeal reflux (GPR), also called laryngopharyngeal reflux (LPR), is the movement of gastric contents, bile acids and pancreatic enzymes up to the larynx and the pharynx. These substances have the potential to irritate or injure the tissues and may result in a variety of otorhinolaryngological manifestations such as globus pharyngeus (1), hoarseness, posterior laryngitis, vocal fold edema (2), pachydermia, vocal polyps, contact ulcers (3), and laryngeal cancer (4-10).

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Manuscript received: 23.03.2004 **Accepted: 12.04.2004**

Laryngeal squamous cell carcinoma accounts for 26% of all cases of head and neck squamous cell carcinoma, and the cause is likely multifactorial (11). Since the first reports from Cherry and Margulies (12) and Delahunty and Cherry (13), LPR has received increasing attention as a possible co-factor in laryngeal carcinoma. Although reflux has not yet been proven to be a carcinogenic co-factor, it is clear that reflux may cause acute and chronic laryngeal inflammation. It is known that gastroesophageal reflux may result in Barrett's esophagus and cancer development in the esophagus (14). In non-smoking patients such a mechanism may also be a contributing factor in the development of laryngeal carcinoma (11). Glanz and Kleinsasser (15) described 35 cases of chronic hypertrophic laryngitis who developed laryngeal carcinomas. Ward and Hanson (9) described 19 non-smoking patients with laryngeal carcinoma.

The rate of metachronous squamous cell carcinomas of the upper aerodigestive tract including the larynx is reported to be between 5% and 35% of cases (7). The esophagus is the second most common site and, consequently, it has been postulated that gastroesophageal reflux may be a carcinogenic co-factor.

MATERIALS AND METHODS

Twenty-two patients (mean age: 59.3, range: 43-75, 20 males, 2 females) with histologically proven laryngeal epidermoid carcinomas admitted to ENT, Head and Neck Department of Ankara Numune Research and Training Hospital were selected for this study.

The control group consisted of 25 patients (mean age: 50.8, range: 34-65, 19 males, 6 females) admitted to Turkey Yüksek İhtisas Hospital's Department of Gastroenterology with heartburn and/or dyspepsia complaints in whom gastroscopy was performed. The endoscopic examination of these patients did not reveal any pathology and they were sent for 24-hour pH measurement in the motility unit.

All patients, following a detailed history, were examined by videolaryngostroboscopy for TNM classification in the cancer group and for the laryngeal findings in the control group. Then esophageal manometry (8 channel, dent-sleeve catheter, water perfusion) was performed in all patients and the control cases to localize the lower esophageal sphincter. The probe was placed 5 cm above the lower esophageal sphincter. Double probe pH monitorization was performed (Digitrapper MK III, portable, Synectics Medical AB, Stockholm, Sweden) with 2 channels, 15 cm apart, single use catheter (Zinetics, Salt Lake City, USA). Both probes were connected to a pH recorder worn by the patient. During the 24-hour measurement, patients pointed out on the records their meals, sleeping time and beginning of the complaints as heartburn. No dietary restriction was used.

De Meester's criteria (16) was used for the distal esophagus. In this software program the following are taken into consideration and scored: pH falls less than 4 above the lower esophageal sphincter, % duration of pH falls in upright and supine position, the reflux rates, number of the pH falls lasting more than five minutes and longest reflux episodes. Scores over 15 are accepted as pathologic.

For the proximal esophagus, pH falls less than 4 lasting more than 1% of the total time was accepted as pathologic. Proximal pH falls that did not accompany the falls in the distal esophagus were not taken into consideration (Figure 1, 2, 3).

For the statistical analysis between the cancer and control groups chi-square and Mann-Whitney U tests were used. P values less than 0.05 were accepted as significant.

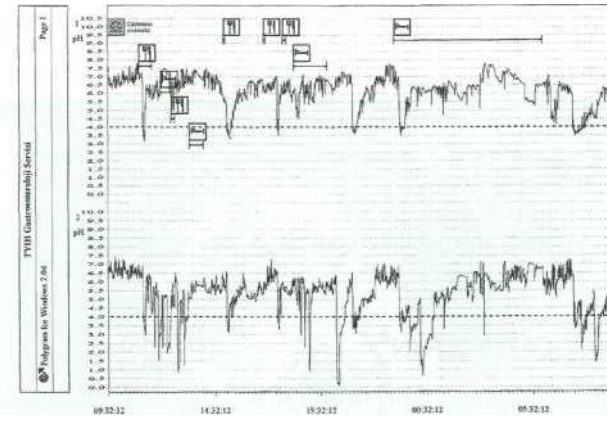

Figure 1. 24 hour pH measurement of a non-smoking patient with laryngeal carcinoma with pathologic gastroesophageal and laryngopharyngeal reflux

RESULTS

Eleven of the 22 laryngeal cancer patients (50%) and eight of the 25 control patients (32%) revealed gastroesophageal reflux (GER) (p: 0.214). On the

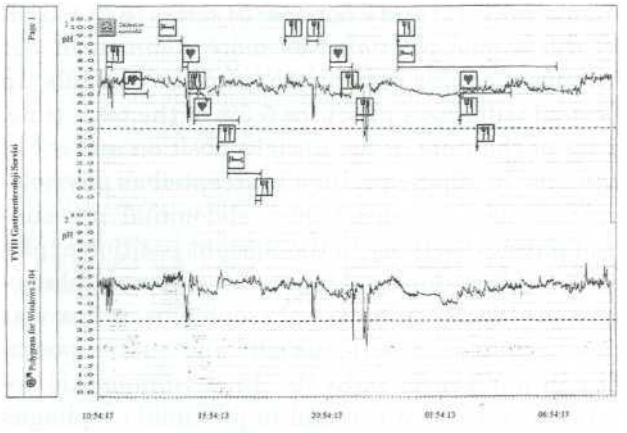

Figure 2. 24 hour pH measurement of a non-smoking patient with laryngeal carcinoma with normal gastroesophageal but pathologjic laryngopharyngeal reflux

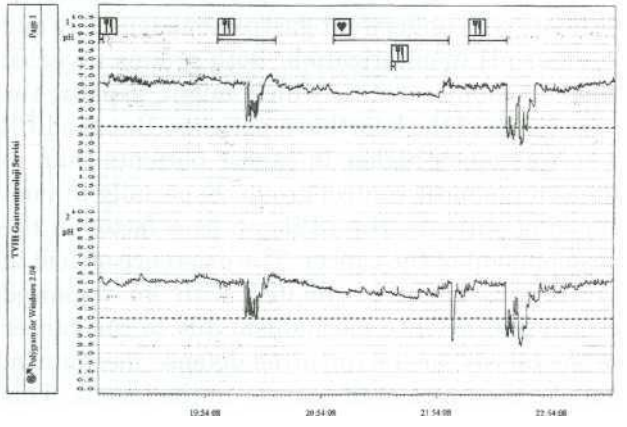

Figure 3. Enlarged view of the trace 3 revealing normal gastroesophageal reflux but pathologic laryngopharyngeal reflux with more than %1 of the total time

other hand 14 patients with laryngeal cancer (63.9%) and only five control patients (20%) revealed LPR (p: 0.003) (Table 1).

Eighty percent of the laryngeal cancer patients (18/22) were smokers; there were only two patients who never smoked, and one of them revealed pathologic LPR only. Two other patients had quit smoking 16 and 25 years previously. They both had pathologic GER and LPR.

Table 1. Gastroesophageal (GER) and laryngopharyngeal reflux (LPR) rates of the patients and controls

	GER (+)	GER (-)	LPR (+)	LPR (-)
Laryngeal Ca n:22	11 (50%)	11 (50%)	14 (63.9%)	8 (36.4%)
Controls n:25	8 (32%)	17 (68%)	5 (20%)	20 (80%)
P	0.214		0.003	

Table 2. Gastroesophageal reflux rates in reflux-positive patients and controls

	Upright (% average)	Supin (% average)
Laryngeal Ca (11/22)	8.18	12.10
Controls (8/25)	12.50	6.25
p	0.098	0.02

In GER-positive cancer patients the GER rate was higher than the reflux-positive control cases in the supine position (12.10% vs 6.25%, p: 0.02). In the upright position control cases revealed higher reflux rates than the cancer patients (8.18% vs 12.50%, p: 0.098) (Table 2). LPR rate was higher in laryngeal cancer patients both in upright (9.29% vs 7.67%) and supine (4.83% vs 3.50%) positions, but the differences were not significant (Table 3).

Table 3. Laryngopharyngeal reflux rates in reflux-positive patients and controls

	Upright (% average)	Supine (% average)
Larynx Ca (11/22)	9.29	4.83
Controls (8/25)	7.67	3.50
P	0.6	0.6

DISCUSSION

Smoking is an important factor in the etiology of laryngeal carcinoma, but mucosal damage from GPR may also contribute (17). Reflux in the distal esophagus to a certain degree is considered physiologic; this part of the esophagus is spared from the corrosive effect of gastric juice by a number of defense mechanisms including esophageal peristaltic movements, with acid clearance, tone of the lower esophageal sphincter and the resistance of the esophageal mucosa (7, 18-21). Bicarbonate in the saliva following acid exposure neutralizes the acid (21). The squamous epithelial lining of the esophagus is quite resistant but prolonged acid exposure may lead to adenocarcinoma development (22, 23). Upper esophageal sphincter is made up of the inferior constrictor muscle's thyropharyngeal and cricopharyngeal segments and some fibers from the esophagus. It is the last barier against gastic acid before entering the larynx. Its sphincteric action against gastric contents is of utmost importance as the tissues above that barrier, including larynx, pharynx and tracheobronchial tree, can not handle the acid exposure. Animal studies

have shown that gastric fluids may cause severe damage to the upper airway mucosa (13, 24). Bile, pepsin and gastric acid all contribute to the damage created in the larynx (25).

Abnormal pH findings were defined as a total percentage of esophageal acid exposure time of 6% or more as determined with the esophageal probe or any reflux event detected with the pharyngeal probe (17). In a group of patients with and without laryngeal cancer, Chen et al. (17) reported 34 out of 63 laryngeal and pharyngeal cancer patients (54%) with abnormal pH monitoring results. In 10 patients esophageal acid exposure and in seven patients pharyngeal acid exposure was abnormal. Of the 735 patients without malignancies, 365 (50%) had abnormal pH monitoring results. In this population of patients abnormal pH monitoring results were common, occurring in 399 of 798 (50%) patients, but no significant difference was found between results in those with and without laryngeal and pharyngeal carcinomas.

Cancer development by acid exposure following inflammatory disease was first suggested by Glanz and Kleinsasser in 1976 (15). In 1988 Morrison (8) and Ward (9) both postulated a causal relationship in LPR, laryngeal inflammation and carcinoma development in non-smokers, relying on history and barium esophagography. Smit (26) found pathological GPR in 82% of total laryngectomized patients using double probe 24-hour monitoring.

Our LPR rate in laryngeal cancer patients (63.9%) is lower than Smit et al. but higher than Koufman's (58%) (7) and Copper's (5) series (62%). GER in the supine position was more common in our laryngeal cancer patients than in the controls. In normal subjects a pH<4 for 5.5% of the total time, 8.2% of the time in the upright position and 3% of the time in supine position is accepted as physiologic (27, 28). Increased intra-abdominal pressure and physical activity in the upright position explain the reflux during daytime as a normal phenomenon (16, 29). In proximal esophagus, reflux was more common in both upright and supine positions in our cancer patients. In asymptomatic volunteers no acid was found in proximal esophagus and none in supine position (4, 7, 30).

CONCLUSION

In this study a group of patients with laryngeal cancer was compared with a group of symptomatic patients who underwent gastroesophagoscopy and 24-hour pH monitorization. Both groups revealed GER in similar rates, which might explain the complaints of the heartburn patients. But the LPR rate was much higher in cancer patients than in the symptomatic control group. Especially in non-smoking patients, the LPR can be a factor in the development of the cancer. The existence of acid in the larynx might be related with an impaired esophageal defense mechanism due to the cancer in the larynx, or the impaired defense mechanism may be the cause of the cancer in the larynx. This argument needs further research. We believe that recurrent laryngeal carcinomas in a non-smoking population will help us more in understanding the mechanism underlying this phenomenon.

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