

Gastroesophageal Reflux Disease in Patients with Minimal Associated Pathological Lesions of the Vocal Folds with Associated Symptoms and Laryngeal Findings

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Abstract: The purpose of this current study is to investigate the role of gastroesophageal reflux disease (GERD) as a risk factor for Minimal Associated Pathological Lesions (MAPLs) of the vocal folds with associated symptoms and laryngeal findings, and to assess the prevalence of GERD in these patients. This study included one hundred and fourteen patients with MAPLs and associated symptoms who have met the inclusion criteria. The patients were 72 (63%) males and 42 (37%) females with age ranged from 19 to 72 years. All the patients were assessed according to a protocol including auditory perceptual analysis (APA), E.N.T examination, vocal fold augmentation and documentation via video stroboscopic system, acoustic analysis of patient's voice, and finally esophagogastroduodenoscopy (EGD) and lower esophageal biopsies were taken for histopathological evaluation. Results revealed that the MAPLs of the vocal folds and associated laryngeal findings were significantly higher in GERD compared with non-GERD patients ($P < 0.05$) except for vocal folds polyps, vocal folds nodules and chronic laryngitis ($P > 0.05$). In conclusion, the prevalence of GERD in patients with MAPLs is high, and GERD may manifest atypically as ENT symptoms without symptoms of heartburn and regurgitation.

Key words: Gastroesophageal Reflux Disease, Minimal Associated Pathological Lesions.

INTRODUCTION

Gastroesophageal Reflux Disease (GERD) is defined as a backward flow of gastric contents into the esophagus (Cummings, 1993). GERD is a very common condition affecting 25-40% of the population (Jones, 1995). In GERD, the gastroduodenal contents leak back into the esophagus, go through the upper esophageal sphincter and reach the aero-digestive airways (Moraes-Filho *et al.*, 2002; Cuenca-Abente *et al.*, 2006). Such an episode is called laryngopharyngeal reflux (LPR) (Jacob *et al.*, 1991; Ozturk *et al.*, 2006).

Laryngopharyngeal reflux is a type of reflux-related disease characterized by the backflow of gastric contents from the stomach and esophagus into the pharynx and larynx (Beaver *et al.* 2003; Rees and Belfasky, 2008). It has been reported in up to 10% of patients presenting to an otolaryngologist's office (Koufman, 1991).

Gastroesophageal reflux disease has been increasingly recognized as a cause of chronic laryngeal symptoms via LPR. Patients with chronic laryngitis often experience throat burning, throat clearing, chronic cough, hoarseness of voice and globus (Koufman, 1991). The reported prevalence of reflux disease is about 80% in patients with hoarseness or other voice complaints (Katz, 1990).

The group of Minimal Associated Pathological Lesions (MAPLs) of the vocal folds includes benign lesions which are caused by vocal trauma. They may occur as a result of long standing non-organic voice disorders. This group includes: vocal folds nodules, vocal folds polyps, contact granulomas, vocal folds cysts and Reinke's edema. Many factors may contribute in the production of these disorders (Barakah *et al.*, 2012).

Heightened awareness of LPR can lead to overdiagnosis of the condition because the typical LPR symptoms (excessive throat clearing, cough, hoarseness, and globus pharyngeus) are nonspecific and can also be caused by infections, vocal abuse, allergy, smoking, inhaled environmental irritants, and alcohol abuse (Ford, 2005).

There is a danger in failing to recognize LPR, while over diagnosis of LPR can lead to unnecessary costs and missed diagnoses. When a medical practitioner fails to recognize LPR, patients have prolonged symptoms and delayed healing.

Laryngopharyngeal reflux can cause subglottic stenosis and laryngospasm, dysphonias, pharyngitis, asthma, pneumonia, nocturnal choking, and dental diseases. It seems that not only reflux of gastric contents into the esophagus but also reflux up to or above the upper esophageal sphincter may cause laryngological complaints. This phenomenon is called gastropharyngeal reflux (GPR) or laryngopharyngeal reflux (Ford, 2005).

In patients with GERD, reflux esophagitis (RE) is more easily diagnosed definitely by endoscopy (Lai *et al.*, 2008). Endoscopic GERD can be diagnosed if definite mucosal breaks are observed in the distal esophagus or if strictures, ulcers, and columnar metaplasia are noted. The two most widely used classification systems for endoscopic GERD are the Savary-Miller and the Los Angeles Classifications (Lundell *et al.*, 1999).

Reports on the relation between GPR and otolaryngological symptoms are scarce. Therefore, we decided to evaluate the role of GERD in patients with MAPLs of the vocal fold with associated symptoms and laryngeal findings and to determine the prevalence of GERD among cases with laryngeal symptoms.

Aim of the Work:

The goal of this study is to evaluate the role of Gastroesophageal reflux disease as a risk factor for Minimal Associated Pathological lesions of the vocal folds and to assess the prevalence of GERD in these patients.

Patients and Methods:

Patients:

This study was conducted on subjects who attended the Phoniatics Clinic, Sohag University Hospitals with Minimal Associated Pathological lesions of the vocal folds with associated symptoms and laryngeal findings during the period from August 2010 to August 2012. One hundred and fourteen patients with Minimal Associated Pathological lesions of the vocal folds with associated symptoms and laryngeal findings have met the inclusion criteria.

Inclusion Criteria:

Consecutive patients attending the Phoniatics Clinic, Sohag University, who were diagnosed as patients with MAPLs and associated symptoms and who agreed to be included in this research and ready for its obligations were considered suitable for the study.

The list of MAPLs included vocal folds nodules, polyps, cysts, Reink's edema, and contact granulomas with associated laryngeal findings which include posterior laryngitis and chronic laryngitis. The list of complaints included difficult swallowing, choking during night, cough, stridor, frequent throat clearing, feeling of a lump and typical symptoms of reflux (heart burn and regurgitation).

Exclusion Criteria:

We excluded any patient who has any of the following: past or present smoker, chronic cough attributable to known chronic pulmonary or tracheobronchial disease, professional voice users (e.g. singer, teacher), excessive voice use, exposure to occupational or environmental pollutants, history of seasonal allergic rhinitis, use of H2-receptor antagonists or proton pump inhibitors in the previous month, previous neck/glottal surgery, radiotherapy or malignancy, pharyngolaryngeal infection in the previous 3 months, tracheal intubation in the previous 12 months and use of inhaled corticosteroids (Vaezi *et al.*, 2006; Qua *et al.*, 2007).

Methods:

Patients who met the inclusion criteria were given a clear explanation of the study objectives and plan of the study and signed informed consent to participate in the study. All patients were subjected to the following protocol:

I- Protocol of assessment described by kotby (1986). The protocol includes:

Elementary Diagnostic Procedures Included:

- Personal history, complaint, analysis of symptoms, full ENT, head and neck examination.
- Auditory perceptual assessment (APA): during the history taken the clinician scored the over all grad of the change of voice from 0 to 3 (0 means normal, 1 means mild dysphonia, 2 means moderate degree of dysphonia, 3 means severe degree of dysphonia). The character of dysphonia also were assessed (Strained, Leaky, breathy and irregular) and scored 0 to 3. Pitch, loudness, register, and glottal attach were evaluated.

Clinical Diagnostic Aids Included:

- Videostroboscopic evaluation was done by using Kay Pentax stroboscopic model RLS9100B (Kay Elemetrics Corporation, Englewood, NJ), camera (endovision DX _ com model 20230020, Stroz) and telescope (wolf model 445057).

Additional Instruments Included:

- Acoustic analysis of vowel / a / by asking the patient to sustained / a / vowel at comfortable level for approximate 2 seconds. This was achieved by the multidimensional voice program (MDVP) model 4300 (Kay Elemetrics Corporation, Englewood, NJ).
- Aerodynamic evaluation was obtained by using Kay aerophone II (Kay Elemetrics Corporation, Englewood, NJ). Patients also were asked to sustained / a / vowel as long as possible after a maximum inhalation to obtain the maximum phonation time (MPT).

2- Esophagogastroduodenoscopy (EGD):

All patients were, at first, attended in Phoniatics Clinic and then sent for EGD evaluation. Complete endoscopic examination using a video endoscope (videoscope Olympus GIF-XQ 260) was done, stressing on any abnormality in the lower esophagus. The degree of esophagitis noted during EGD was graded according to the Loss-Angeles (LA) classification. Patients with mucosal breaks were considered to have erosive reflux disease (ERD). Patients were considered to have non-erosive reflux disease (NERD) if they had typical symptoms of GERD in the absence of esophageal mucosal injury (Hershcovici and Fass, 2010). All patients were subjected to esophageal biopsy for histopathological examination. In each subject, four specimens were taken 5 cm above the squamo-columnar junction by a biopsy forceps (Olympus KW2415S). All the specimens were 10% formalin fixed. The patients were grouped as GERD and non-GERD based on the above criteria.

3- Histopathological Evaluation:

Tissue sections were obtained from the paraffin embedded tissue blocks prepared from formalin fixed biopsies, and stained with Hematoxylin and Eosin stain. The H&E stained sections were examined for any pathological changes e.g, esophagitis, columnar metaplasia (Barrett's esophagus), mucosal erosions.

Statistical Analysis:

Statistical analysis was performed using SPSS version 10. Frequency, percentage, mean and standard deviation were calculated for patients with laryngeal disorder and were compared between GERD and non GERD groups using the chi-square test for all categorical variables except for reflux symptoms and Reinke's oedema where Fisher's exact test we used. Spearman's correlation coefficient (rho) was used for the detection of correlation.

Results:

During the study period, 114 patients with Minimal Associated Pathological Lesions of the vocal fold with associated symptoms and laryngeal findings who underwent endoscopic examination were recruited into the study. The age of the patients ranged from 19 to 72 years with a mean age of 43.31±11.81 years. They were 72 (63%) males and 42 (37%) females. Regarding gastroesophageal reflux disease; 22 (19.3%) patients did not have GERD as defined by the absence of typical symptoms (heartburn and/or regurgitation), and normal endoscopic and histological features. 92 (80.7%) patients had GERD as defined by typical symptoms. Of them, 9 (7.9%) had an apparently normal esophageal mucosa at endoscopy (NERD), whilst 83 (72.8) had erosive reflux disease (ERD) (Figure 1).

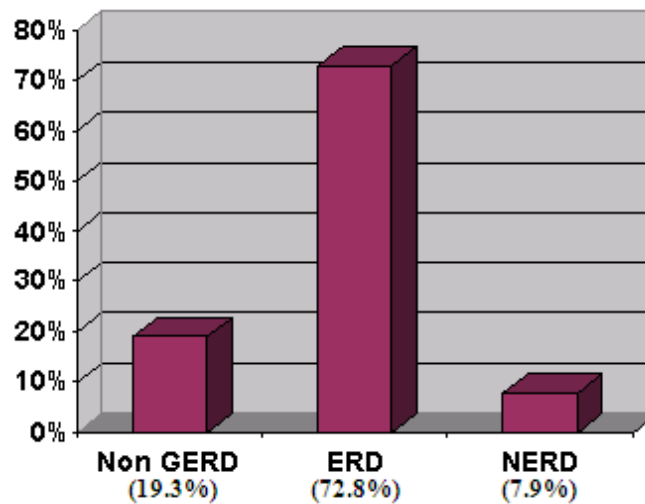


Fig. 1: Percentage of non GERD and GERD (ERD + NERD) patients.

Histopathological assessment of patients with GERD (Figure 2): Among the 83 patients affected by ERD, 47 (56.6%) had mild esophagitis, 21 (25.3%) had moderate esophagitis, 12 (14.5%) had severe esophagitis, and 3 (3.6%) had metaplasia. Among patients affected by NERD only 7 (77.8%) patients had mild esophagitis, while the remaining 2 (22.2%) had severe chronic inflammatory cell infiltrates.

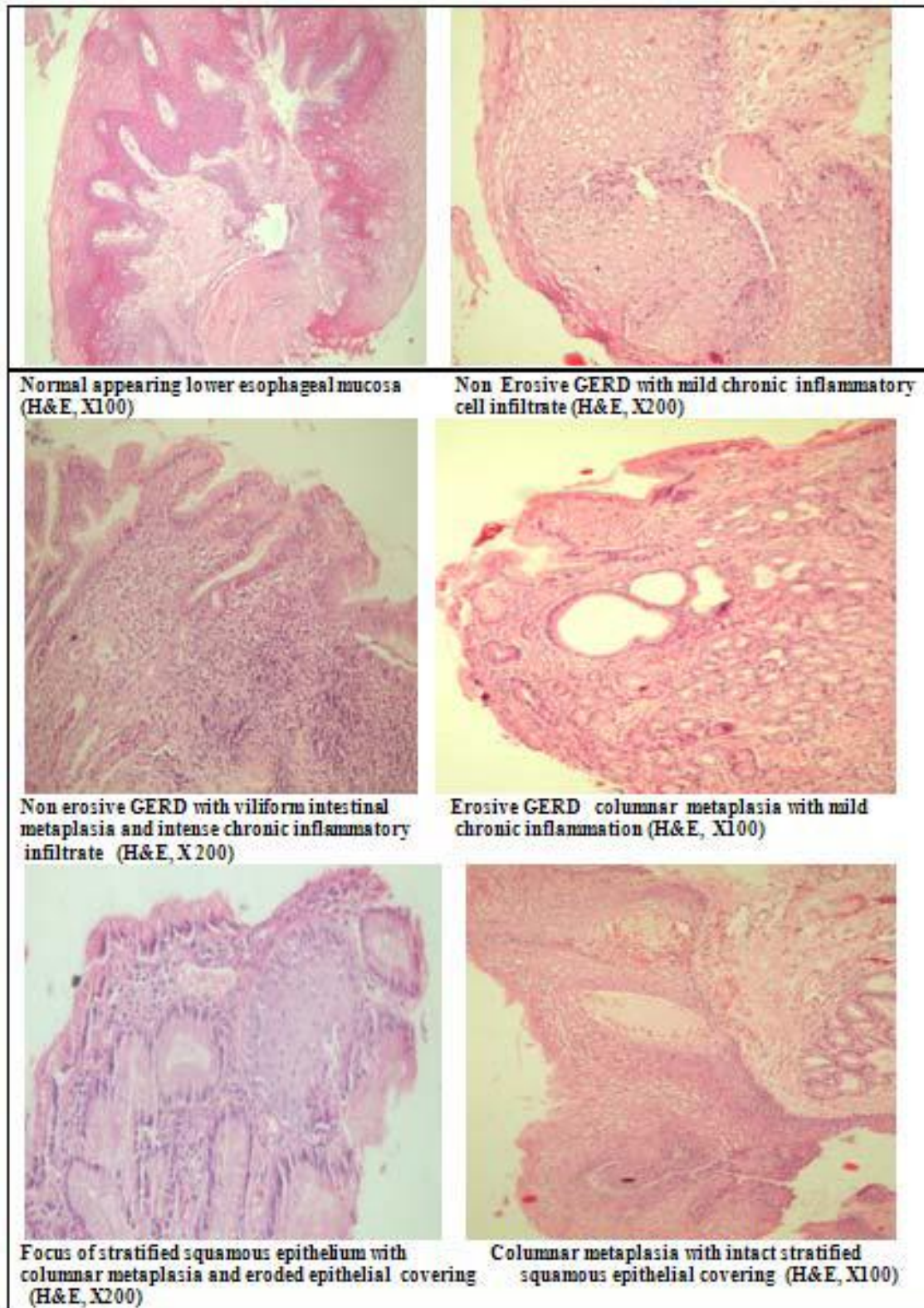


Fig. 2: Photomicrographs of lower esophageal mucosa, showing normal appearing mucosa, and various changes which occur in the mucosa of GERD patients.

The distribution of laterality of MAPLs (Table 1): In our study, most patients with vocal folds polyps had unilateral lesions, most patients with contact granulomas and Rienke's edema had bilateral lesions, while all patients with vocal folds nodules had bilateral lesions, and all patients with vocal folds cysts had unilateral lesions.

Table 1: The distribution of laterality of MAPLs.

MAPLs	Bilateral	Unilateral
Vocal folds polyps	3	32
Contact granulomas	22	1
Vocal folds nodules	22	0
Vocal folds cysts	0	19
Rienke's edema	13	2

Distribution of LPR symptoms in relation to endoscopic and biopsy results (Table 2): The most common laryngeal complaints were frequent throat clearing and Voice fatigue present in 72 (63.2%) and 67 (58.8%) of patients respectively. There is statistically significant difference in LPR symptoms (frequent throat clearing, voice fatigue, and choking during night) between patients with GERD versus those without; P value <0.05.

Correlation between different laryngoscopic findings regarding Loss-Angeles Classification (Table 3): There is non significant correlation between laryngeal findings and the severity of esophagitis (p >0.05).

Distribution of MAPLs and associated laryngeal findings in relation to endoscopic and biopsy results (Table 4): The most common MAPLs were vocal fold polyp and contact granuloma present in 35 (30.7%), 23 (20.2%) of the patients respectively. The most common associated laryngeal finding was posterior laryngitis present in 56 (49%) patients. Laryngeal findings are significantly higher in GERD compared with non-GERD patients (P <0.05), except for vocal fold polyp, vocal fold nodule and chronic laryngitis (p > 0.05).

Table 2: Distribution of LPR symptoms in relation to endoscopic and biopsy results.

	N (%)	Non GERD	GERD (ERD + NERD)	P value
	Total = 114	N=22 (19.3 %)	N=92 (80.7 %)	
Symptoms of reflux	79 (69.3%)	0 (0 %)	79 (100 %)	0.001
Frequent throat clearing	72 (63.2%)	15 (21%)	57 (79 %)	0.005
Voice fatigue	67 (58.8%)	13 (19.4%)	54 (80.6%)	0.003
Choking during night	53 (46.5%)	10 (19 %)	43 (81 %)	0.012
Dysphagia	37 (32.5%)	10 (27%)	27 (73 %)	0.506
Cough	37 (32.5%)	8 (21.6 %)	29 (78.4 %)	0.134
Sensation of lump	34 (29.8%)	8 (23.5 %)	26 (76.5 %)	0.256

Table 3: Correlation between different laryngoscopic findings regarding Loss-Angeles Classification.

ERD N = 83 (72.8%)	Loss-Angeles Classification	Posterior laryngitis	Vocal fold polyp	Contact granuloma	Vocal fold nodules	Chronic laryngitis	Vocal fold cyst	Reinke's edema
		N=56	N=35	N=23	N=22	N=20	N=19	N=15
A 21(25.3%)	A	12 (21.4%)	5 (14.3%)	8 (35%)	2 (9%)	3 (15%)	4 (21%)	2 (13.3%)
	B	19 (34%)	9 (25.7%)	7 (30.4%)	7 (32%)	7 (35%)	7 (36.8%)	10 (66.7%)
	C	5 (9%)	5 (14.3%)	2 (8.7%)	3 (13.6%)	2 (10%)	1 (5%)	2 (13.3%)
	D	6 (10.7%)	2 (5.7%)	2 (8.7%)	3 (13.6%)	1 (5%)	2 (10.5%)	0 (0%)
rho		-0.057	0.038	-0.172	0.158	-0.024	-0.051	0.039
P value		0.607	0.736	0.121	0.154	0.827	0.648	0.729

Table 4: Distribution of MAPLs and associated laryngeal findings in relation to endoscopic and biopsy results.

MAPLs & associated Laryngeal findings	N (%)	Non GERD	GERD (ERD + NERD)	P value
	Total = 114	N=22 (19.3 %)	N=92 (80.7 %)	
Posterior laryngitis	56 (49.1%)	10 (18 %)	46 (82 %)	0.004
Vocal folds polyps	35 (30.7%)	12 (34 %)	23 (66 %)	0.662
Contact granulomas	23 (20.2%)	3 (13 %)	20 (87 %)	0.038
Vocal folds nodules	22 (19.3%)	4 (18 %)	18 (82 %)	0.146
Chronic laryngitis	20 (17.5%)	5 (25 %)	15 (75 %)	0.507
Vocal folds cysts	19 (16.7%)	2 (10.5 %)	17 (89.5 %)	0.035
Reinke's edema	15 (13.2%)	1 (7 %)	14 (93 %)	0.037

Discussion:

According to Koufmann (2002), laryngeal epithelium is 100 times more sensitive than that of the esophagus. Therefore, the reflux of small amounts of gastric secretion containing hydrochloric acid, pepsin and other digestive enzymes is sufficient to cause serious lesions in the larynx (Potluri *et al.*, 2003).

Laryngeal examination with special emphasis on the posterior location of tissue injury can be helpful for the diagnosis of LPR (Vaezi, 2003a). The association between acid reflux and laryngitis is due to the presence of the upper airway in close proximity to the esophagus. This location places the vocal fold epithelium at high risk for exposure to and damage by the reflux (Johnston *et al.*, 2004; Johnston *et al.*, 2006). In addition to direct

contact with acid, vagally mediated throat clearing and coughing can cause mechanical injuries leading to laryngitis (Axford, 2001).

In our study, most patients with vocal folds polyps had unilateral lesions, most patients with contact granulomas and Rienke's edema had bilateral lesions, while all patients with vocal folds nodules had bilateral lesions, and all patients with vocal folds cysts had unilateral lesions.

In our study, the prevalence of GERD among patients with laryngeal symptoms was 80.7 %. This is in agreement with Katz (1990), who reported prevalence of GERD of up to 80% in patients with hoarseness and other voice complaints. On the other hand some other studies showed that the prevalence of GERD in patients with laryngeal symptoms ranged from 20%-62 % (Koufman *et al.*, 2000; Hamamoto *et al.*, 2004; Ahmed *et al.*, 2006; Cammarota *et al.*, 2006; Jonaitis 2006).

We found frequent throat clearing, voice fatigue, and choking during night significantly more common in GERD patients than in non GERD ($p < 0.05$). Ahmad and Batch (2004), who examined 303 patients with reflux found voice change, globus, sore throat, dysphagia and cough, were the predominant symptoms.

Our study showed that there is non significant correlation between laryngeal findings and the severity of esophagitis ($P > 0.05$). So the severity of esophagitis could not act as a predicting factor for LPR. This is in agreement with Lai *et al.* (2008), who found that the severity of esophagitis was not a risk factor of LPR. This finding is contradictory to the result of Jaspersen *et al.* (2003), who reported that severe esophagitis and longer duration of GERD were significantly related to the extra-esophageal disorder. Also, Coelho *et al.* (2010), found the presence of laryngeal changes more prevalent in patients with severe esophagitis ($P < 0.05$).

Posterior Laryngitis:

In our study, posterior laryngitis was the most common laryngeal finding present in 56 (49.1%) of the total studied subjects, 46 (82%) of them having GERD which was statistically significant when compared to these without GERD. This is in agreement with Tauber *et al.* (2003), who found that 85% of GERD-positive patients had posterior laryngitis. Also, Koufman described posterior laryngitis in 74% of all patients with GERD (Koufman, 2002). We agree with Catalano *et al.* (2004), in that patients affected with posterior laryngitis had a significantly higher prevalence of esophagitis of varying degrees ($p < 0.01$).

Vocal Folds Polyps:

We found vocal fold polyps in 35 (30.7 %) of the patients patients, 23 (66%) of them having GERD. This is in agreement with Chung *et al.* (2009), who found 75% of patients with vocal fold polyp had LPR. However, we found insignificant difference in frequency of vocal fold polyps in patients with GERD compared to those without ($P=0.662$).



Vocal fold polyps

Contact Granulomas:

In our study, Contact granuloma was present in 23 (20.2%) of the total studied subjects, 20 (87%) of them had GERD which was statistically significant when compared to those without GERD. This is in agreement with the study published by Ylitalo and his colleague (2002), in that contact granuloma was significantly more prevalent in patients with GERD ($P < 0.05$).

Vocal Folds Nodules:

Vocal fold nodules were present in 22 (19.3%) of the studied patients, 18 (82%) of them had GERD. This is in agreement with Chung *et al.* (2009) who found 66% of vocal nodule patients had LPR. However, we found insignificant difference in frequency of vocal fold nodules in patients with GERD compared to those without ($P= 0.146$). On the other hand Kuhn *et al.* (1998), and Catalano *et al.* (2004), found significantly higher prevalence of esophagitis in patients with vocal cord nodules ($P < 0.05$).



Vocal nodule

Chronic Laryngitis:

Vaezi (2003b), estimated that 50%-60% of chronic laryngitis and difficult to treat sore throat may be related to GERD. We found 20 (17.5 %) of the studied patients had chronic laryngitis, 15 (75 %) of them had GERD. There is insignificant difference in frequency of chronic laryngitis in patients with GERD compared to those without ($P = 0.507$).

Vocal Folds Cysts:

To our knowledge our study is the first study that reports the prevalence of vocal folds cysts. Vocal folds cysts were present in 19 (16.7%) of the studied patients, 17 (89.5%) of them had GERD. All the lesions were unilateral and significantly higher in GERD compared with non-GERD patients ($P = 0.035$).



Vocal fold cyst & posterior laryngitis

Reinke's Edema:

We found Reinke's edema in 15 (13.2%) of the total studied subjects, 14 (93%) of them had GERD, with significant difference in frequency of Reinke's edema in patients with GERD compared to those without ($P = 0.037$). Also, Chung *et al.* (2009), found patients with Reinke's edema had a significantly higher prevalence of pathologic laryngopharyngeal reflux than the controls ($P = 0.016$).



Bilateral Reinke's edema

Concolusion:

The prevalence of gastroesophageal reflux disease in patients with Minimal Associated Pathological lesions is high, and GERD may manifest atypically as ENT symptoms, without symptoms of heartburn and regurgitation.

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