The Relationship

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Original Article

The Relationship between Laryngopharyngeal Reflux Based on Pepsin Value and Clinical Characteristics of Laryngeal Cancer Patients

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Abstract

Introduction: Laryngopharyngeal reflux (LPR) is a suspected risk factor for laryngeal cancer. High prevalence of LPR is observed in patients suffering from laryngeal cancer. Hence, we studied the association between the presence and levels of LPR (as measured by pepsin value) and selected characteristics of laryngeal cancer patients. **Materials and Methods:** An observational analytic study involving 26 patients diagnosed with laryngeal cancer was designed. All patients provided sputum twice to be evaluated later for pepsin level (pepsin I and pepsin II) using ELISA. Data analysis was performed using Statistical Package for the Social Sciences software (SPSS, Inc. version 23.0, Chicago). **Results:** Twenty-four out of 26 patients were male with a mean age of 60.65 ± 8.41 years, 7 were severe drinkers, 12 were severe smokers, and 24 patients had late-stage laryngeal cancer. All patients were diagnosed with LPR. There was a significant association of pepsin I (daytime/provoked LPR) level with alcohol consumption ($P = 0.002$) and a significant difference between the value of pepsin I in heavy and light smokers ($P = 0.039$). **Conclusion:** LPR was significantly correlated with alcohol consumption and smoking status among the laryngeal cancer patients. It is recommended that avoiding alcohol consumption and smoking can significantly curtail LPR and hence potentially the incidence of laryngeal cancer.

Keywords: Laryngeal cancer, laryngopharyngeal reflux, pepsin

Introduction

Laryngeal cancer is a frequent head and neck cancer that constitutes approximately 30%–50% of all cancers in this anatomic area. It usually affects men with a mean age of 50–60 years. In 2008, the World Health Organization[1] reported the incidence rates of laryngeal cancer worldwide as 5.5/100,000 in men and 0.6/100,000 in women (2.4/100,000 population-wide). Risk factors include smoking, alcohol consumption, human papillomavirus infection, genetic susceptibility, radiation, and environmental conditions (e.g., exposure to cement dust and asbestos). Due to its multifactorial risks, the pathogenesis of this cancer remains elusive. Laryngopharyngeal reflux (LPR) is also reported to be another risk factor for laryngeal cancer.[2] LPR is defined as retrograde backflows of stomach contents into the larynx, pharynx, and upper airway due to disrupted function of the upper esophageal sphincter. The stomach backflows contain acid and pepsin that cause injury to laryngeal mucosa. This mucosa is a thin and fragile layer, and thus, it is more vulnerable to chemical injury than esophageal mucosa.[1-7]

Many studies have associated LPR with laryngeal cancer.[8] However, a causal relationship has yet to be established. The current gold standard test for reflux is double-probe 24-h pH monitoring. This method is considered far from ideal because of its low sensitivity (50%–80%) and invasive nature (up to 12% of patients could not tolerate this procedure). Therefore, a more sensitive, noninvasive, and inexpensive method, such as pepsin assay, is needed to diagnose reflux. Knight *et al.*[10] in 2005 showed that ELISA for pepsin level in sputum had a

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sensitivity and specificity of 100% and 89%, respectively. It is a highly sensitive and specific test compared to a pH-meter. Samuels and Johnston[11] in 2010 stated that pepsin was the most sensitive and specific marker for extraesophageal reflux; it could directly detect reflux in the respiratory tract that could not be reached by a pH-meter or multichannel intraluminal impedance test.[2,8-11] Hence, this study was designed to highlight the presence and intensity of LPR, based on the pepsin value, in relationship with the clinical characteristics of laryngeal cancer patients.

Materials and Methods

This is an observational analytic study with 26 laryngeal cancer patients who attended the Ear, Nose, and Throat Outpatient Clinic, Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia. All the patients participated consecutively in periods from September 2013 to March 2014. The Ethics Committee of the Faculty of Medicine, Universitas Indonesia, approved the study. All patients who met the inclusion criteria were informed verbally and in writing and signed consent form. Characteristic data of the patient included alcohol consumption, i.e., categorized as Haworth–Hoeppner classification, someone with a history and/or currently still consuming alcohol at least 1x/month with 4–5 glasses/event or 1–2x/week with 2–3 cups per event or 5x/week with 1 glass/event; smoking status, i.e., categorized as nonsmoker (0 cigarette, light [1–200 cigarettes], moderate [201–600 cigarettes], and heavy smokers [>600 cigarettes]); and laryngeal cancer stage, i.e., categorized as early Stage (I–II) and advanced Stage (III–IV).

All patients were asked to collect sputum twice in a 1-cc collection tube. First, the patients were asked to collect the sputum 30 min after eating; this sample was identified as the pepsin I (daytime pepsin for provoked LPR) level. Second, the patients collected sputum in the first 15 min after waking in the morning; this sample was identified as the pepsin II (nocturnal pepsin for unprovoked LPR) level. Citric acid 0.5 cc was added in the collection tubes as a bactericide and to maintain the pepsin in an acid environment. All the collection tubes were kept at −80°C until the ELISA examination. The ELISA test was performed with human pepsin reagent USCN SEA632Hu (Wuhan USCN Business Co. Ltd., Wuhan, Hubei, PRC). The pepsin result was deemed to be positive if the pepsin value from pepsin I and/or II level was ≥108.1 pg/mL, and the diagnosis of LPR was established if there was a positive pepsin value. Univariate analysis was used for categorical and numerical data scal Numerical data were tested for normality of the data using Shapiro–Wilk test. If the data distribution was not normal ($P < 0.05$), the data were presented as median value with its minimum–maximum value. Otherwise, if normal data distribution was obtained ($P > 0.05$), t ata were presented as mean with its standard deviation. Bivariate analysis was used to assess the relationship between each independent variable and the dependent variable with a significance value of $P < 0.05$.

Results

Twenty-four of 26 patients were male with a mean age of 60.65 ± 8.41 years. Seven patients were heavy alcohol drinkers, 12 were heavy smokers, and 24 presented with late-stage laryngeal cancer. LPR was seen in all patients, with an average pepsin I (daytime/provoked LPR) level of 488.88 (93.75–1702.95) pg/mL and an average pepsin II (nocturnal/unprovoked LPR) level of 584.25 ± 311.73 pg/mL.

There was no difference between the mean values of pepsin I (626.1 ± 412.0) pg/mL and pepsin II (601.7 ± 317.5) pg/mL in men as well as in women (pepsin I level of 447.2 ± 215.0 pg/mL and pepsin II level of 374.9 ± 125.5 pg/mL). There was no significant relationship between the pepsin I and II level with age. However, the mean of pepsin I was significantly higher among the alcohol consumption patients as compared to the nondrinkers ($P = 0.002$) [Table 1]. A significant difference was also observed in pepsin I levels between the light and heavy smokers ($P = 0.039$) [Table 2]. There was no significant difference between pepsin I and II levels in early and late laryngeal cancer stage ($P = 0.88$ and $P = 0.920$). There was no significant relationship between the pepsin II level with the four groups of combination of smoking and alcohol status; however, the mean of pepsin I was significantly different between the four groups of combination of smoking and alcohol status ($P = 0.033$) [Table 3]. A significant result was also observed in the pepsin I levels between smoking and alcohol versus smoking-only group ($P = 0.010$) and between smoking and alcohol versus neither smoking nor alcohol group ($P = 0.015$) [Table 3]. There was no significant difference between pepsin I level between smoking only versus neither smoking nor alcohol group ($P = 0.655$).

Discussion

All laryngeal cancer patients in this study had LPR with a mean value of pepsin much lower than that found in Wang *et al*.[12] and Knight *et al*.,[10] whose research showed average pepsin levels of 199,590 pg/mL and 180,000 pg/mL, respectively. This difference could be due to differences in research subject, sputum collections, and food and beverage consumption. The

Table 1: Laryngopharyngeal reflux based on alcohol consumption status (n=26)

	Pepsin I (pg/mL)	*P*	Pepsin II (pg/mL)	*P*
Alcohol consumption patients (n=7)	1011.2±363.4*	0.002^^	628.5±273.6*	0.670^
Nonalcohol consumption patients (n=19)	465.4±306.7*		567.9±330.1*	

*Mean value±SD, ^Unpaired *t*-test, ^^Mann-Whitney test. SD: Standard deviation

Table 2: Laryngopharyngeal reflux based on smoking status (*n*=26)

Smoking status	Pepsin I (pg/mL)	*P*	Pepsin II (pg/mL)	*P*
Nonsmoker (*n*=4)	518.8±335.3*	0.173^^^	443.8±248.2*	0.240^^^
Light (*n*=4)	298.3±128.4*	0.039***	433.7±207.2*	
Moderate (*n*=6)	546.3±375.2*		511.7±394.3*	
Heavy (*n*=12)	781.2±439.1*		717.5±289.8*	

*Mean value±SD, ^^^One way ANOVA test, ***Post hoc test between the heavy and light smokers. SD: Standard deviation

Table 3: Laryngopharyngeal reflux based on smoking and alcohol status (*n*=26)

Smoking and alcohol status	Pepsin I (pg/mL)	*P*	Pepsin II (pg/mL)	*P*
Smoking and alcohol (*n*=6)	1020.5±397.2*	0.033^^^^	645.6±295.6*	0.799^^^
Smoking only (*n*=16)	482.7±324.5*		590.2±345.8*	
Alcohol only (*n*=1)	955.9*		526.0*	
Neither alcohol or smoking (*n*=3)	373.1±203.2*		416.4±296.5*	

*Mean value±SD, ^^^One way ANOVA test, ^^^^Kruskal-Wallis test. *Post hoc* among the pepsin I: Mann-Whitney test between smoking and alcohol versus smoking only, *P*=0.010, and between smoking only versus neither smoking nor alcohol, *P*=0.655. Unpaired *t*-test between smoking and alcohol versus neither smoking nor alcohol, *P*=0.015. SD: Standard deviation

low value of pepsin in our laryngeal cancer patients suggests that mucosal damage due to pepsin can occur even at a low concentration. This result is comparable with Wang *et al.*[12] and Andriani *et al.*,[13] who found low concentrations of pepsin in patients with a high reflux finding score (RFS) and reflux symptom index.

The proportion of patients with LPR in this study was higher than in previous studies. Ozlugedik *et al.*[9] (Turkey) in 2006 found that 62% of patients with laryngeal cancer had LPR, and Tae *et al.*[2] (Korea) found LPR in 86.2% of patients. The difference in the proportion of patients with LPR could be due to the method used to diagnose it. While other studies used double-probe 24-h pH monitoring for LPR detection, we used the more sensitive and specific ELISA-based pepsin assay.[2,9] LPR in laryngeal cancer was seen in both sexes and at all ages and disease stages. Our study found a significant relationship between pepsin I (daytime/provoked LPR) value and alcohol consumption and a significant difference in the pepsin I value between light and heavy smokers, between smoking and alcohol versus smoking only, and between smoking and alcohol versus neither smoking nor alcohol. This finding is in agreement with the literature that has stated smoking and alcohol consumption could trigger LPR and are therefore considered as risk factors for laryngeal cancer. Alcohol consumption affects the lower and upper esophageal sphincter, exacerbating the delay in gastric emptying and changing the motility of the esophagus.[14-18]

Based on this study, it is important to build community awareness of LPR and its management. The high incidence of LPR in laryngeal cancer from this and other studies indicates that LPR could be considered as a possible determinant factor in laryngeal cancer. Further, LPR is related to alcohol consumption and smoking status among the laryngeal cancer patients. It is hence recommended to prevent laryngeal cancer by avoiding alcohol consumption and smoking. Treatment of LPR can potentially prevent laryngeal cancer, and ELISA test for pepsin level in sputum could be a supporting examination for LPR, especially in laryngeal cancer patients, as it is a noninvasive and inexpensive method.

Conclusion

LPR was significantly correlated with alcohol consumption and smoking status among laryngeal cancer patients. The high incidence of LPR in laryngeal cancer from this and other studies indicates that LPR could be considered as a possible determinant factor in laryngeal cancer. It is recommended that avoiding alcohol consumption and smoking can significantly curtail LPR and hence, potentially the incidence of laryngeal cancer.

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Conflicts of interest

There are no conflicts of interest.

References

1. World Cancer Research Fund/American Institute for Cancer Research. Worldwide Cancer Data. Available from: https://www.wcrf.org/dietandcancer/cancer-trends/worldwide-cancer-data. [Last accessed on 2018 Jan 23].
2. Tae K, Jin BJ, Ji YB, Jeong JH, Cho SH, Lee SH. The role of laryngopharyngeal reflux as a risk factor in laryngeal cancer: A preliminary report. Clin Exp Otorhinolaryngol 2011;4:101-4.
3. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69-90.
4. Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. Eur J Cancer 2010;46:765-81.
5. Francis DO, Maynard C, Weymuller EA, Reiber G, Merati AL, Yueh B. Reevaluation of gastroesophageal reflux disease as a risk factor for laryngeal cancer. Laryngoscope 2011;121:102-5.
6. Dietz A, Ramroth H, Urban T, Ahrens W, Becher H. Exposure to cement dust, related occupational groups and laryngeal cancer risk: Results of a population based case-control study. Int J Cancer 2004;108:907-11.
7. Ramroth H, Ahrens W, Dietz A, Becher H. Occupational asbestos

exposure as a risk factor for laryngeal carcinoma in a population-based case-control study from Germany. Am J Ind Med 2011;54:510-4.
8. Koufman JA. The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): A clinical investigation of 225 patients using ambulatory 24-hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal injury. Laryngoscope 1991;101:1-78.
9. Ozlugedik S, Yorulmaz I, Gokcan K. Is laryngopharyngeal reflux an important risk factor in the development of laryngeal carcinoma? Eur Arch Otorhinolaryngol 2006;263:339-43.
10. Knight J, Lively MO, Johnston N, Dettmar PW, Koufman JA. Sensitive pepsin immunoassay for detection of laryngopharyngeal reflux. Laryngoscope 2005;115:1473-8.
11. Samuels TL, Johnston N. Pepsin as a marker of extraesophageal reflux. Ann Otol Rhinol Laryngol 2010;119:203-8.
12. Wang L, Liu X, Liu YL, Zeng FF, Wu T, Yang CL, *et al.* Correlation of pepsin-measured laryngopharyngeal reflux disease with symptoms and signs. Otolaryngol Head Neck Surg 2010;143:765-71.
13. Andriani Y, Akil MA, Gaffar M, Punagi AQ. Deteksi pepsin pada penderita refluks laringofaring yang didiagnosis berdasarkan reflux symptom index dan reflux finding score. ORLI 2011;41:121-7.
14. Dağli S, Dağli U, Kurtaran H, Alkim C, Sahin B. Laryngopharyngeal reflux in laryngeal cancer. Turk J Gastroenterol 2004;15:77-81.
15. Vardouniotis AS, Karatzanis AD, Tzortzaki E, Athanasakis E, Samara KD, Chalkiadakis G, *et al.* Molecular pathways and genetic factors in the pathogenesis of laryngopharyngeal reflux. Eur Arch Otorhinolaryngol 2009;266:795-801.
16. Galli J, Cammarota G, Calò L, Agostino S, D'Ugo D, Cianci R, *et al.* The role of acid and alkaline reflux in laryngeal squamous cell carcinoma. Laryngoscope 2002;112:1861-5.
17. Sadri M, McMahon J, Parker A. Laryngeal dysplasia: Aetiology and molecular biology. J Laryngol Otol 2006;120:170-7.
18. Lewin JS, Gillenwater AM, Garrett JD, Bishop-Leone JK, Nguyen DD, Callender DL, *et al.* Characterization of laryngopharyngeal reflux in patients with premalignant or early carcinomas of the larynx. Cancer 2003;97:1010-4.

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