

Evaluation of the likelihood of reflux developing in patients with recurrent upper respiratory infections, recurrent sinusitis or recurrent otitis seen in ear-nose-throat outpatient clinics

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Gastroesophageal reflux is considered a risk factor for recurrent or persistent upper and lower respiratory tract conditions including asthma, chronic cough, sinusitis, laryngitis, serous otitis and paroxysmal laryngospasm. Fifty-one subjects with recurrent (more than three) episodes of upper respiratory tract infection (URTI), serous otitis or sinusitis who had been admitted to an ear-nose-throat (ENT) outpatient clinic during the previous year were enrolled in the present study to evaluate the presence of laryngeal and/or esophageal reflux. The participants, who were randomly selected, were questioned about symptoms of reflux, including vomiting, abdominal pain, failure to thrive, halitosis, bitter taste in the mouth, chronic cough, heartburn, constipation and hoarseness. All subjects had an endoscopic examination, an otoscopic examination, a tympanogram and upper GI system endoscopy. Esophagitis was diagnosed endoscopically and histologically. The likelihood of occurrence of esophagitis was found to be higher only among subjects with postglottic edema/erythema as determined by pathological laryngeal examination. The reflux complaints reported did not predict the development of esophagitis, but the odds of esophagitis occurring were ninefold greater among subjects with recurrent otitis. Of the subjects, 45.1% were *Helicobacter pylori*-positive. However, no association was found between esophagitis and *Helicobacter pylori* positivity.

The likelihood of the occurrence of esophagitis was found to be increased in the presence of recurrent otitis media and/or postglottic edema, irrespective of the presence of reflux symptoms. We concluded that, in contrast to the situation where adults are concerned, the boundaries for discriminating laryngopharyngeal reflux from gastroesophageal reflux are somewhat blurred in pediatric patients.

Key words: gastroesophageal reflux disease, laryngopharyngeal reflux, esophagitis

Since the publication of the association between reflux and asthma in children in 1976, non-gastrointestinal symptoms and complaints of reflux have gained greater attention. Recognition of reflux has prevented the use of unnecessary treatments in such patients¹⁻³.

Koufman⁴ first differentiated LPR (laryngopharyngeal reflux) from GER (gastroesophageal reflux) in a study of 899 adult patients by looking at the rates of chronic throat-clearing sensation (87% for LPR and 3% for GER) and burning sensation over the

chest (20% for LPR and 83% for GER). The American Broncho-Esophagological Association (ABEA) reported that the most common symptoms in adults with LPR were chronic throat-clearing sensation (98%), chronic cough (97%), hoarseness (95%) and sensation of food being stuck in the throat (95%)^{5,6}. Belafsky et al.^{7,8} developed the *Reflux Symptom Index* (RSI) and the *Reflux Finding Score* (RFS) in order to help standardize LPR diagnosis and monitor the effectiveness of therapy. These scoring symptoms have not gained wide use for children.

Gastroesophageal reflux is considered a risk factor for recurrent or persistent upper and lower respiratory tract conditions including asthma, chronic cough, sinusitis, laryngitis, serous otitis and paroxysmal laryngospasm. However, the prevalence of LPR among children is not definitively known. It has been reported that 50 to 60% of such patients visit ENT outpatient clinics^{1,3,5}.

In the present study, we explored the role of reflux in the development of ENT problems by retrospectively reviewing the presence of reflux complaints, coexisting endoscopically/histologically confirmed esophagitis and pathological findings of laryngeal examination in patients with upper respiratory infection, sinusitis or otitis media.

Material and Methods

Fifty-one subjects with recurrent (more than three) episodes of URTI, serous otitis or sinusitis during the previous year who had been admitted to the ear-nose-throat (ENT) outpatient clinic of the Istanbul University Cerrahpasa School of Medicine from February to October 2007 were enrolled in the study to evaluate the presence of laryngeal and/or esophageal reflux. The subjects were randomly selected. Prior to commencing the trial, approval was obtained from the Ethics Committee of the Istanbul University Cerrahpasa School of Medicine (date: 06.02.2007/no.: 3756). All subjects participated in the study voluntarily, and written consent was obtained from the parents of the children involved.

Patients with an anatomic disorder, a genetic malformation, cystic fibrosis, an immune deficiency or any other chronic disease, as well as patients who had previously been treated

for reflux, were excluded. Medical history, age, gender, complaints and findings of physical examination at admission were recorded on a follow-up form for each patient. Subjects were questioned about symptoms of reflux, including vomiting, abdominal pain, failure to thrive, halitosis, bitter taste in the mouth, chronic cough, burning sensation over the chest, constipation and hoarseness.

Endoscopic ENT exams, otoscopic exams and tympanograms were performed for all patients. All examinations and assessments were completed by the same physician to achieve standardization. Participants were assessed for tonsil hypertrophy, adenoid vegetation, postglottic edema/erythema, arytenoid edema/erythema, ventricular narrowing, vocal cord edema and cobblestone appearance behind the hypopharynx during endoscopic ENT examination. The grading of symptoms was as follows: 0, normal; 1, mild; 2, severe. Otoloscopic examination evaluated the characteristics of the tympanic membrane and middle meatus. Tympanogram results were categorized into three types: type A, normal; type B, serous otitis; type C, Eustachian dysfunction.

Subsequently, upper GIS endoscopy was performed on all subjects by the same pediatric gastroenterologist using flexible endoscopy; the Los Angeles classification system was utilized to grade reflux esophagitis⁹. During endoscopy, biopsy specimens were obtained from approximately 5 cm or 10 cm above the lower esophagus, depending on the age of the patient.

Statistics

The odds ratio (OR) and 95% confidence interval (95% CI) for data were calculated from the coefficients estimated by the logistic regression model. A *p*-value of 0.05 or less was considered statistically significant and all reported *p*-values were two-sided. Data were analyzed using SPSS 16.0 software.

Results

The study sample consisted of 25 male (49%) and 26 female (51%) patients with an age range of 3 to 15 years. Mean age was 7.15 ± 3.18 years. 84.3% of patients had recurrent upper respiratory tract infection, 35.3% had recurrent serous otitis and 33.3% had recurrent sinusitis.

Table I. History of Complaints in Patients

Complaints	n=51	%
Vomiting	11	21.6
Abdominal pain	15	29.4
Failure to thrive	13	25.5
Hoarseness	17	33.3
Halitosis	33	64.7
Bitter taste in the mouth	13	25.5
Chronic cough	43	84.3
Burning sensation over the chest	14	27.4
Constipation	23	45.1
Recurrent URTI	43	84.3
Recurrent serous otitis	18	35.3
Recurrent sinusitis	17	33.3

When subjects were questioned regarding previous complaints of reflux (vomiting, abdominal pain, failure to thrive, halitosis, bitter taste in the mouth, chronic cough, burning sensation over the chest, constipation, hoarseness), chronic cough appeared to be the most common complaint (84.3%; 43/51) (Table I). None of the subjects had received antireflux treatment.

Endoscopic ENT examination showed the presence of tonsil hypertrophy in 27.5% (n=14), adenoid vegetation in 19.6% (n=10), postglottic edema/erythema in 13.7% (n=7), arytenoid edema/erythema in 15.7% (n=8), vocal cord edema in 11.8% (n=6) and cobblestone appearance behind the hypopharynx in 5.9% (n=3) of the subjects; all of these were severe.

Otosopic examination showed a dull appearance of the tympanic membrane in 35.3% (18/51) and serous discharge in the middle meatus in 33.3% (17/51) of the subjects. A type B curve was observed during the tympanogram in 35.3% (18/51) of the subjects, which indicated the presence of serous otitis.

Endoscopic examination revealed esophagitis in a total of 53% (27/51) of the subjects (27.5% Stage A (14/51) and 25.5% (13/51) Stage B). All of the patients with endoscopically diagnosed esophagitis also had histological esophagitis. We found that 11 patients had histological esophagitis without endoscopic esophagitis. The total number of patients histologically diagnosed with esophagitis was 38.

When the development of endoscopically/histologically confirmed esophagitis (38/51) was examined according to the complaints described by the subjects, esophagitis was more likely to occur among those suffering from constipation (odds ratio: 10.2, 95% confidence interval: 1.13-91.60), but the other symptoms were not associated with a likelihood of developing esophagitis (Table II).

When the likelihood of occurrence of endoscopic and/or histologic esophagitis was evaluated according to the presence of recurrent URTI, recurrent sinusitis or recurrent serous otitis, an increased risk of developing esophagitis was found only in patients with recurrent serous otitis (odds ratio: 8.87, 95% confidence interval: 1.02-77.07).

When the likelihood of occurrence of endoscopic and/or histologic esophagitis was evaluated based on the pathological findings of laryngeal examination, the risk of developing esophagitis was higher only among patients with postglottic edema (odds ratio: 35.35, 95% confidence interval: 2.54-491) (Table II).

When the likelihood of developing recurrent serous otitis was evaluated based on the history of complaints and the pathological findings of laryngeal examination, the risk of developing recurrent serous otitis was found not to be affected by the presence of any complaints or examination findings (Table III).

Of 38 subjects diagnosed with endoscopic and/or histologic esophagitis, 45.1% (23/51) were

Table II. Evaluation of the Likelihood of Developing Endoscopic/Histologic Esophagitis on the Basis of Complaint, Recurrent Disease and Pathological Findings of Laryngeal Examination

	Esophagitis	No esophagitis	Odds ratio	95% CI
N	74.5% (38/51)	25.5% (13/51)		
Type of complaint				
Failure to thrive	31.6% (12/38)	7.7% (1/13)		
Vomiting	21.1% (8/38)	23.1% (3 /13)		
Abdominal pain	34.2% (13/38)	15.4% (2/13)		
Halitosis	81.6% (31/38)	76.9% (10/13)		
Bitter taste in the mouth	23.7% (9/38)	30.8% (4/13)		
Burning sensation over the chest	39.5% (15/38)	23.1% (3/13)		
Chronic cough	86.8% (33/38)	76.9% (10/13)		
Hoarseness	42.1% (16/38)	23.1% (3/13)		
Constipation	55.3% (21/38)	15.4% (2/13)	10.2	1.13-91.60
Recurrent disease				
Recurrent URTI	84.2% (32/38)	84.6% (11/13)		
Recurrent sinusitis	39.5% (15/38)	15.4% (2/13)		
Recurrent otitis	44.7% (17/38)	7.7% (1/13)	8.87	1.02-77.07
Pathological laryngeal examination				
Cobblestone appearance of the hypopharynx	36.8% (14/38)	15.4% (2/13)		
Vocal cord edema	78.9% (30/38)	30.8% (4/13)		
Ventricular obstruction	42.1% (16 /38)	30.8% (4/13)		
Arytenoid edema/erythema	73.7% (28/38)	30.8% (4/13)		
Postglottic edema/erythema	84.2% (32/38)	15.4% (2/13)	35.35	2.54-491

found to be positive for *Helicobacter pylori* (HP). When the risk for *Helicobacter pylori* positivity was evaluated according to the complaint history of the subjects, the likelihood of being positive was found to be increased among subjects with abdominal pain (odds ratio: 0.11, 95% confidence interval: 0.015-0.85), but no effect was observed for the other complaints (Table IV).

When the risk for *Helicobacter pylori* positivity was evaluated according to the presence of recurrent URTI, recurrent sinusitis or recurrent serous otitis in the subjects, the likelihood of being positive was not affected by any of these factors (Table IV).

Finally, when the risk for *Helicobacter pylori* positivity was assessed using pathological findings of laryngeal examination, the likelihood of being positive was not affected by any of the factors considered (Table IV).

Discussion

The prevalence of esophagitis has been reported

to be lower among cases with laryngopharyngeal reflux than among those with typical reflux. Koufman et al.¹⁰ detected endoscopic or histologic esophagitis in only 20% of patients with reflux presenting with non-esophageal signs and symptoms. However, Yellon and Goldberg¹¹ reported that 54% of patients with posterior laryngitis had endoscopic or histologic esophagitis. In this study, endoscopic esophagitis was detected in 52.9% of the subjects and histologic esophagitis in 74.5%. The risk for constipation was increased by 13% among patients with esophagitis compared to those without esophagitis.

Vavricka et al.¹² compared laryngeal findings of adult patients and control subjects and reported that changes in the laryngeal tissue of patients with reflux as detected by upper GIS endoscopy were similar to those of control subjects and that the presence of a cobblestone appearance in the hypopharynx was significant among subjects with reflux in comparison to the control group. Other studies have reported a 70% specificity and 77% sensitivity of postglottic

Table III. Evaluation of the Likelihood of Developing Recurrent Serous Otitis on the Basis of Complaint and Pathological Findings of Laryngeal Examination

	Serous otitis	Non-serous otitis	Odds ratio	95% CI
N	35.3% (18/51)	64.7% (33/51)		
Complaints				
Failure to thrive	38.9% (7/18)	18.2% (6/33)		
Vomiting	16.7% (3/18)	24.2% (8/33)		
Abdominal pain	33.3% (6/18)	27.3% (9/33)		
Halitosis	88.9% (16/18)	75.8% (25/33)		
Bitter taste in the mouth	27.8% (5/18)	24.2% (8/33)		
Burning sensation over the chest	33.3% (6/18)	36.4% (12/33)		
Chronic cough	88.9% (16/18)	81.8% (27/33)		
Hoarseness	50.0% (9/18)	30.3% (10/33)		
Constipation	55.6% (10/18)	39.4% (13/33)		
Pathological laryngeal examination				
Cobblestone appearance of the hypopharynx	22.2% (4/18)	36.4% (12/33)		
Vocal cord edema	83.3% (15/18)	57.6% (19/33)		
Ventricular obstruction	44.4% (8/18)	36.4% (12/33)		
Arytenoid edema/erythema	77.8% (14/18)	54.5% (18/33)		
Postglottic edema/erythema	72.2% (13/18)	63.6% (21/33)		

edema/erythema for predicting LPR^{13,14}. In our study, when the likelihood of occurrence of endoscopic and/or histologic esophagitis was evaluated based on the pathological findings of laryngeal examination, the risk for occurrence of esophagitis was higher only among patients with postglottic edema (odds ratio: 35.35, 95% confidence interval: 2.54-491) (Table II). Postglottic edema/erythema was present in 66.6% of our subjects.

Some studies in adults have suggested that GERD contributes to development of chronic cough at a rate between 21% and 41%. However, other studies report no such contribution. Pediatric studies have reported GERD causing chronic cough at a rate between 3% and 8%^{2,15,16}. On the other hand, Sifrim et al.¹⁷ considered cough to actually be causing reflux in at least half of the reflux episodes in their study. Chang et al.¹⁸ reported the coexistence of reflux and cough independent of esophagitis, and associated with bacterial infections of the airways. In our study, constipated patients were found to have an increased likelihood of occurrence of esophagitis when the risk for endoscopic and/or histologic esophagitis was assessed in connection with complaint history (odds ratio: 10.2, 95% confidence interval:

1.13-91.60), but other complaints, including cough, did not display any such effect (Table II).

Ulualp and Toohill¹⁹ reported an increased prevalence of LPR among patients with chronic sinusitis. In recent years, reflux has been suggested as a causative factor facilitating and initiating chronic sinusitis. Bothwell et al.²⁰ reported that 89% of children with resistant chronic sinusitis improved with reflux treatment, with no need for surgical intervention. Studies have reported an association between both chronic sinusitis and chronic recurrent serous otitis and LPR. Recurrent sinusitis was present in 33.3% of our subjects. In the present study, the risk for esophagitis was not increased among patients with recurrent sinusitis when the likelihood of occurrence of endoscopic and/or histologic esophagitis was assessed according to the presence of recurrent URTI, recurrent sinusitis or recurrent serous otitis (Table II).

It is known that nasopharyngeal inflammation aggravates otitis by causing obstruction in the Eustachian tube. However, some studies have reported that the prevalence of otitis among children with GER was not different from that in a control group^{3,13,15}. Using a pH meter, Poelmans et al.²¹ detected reflux in 17 of 21 adult patients with chronic otitis (80%),

who responded very well to treatment with a proton pump inhibitor (PPI). Rozmanic et al.²² diagnosed GERD in 55% of 27 patients with chronic or recurrent serous otitis. Tasker et al.²³ showed that pepsin or pepsinogen levels were 1,000-fold higher in middle ear fluid than in serum in 80% of 54 children with chronic serous otitis. In another study, while the pepsin/pepsinogen ratio of middle ear fluid was increased among pediatric patients with chronic or recurrent serous otitis, there was no increase in GER complaints²⁴. Marko et al.²⁵ reported a higher occurrence of sequelae among GERD patients with middle ear problems. In the present study, when the likelihood of occurrence of endoscopic and/or histologic esophagitis was assessed on the basis of recurrent URTI, recurrent sinusitis or recurrent serous otitis, a significant increase—nearly ninefold—in the risk for occurrence of esophagitis was found only among patients with recurrent serous otitis (odds ratio: 8.87, 95% confidence interval: 1.02-77.07). Recurrent serous otitis was present in 35.3% of our subjects. When the likelihood of developing recurrent serous otitis was assessed

according to complaint history and pathological findings of laryngeal examination, there were no complaints or examination findings that affected the risk for occurrence of recurrent serous otitis (Table III).

Changes in voice quality are reported in 6 to 23% of school age children. In adults, hoarseness is the most common and prominent symptom of laryngopharyngeal reflux²⁶⁻²⁸. Koufman et al.⁵ reported that 50% of adults with LPR suffered from hoarseness. Information concerning this symptom in children is insufficient. Putnam and Orenstein²⁹ first reported in 1992 that hoarseness in pediatric patients could be resolved by reflux treatment. Vocal cord nodules are considered to be the most common cause of hoarseness²⁸. Coexistence of hoarseness and vocal cord nodules was found at a rate of 67% in a prospective study by Gumpert³⁰ and 82% in a retrospective review by Mandell³¹. Hoarseness was reported by 33.3% of our subjects, but no significant association was found between this symptom and esophagitis in the present study.

Table IV. Evaluation of the Likelihood of *H. pylori* Positivity on the Basis of Complaint, Recurrent Disease and Pathological Findings of Laryngeal Examination

	<i>H. Pylori</i> (+)	<i>H. Pylori</i> (-)	Odds ratio	95% CI
N	45.1% (23/51)	54.9% (28/51)		
Complaints				
Failure to thrive	13.0% (3/23)	35.7% (10/28)	0.11	0.015-0.854
Vomiting	13.0% (3/23)	28.6% (8/28)		
Abdominal pain	39.3% (11/28)	17.4% (4/23)		
Halitosis	73.9% (17/23)	85.7% (24/28)		
Bitter taste in the mouth	26.1% (6/23)	25.0% (7/28)		
Burning sensation over the chest	30.4% (7/23)	39.3% (11/28)		
Chronic cough	91.3% (21/23)	78.6% (22/28)		
Hoarseness	34.8% (8/23)	39.3% (11/28)		
Constipation	30.4% (7/23)	57.1% (16/28)		
Recurrent disease				
Recurrent URTI	78.3% (18/23)	89.3% (25/28)		
Recurrent sinusitis	34.8% (8/23)	32.1% (9/28)		
Recurrent otitis	26.1% (6/23)	42.9% (12/28)		
Pathological laryngeal examination				
Cobblestone appearance of the hypopharynx	17.4% (4/23)	42.9% (12/28)		
Vocal cord edema	60.9% (14/23)	71.4% (20/28)		
Ventricular obstruction	39.1% (9/23)	39.3% (11/28)		
Arytenoid edema/erythema	56.5% (13/23)	67.9% (19/28)		
Postglottic edema/erythema	56.5% (13/23)	75.0% (21/28)		

The role of *Helicobacter pylori* in the development of LPR is unclear. Oridate et al.³² suggested that HP toxins increased respiratory sensitivity by augmenting reflux and caused a sensation of having foreign material in the throat via reflex cough. While Tezer et al.³³ reported an association between HP and the grade of laryngitis and esophagitis, Ercan et al.³⁴ found no correlation between HP and LPR. Rubin et al.³⁵ suggested that the pharynx could be exposed to HP from the stomach in LPR. There are no studies demonstrating the presence of *Helicobacter pylori* in the larynx^{36,37}. Moreover, there is no clear association between *Helicobacter pylori* and GERD. Some studies have suggested that HP may have a protective effect against the development of GERD. *Helicobacter pylori* is believed to increase LES (lower esophageal sphincter) pressure by raising gastrin levels. It has also been suggested that *Helicobacter pylori* may damage the lower esophageal sphincter and esophageal mucosa by increasing the presence of inflammatory substances³⁶⁻³⁸. Postma et al.³⁹ reported that esophageal acid clearance was better in patients with both GERD and LPR than in those with LPR alone. Sarnelli et al.⁴⁰ reported that HP treatment increased the exposure of the upper esophagus to acid in GERD and delayed esophageal acid clearance.

Helicobacter pylori positivity was found in 45.1% (23/51) of our subjects. Assessment of patients for *Helicobacter pylori* positivity on the basis of pathological findings of laryngeal examination showed that no specific finding affected the likelihood of such positivity. The risk for *Helicobacter pylori* positivity was found to be increased by 11% among patients with abdominal pain in an analysis of *Helicobacter pylori* positivity on the basis of complaint history, but other complaints did not provide any predictive information. When the risk for *Helicobacter pylori* positivity was assessed in relation to the presence of recurrent URTI, recurrent sinusitis or recurrent serous otitis, none of these factors were found to have an influence (Table IV).

In conclusion, our study found that the likelihood of occurrence of esophagitis in ear-nose-throat patients was increased in the presence of recurrent otitis media and/or postglottic edema, irrespective of the presence of reflux symptoms. We also may say that,

in contrast to the situation where adults are concerned, laryngopharyngeal reflux cannot be readily discriminated from gastroesophageal reflux in pediatric patients. Because of the small number of patients in the present study, more extensive investigations concerning this issue are needed.

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