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Original Article / Çalışma - Araştırma

The relationship between heterotopic gastric mucosa in the cervical esophagus and laryngopharyngeal reflux

Servikal özofagus yerleşimli heterotopik gastrik mukoza ile larengofarengeal reflü ilişkisi

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Objectives: This study aims to investigate the possible correlations between the heterotopic gastric mucosa (HGM) islets in the cervical esophagus and laryngopharyngeal reflux (LPR).

Patients and Methods: Between May 2010 and April 2011, 45 patients (36 females, 9 males; mean age 39.8±14.1 years; range 18 to 72 years) who had reflux symptom index (RSI) >10 and reflux finding score (RFS) >7 were included. The study group consisted of 21 patients who were diagnosed with HGM islets in the cervical esophagus, while control group consisted of 24 patients without any HGM islets assessed by upper gastrointestinal system endoscopy. Esophagus manometric examination and dual-channel 24-hour pH monitoring were performed on all patients.

Results: Pretreatment mean RSI and RFS were 25.6±3.5 and 15.1±3.4 in group 1, while it was found to be 21.1±4.4 and 11.9±2.6 in group 2 (p=0.001, p=0.001). A total of 29.7% of patients who underwent pH monitoring had distal reflux, whereas 43.2% of them had proximal reflux. In group 1, distal reflux was observed in 15.4% and proximal reflux was found in 54% of the patients, while distal reflux was observed in 38% and proximal reflux was found in 38% of the patients in group 2 (p=0.152; p=0.27). Fourteen patients diagnosed with HGM had antral- and seven patients had fundal-type epithelium.

Conclusion: Our study results suggest that HGM islets may be considered as an etiological factor in the patients with severe LPR with isolated proximal reflux based on the 24-hour pH monitoring.

Key Words: Ambulatory 24-hour esophageal pH monitoring; gastric mucosa; laryngopharyngeal reflux.

Amaç: Çalışmada servikal özofagus yerleşimli heterotopik mide mukozası (HGM) adacıkları ile larengofarengeal reflü (LPR) arasında olası korelasyon varlığı araştırıldı.

Hastalar ve Yöntemler: Mayıs 2010 - Nisan 2011 tarihleri arasında reflü semptom indeksi (RSİ) >10, reflü bulgu skoru (RFS) >7 olan toplam 45 hasta (36 kadın, 9 erkek; ort yaş 39.8±14.1 yıl; dağılım 18-72 yıl) çalışmaya dahil edildi. Üst gastrointestinal sistem endoskopi değerlendirmesinde servikal özofagusta yerleşimli HGM adacıkları tanısı konulan 21 hastadan çalışma grubu, edilmeyen 24 hastadan ise kontrol grubu oluşturuldu. Tüm hastalara özofagus manometrik incelemesi ve çift kanallı 24 saatlik pH monitörizasyonu yapıldı.

Bulgular: Tedavi öncesi RSİ ve RFS ortalamaları grup 1'de sırasıyla 25.6±3.5 ve 15.1±3.4 iken, grup 2'de bu ortalamalar 21.1±4.4 ve 11.9±2.6 idi (p=0.001, p=0.001). pH monitörizasyonu yapılan hastaların toplamında %29.7 oranında distale, %43.2 oranında proksimale reflü izlendi. Grup 1'de hastaların %15.4'ünde distale reflü gözlenirken, %54'ünde proksimale reflü bulundu, grup 2'de ise hastaların %38'inde distale reflü izlenirken, %38'inde proksimale reflü bulundu (p=0.152; p=0.27). Heterotopik mide mukozası saptanan hastaların 14'ünde antral tip, yedisinde ise fundik tip epitelyum bulunmaktaydı.

Sonuç: Çalışma sonuçları, şiddetli LPR düşünülen ve 24 saatlik pH monitörizasyonu sonucunda izole proksimale reflü saptanan hastalarda, HGM adacıklarının da etyolojik faktörler arasında olabileceğini göstermektedir.

Anahtar Sözcükler: Yirmi dört saat özofageal pH monitörizasyonu; mide mukozası; larengofarengeal reflü.

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Laryngopharyngeal reflux (LPR), an atypical variant of gastroesophageal reflux, is the back-flow of contents of the stomach beyond the upper esophageal sphincter without gagging or vomiting. It may cause non-specific symptoms of irritation and mucosal lesions in the larynx, trachea, pharynx and oral cavity due to contact with acid and pepsin refluxing from the stomach.

Heterotopic gastric mucosa (HGM) may be found as single, double or triple gastric epithelial islets with orange-red color and well-defined borders in the upper $^1/_3$ part of the esophagus.[1,2] Heterotopic gastric mucosa located in the cervical esophagus causes symptoms similar to LPR and may cause local complications such as pachydermia, stenosis, tracheoesophageal fistula, hemorrhage, perforation and even malignant transformation due to its acid production wherever it is located.[3-5] The similarity in symptoms and difficulty of techniques to diagnose HGM may cause misdiagnosis of this particular disease as LPR.

In this study, our aim was to investigate the possible correlations between the HGM islets located in the cervical esophagus and the symptoms and laryngeal findings of LPR disease.

PATIENTS AND METHODS

Forty-five (36 females, 9 males; mean age 39.8±14.1; range 18 to 72 years) patients who were admitted to our clinics with symptoms of recurrent or chronic cough, hoarseness, globus pharyngeus and excessive throat cleaning between May 2010 and April 2011 were enrolled in our study. These patients were diagnosed as LPR and other laryngeal diseases were ruled out.

Reflux symptom index (RSI) and reflux finding score (RFS) were applied to each patient to determine their symptoms and signs quantitatively. Reflux symptom index is a survey composed of nine questions (including hoarseness, cleaning throat, nose and throat efflux, difficulty in swallowing, coughing after eating or lying down, difficulty in breathing, troublesome cough, sensation of sticking in throat, heartburn and chest pain) in which the answers are graded from 0 to 5; 0 meaning no symptoms and 5 meaning very severe symptoms.[6]

During telescopic laryngoscopy a Hopkins 90° 5.8 mm Telescope (Karl Storz, Tuttlingen, Germany) was used. The images were saved and then evaluated by two otorhinolaryngologists who were totally blinded to the study. To calculate RFS, the presence or absence of pseudosulcus vocalis (0: absent, 2: present), ventricular obliteration (0: absent, 2: partial, 4: complete), erythema (0: absent, 2: only at arytenoids, 4: diffuse), vocal cord edema (0: absent, 1: mild, 2: moderate, 3: severe, 4: polypoid), diffuse laryngeal edema (0: absent, 1: mild, 2: moderate, 3: severe, 4: polypoid), hypertrophy of posterior commissure (0: absent, 1: mild, 2: moderate, 3: severe, 4: polypoid), granulation in the interarytenoid area (0: absent, 2: present) and presence of thick endolaryngeal mucus (0: absent, 2: present) were considered and scored.[7]

Patents who had both RSI>13 and RFS>7 were included in our study. Patients who had any systemic diseases such as diabetes mellitus, hypertension, bronchial asthma, acute or chronic infective inflammatory disease and who were taking continuous medications such as theophylline, anticholinergics, calcium channel blockers and oral contraceptives were excluded. Malignant diseases and hiatal hernia diagnosed with upper gastrointestinal system endoscopy were the other exclusion criteria. The local ethics committee approved our study and informed consent was obtained from all the patients.

Upper gastrointestinal endoscopy was applied to all the patients using an Olympus GIF XQ endoscope (Olympus Corp, Tokyo, Japan). The largest diameter and the distance of the lesion from the central incisive teeth were measured in patients who had HGM islets at the cervical esophagus level. Biopsies for histopathological examination were taken from each patient to confirm diagnosis.

The study group was formed from 21 (17 females, 4 males) patients detected to have HGM islets at the cervical esophagus during upper gastrointestinal endoscopy and control group was formed from 24 (19 females, 5 males) patients were not detected to have HGM islets at the cervical esophagus during upper gastrointestinal endoscopy.

Manometric examination of the esophageal trunk and lower esophageal sphincter (LES) was performed in all the patients with a water-perfusioned manometric system (Medical measurement systems) and an 8-channeled Dent-Sleeve catheter (Arndorfer Inc, USA). After this, double channeled 24-hour pH monitorization was performed with a disposable double-sensor pH catheter with a 15 cm interval (Comfort Tec-Sandhill

Scientific Inc., USA) after calibration of the pH probe with solutions which had pH's of one and seven. The first pH probe was located 5 cm over the LES and the second sensor was positioned 15 cm proximal to the first. During pH monitoring, patients were forbidden to have meals with gas, acid, spice and hot food and beverages. Oral intake of the patients was noted during these measurements. Thereafter, the data was transferred to the computer and the analysis was done with polygram software. The time and the number of the pH level <4.0 at the distal and the proximal probes, reflux time longer than 5 minutes, and reflux index were calculated at two different positions separately; supine and upright, and total reflux index was calculated by summation of these indices. Reflux was diagnosed at the proximal and/or distal esophagus if the total reflux index was ≥1% at the proximal and ≥4% at the distal parts. Distal channel DeMeester score was also calculated and reflux was approved with a score ≥14.7.

Lansoprazole 30 mg twice a day per os (p.o.) was administered to the patients after LPR was diagnosed. Patients underwent physical examination before the onset of treatment and at the first and third months of treatment. Before examination, patients fulfilled the RSI survey and findings were scored using RFS.

Statistical analysis

The analysis of the results was performed using the predictive analytics software (PASW, Chicago, Illinois, USA), version 18.0 software for Windows. Data was tested for normal distribution using the Kolmogorov-Smirnov test. To investigate the differences between groups, the Mann-Whitney U-test was used for two groups and the Kruskal-Wallis H test for >2 groups. Spearman correlation coefficient was used for correlation analysis. Chi-square test was performed for categorical variables. Statistical significance was defined as $p<0.05$. Wilcoxon (2 groups) and Friedman (>2 groups) analyses were performed for the comparison of the data before and after treatment. For multiple comparisons of data composed of >2 groups, Bonferroni correction was used. In this analysis, a p value <0.017 was considered significant.

RESULTS

Out of 45 patients, 21 (17 female, 81.0%) patients who were detected to have HGM islets located at the cervical esophagus level formed group 1 and the rest 24 (19 female, 79.2%) patients formed group 2.

Mean RSI and RFS before treatment were 25.6±3.5 and 15.1±3.4 in group 1, 21.1±4.4 and 11.9±2.6 in group 2 (p=0.001, p=0.001). At the first month of treatment, mean RSI and RFS were 11.9±2.8 and 7.7±3.2 in group 1, 8.0±3.1 and 4.3±2.1 in group 2 (p<0.001, p<0.001). At the third month of treatment, mean RSI and RFS were decreased to 4.9±2.7 and 2.3±2.2 in group 1, 2.1±2.0 and 0.5±0.6 in group 2 (p<0.001, p=0.001; Figure 1).

When the symptoms were separately examined, before treatment hoarseness, coughing after eating or lying down, sensation of sticking in throat, heartburn and chest pain were significantly different between two groups (Table 1). The signs of the patients before treatment are shown separately in Table 2.

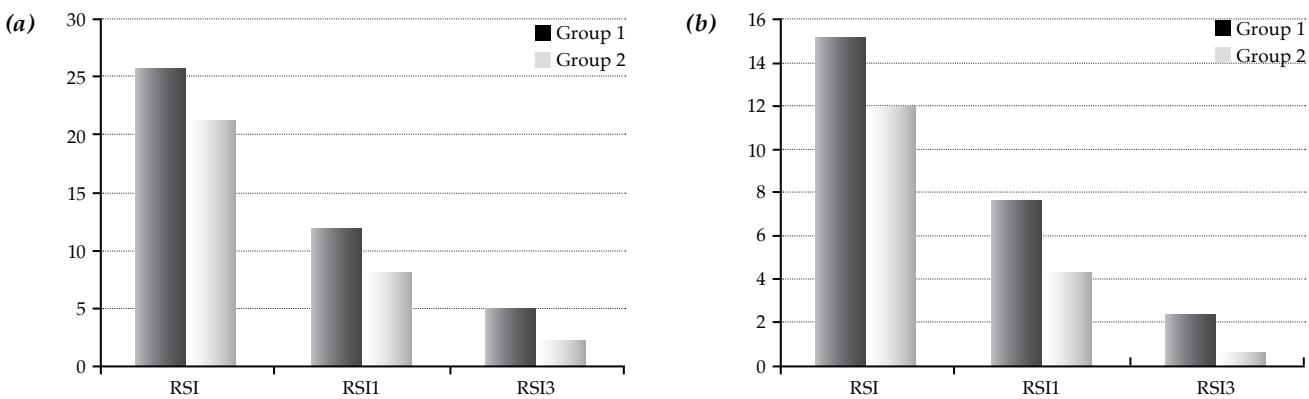

Figure 1. ***(a)*** *Mean values of reflux symptom index (RSI) before treatment, in the first month of treatment (RSI1) and in the third month of treatment (RSI3) in patients with heterotopic gastric mucosa (HGM) islets (group 1) and without HGM islets (group 2).* ***(b)*** *Mean values of reflux finding scores (RFS) before treatment, in the first month of treatment (RFS1) and in the third month of treatment (RFS3) in patients with HGM islets (group 1) and without HGM islets (group 2).*

Twenty-four hours pH monitoring could not be tolerated in one patient and seven patients did not agree to undergo pH monitoring, as a result it could be applied to 13 patients in group 1 and 24 patients in group 2 with a total of 37 patients. Table 3 shows the differences between two groups when the pH monitoring parameters were examined. Eleven (29.7%) of patients who underwent pH monitoring had distal reflux and 16 (43.2%) of them had proximal reflux. In the first group, distal reflux was observed in two (15.3%) patients and proximal reflux was found in seven (54%) patients whereas in the second group, distal reflux was observed in nine (38%) patients and proximal reflux was found in nine (38%) patients (p=0.152; p=0.27). DeMeester score >14.7 was found in two (15%) patients in the first group, and in 12 (50%) patients in the second group (p=0.040). Examination of the pH meter parameters in the study population is shown in Table 3.

No statistical difference was observed between groups when the upper gastrointestinal system endoscopy findings were concerned. None of the patients had an esophageal motility disorder, and no difference was found between lower esophageal sphincter pressures (LESP) between two groups (LESP of group 1: 24.7±6.8; LESP of group 2: 28.0±5.7; p=0.11).

When biopsies from HGM were histopathologically examined, 14 patients (66.7%) had antral type and seven (33.3%) patients had fundal type gastric mucosa and five (23.8%) patients were positive for helicobacter pylori (Hp). No correlation was observed between the type of gastric mucosa, the largest diameter and the length of the lesion to the cutting teeth and other study parameters such as symptoms, findings and pH meter results. Statistically significant differences between symptoms in patients with and without Hp are shown in Table 4.

DISCUSSION

Common symptoms of LPR are cough, hoarseness, changes in voice and difficulty in swallowing whose severity may be determined by several surveys including RSI. In our study, the most important finding was the presence of more severe symptoms in patients with HGM islets. Furthermore, the laryngeal findings of the patients with HGM islets were also more severe in patients with HGM than patients with LPR but without HGM islets. This may be explained as follows: laryngeal mucosa is very sensitive to acid and pepsin, and acid is needed for the activation of pepsin. When the acid production potential of the HGM islets is considered, these islets may activate pepsin by producing acid and cause more damage and more symptoms and signs. Accordingly, HGM should be considered in LPR patients with severe symptoms and signs.

When RSI and RFS were considered, these parameters were still significantly higher in the patients with HGM islets despite treatment with proton pump inhibitors. This is an important finding which may partially explain the drug resistance in LPR patients. It may be hypothesized

Table 1. The symptoms of the patients in two groups before treatment

	Group 1 (n=21)	Group 2 (n=24)	*p*
	Mean±SD	Mean±SD	
H	3.67±0.66	2.88±0.74	0.001
CT	3.29±0.64	2.92±0.65	0.064
NTE	1.57±0.75	1.42±1.02	0.453
DS	2.14±0.96	2.00±1.06	0.598
CAL	2.90±0.77	2.21±0.83	0.004
DB	2.19±1.08	1.63±1.13	0.105
TC	3.81±0.75	3.54±0.59	0.073
ST	3.33±0.73	2.50±0.66	<0.001
HCP	2.67±0.73	2.00±0.72	0.004

H: Hoarseness; CT: Cleaning throat; NTE: Nose and throat efflux; DS: Difficulty in swallowing; CAL: Coughing after eating or lying down; DB: Difficulty in breathing; TC: Troublesome cough; ST: Sensation of sticking in throat; HCP: Heartburn and chest pain; Group 1: Patients with HGM islets; Group 2: Patients without HGM islets.

Table 2. The signs of the patients in two groups before treatment

	Group 1 (n=21)	Group 2 (n=24)	*p*
	Mean±SD	Mean±SD	
PS	0.67±0.97	0.75±0.99	0.773
VO	1.62±0.80	1.58±0.83	0.883
E	3.14±1.01	3.17±1.01	0.936
EVC	2.29±0.64	1.83±0.48	0.011
DLE	1.76±0.70	1.00±0.59	<0.001
HPC	2.80±0.68	2.33±0.56	0.022
G	1.33±0.97	0.50±0.88	0.006
TEM	1.52±0.87	0.75±0.99	0.010

PS: Pseudosulcus; VO: Ventricular obliteration; E: Erythema-Hyperemia; EVC: Edema of vocal cords; DLE: Diffuse laryngeal edema; HPC: Hypertrophy of posterior commissure; G: Granulation; TEM: Thick endolaryngeal mucous layer; Group 1: Patients with HGM islets; Group 2: Patients without HGM islets.

Table 3. Examination of the pH meter parameters in the study population

	Group 1 (n=13)	Group 2 (n=24)	*p*
	Mean±SD	Mean±SD	
DS	13.66±22.26	18.13±14.95	0.039
DRIU	5.93±12.83	7.42±6.24	0.033
DRIS	0.36±0.92	2.04±3.41	0.034
DTRI	3.62±6.97	5.06±4.85	0.092
DRTU	49±97.92	56.59±54.86	0.161
DRTS	2.46±6.28	13.42±22.06	0.029
DTRT	51.46±99.69	70±68.50	0.135
DRNU	68.23±69.47	88.38±68.76	0.265
DRNS	5.23±12.40	16.83±18.49	0.003
DTRN	73.46±80.16	105.13±75.80	0.047
PRIU	2.08±3.08	1.48±1.44	0.632
PRIS	0.01±0.28	0.38±0.80	0.013
PTRI	1.25±1.63	1.01±1.08	0.621
PRTU	17.69±23.48	11.38±12.23	0.264
PRTS	0.60±0.90	2.63±5.38	0.005
PTRT	17.69±23.48	14.08±15.02	0.61
PRNU	42.54±27.31	29.33±27.36	0.056
PRNS	0.77±0.27	3.46±4.75	0.014
PTRN	42.62±27.51	32.79±28.05	0.143

DS: DeMeester Score; DRIU: Distal reflux index in upright position; DRIS: Distal reflux index in supine position; DTRI: Distal total reflux index; DRTU: Distal reflux time in upright position (min.); DRTS: Distal reflux time in supine position (min.); DTRT: Distal total reflux time (min.); DRNU: Distal reflux number in upright position; DRNS: Distal reflux number in supine position; DTRN: Distal total reflux number; PRIU: Proximal reflux index in upright position; PRIS: Proximal reflux index in supine position; PTRI: Proximal total refux index; PRTU: Proximal reflux time in upright position (min.); PRTS: Proximal reflux time in supine position (min.); PTRT: Proximal total reflux time; PRNU: Proximal reflux number in upright position; PRNS: Proximal reflux number in supine position; PTRN: Proximal total reflux time. Group 1: Patients with HGM islets; Group 2: Patients without HGM islets.

Table 4. Statistically significant differences between symptoms in patients with helicobacter pylori positive and negative in group 1

	Hp (+) (n=5)	Hp (-) (n= 16)	*p*
	Mean±SD	Mean±SD	
NTE	0.8±0.45	1.81±0.66	0.003
NTE1	0.4±0.55	1.44±0.89	0.013
DS3	1.2±0.84	2.81±0.83	0.034
CAL3	1±0	0.31±0.48	0.009
ST	4±0.71	3.13±0.62	0.023
ST1	2.4±0.55	1.19±0.66	0.004

NTE: Nose and throat efflux; DS: Difficulty in swallowing; CAL: Coughing after eating or lying down; ST: Sensation of sticking in throat.

that patients with HGM islets are more resistant to drug therapy due to the pathological location of the gastric mucosal cells which may prevent the drug from diffusing into the HGM islets. Another possible explanation is that because HGM islets cause more severe symptoms and signs before treatment, 3 months may not be enough for the pathological lesions to recover completely after treatment. Longer follow-up periods may be needed for those patients with HGM islets for complete recovery.

First discovered by Schmidt et al. in 1805, HGM islets are usually located in the proximal esophagus with an incidence of nearly 1% in patients who undergo upper gastrointestinal endoscopy. These lesions have a diameter of 5-12 cm similar to our findings (mean 7.6±2.3 cm).[8] In our study, we also found that no correlation was present between the diameter and distance from the upper central incisor teeth of the HGM islets and the patients' symptoms, laryngoscopic and 24-hour pH monitoring findings in concordance with the scarce data found in the literature.[9]

The HGM islets are commonly thought to be the remnants of gastric mucosa during the development of the esophagus in fetal life.[10] In addition to this congenital theory, a mixed theory supposes that trauma due to infection and regurgitation may cause loss of squamous cells in the esophagus and during the recovery of this epithelium, ectopic gastric mucosa may start to generate here.[11] In our study, the distal regurgitation was significantly lower in patients with HGM islets which also supported the congenital theory.

Galan et al.[12] were the first investigators who demonstrated acid production of HGM islets without any stimuli, by 24-hour pH monitoring. Patients' symptoms and the acid production of the HGM islets were associated with each other. Regression of symptoms was achieved by proton pump inhibitors and control pH monitoring revealed the cessation of acid production. Extraesophageal symptoms such as cough and throat pain also disappeared in these patients, as a result it was thought that these extraesophageal symptoms in patients with acid regurgitation may be related with HGM islets. Similar results were obtained from different studies.[13] Our results also confirmed these studies. The symptoms and signs of LPR in patients with HGM islets significantly attenuated after proton pump inhibitor therapy

and as well known this method is an useful and easy method in the diagnosis of LPR.[14]

Twenty-four hour pH monitoring is a technique with 62-90% sensitivity in the diagnosis of LPR.[15,16] The intermittent character of the LPR may be the cause for the false-negative results. In our study, LPR in patients with HGM islets could be confirmed only in both distal and proximal reflux 15.4% (53.8% proximal and 15.4% distal reflux) of patients. Accordingly, another explanation for the false-negative results may be the presence of HGM islets. These islets may produce acid which is enough for the destruction of the laryngeal and pharyngeal mucosa but not enough to be detected by 24-hour pH monitoring due to their inability to decrease pH under 4 as a result of the small volume of the gastric cells in the proximal esophagus and neutralization of the acid by the basic saliva. To increase the sensitivity of this test, higher pH values may be selected as a cut-off point during 24-hour pH monitoring.

There are some limitations in our study. Firstly, our study population was small. This was due to the rarity of the patients with HGM islets. Secondly, the follow-up time was relatively short. Maybe longer follow-up times were needed to see the alleviation of symptoms. Thirdly, the RSI survey is subjective nevertheless this survey is commonly used in the studies for the diagnosis and follow-up of patients with LPR.

In conclusion, two major points can be accentuated in our study. The first one is that more severe symptoms and signs of LPR may be associated with HGM islets located in the proximal esophagus and these symptoms and signs attenuate but do not recover completely despite three months of therapy with lansoprazole. The second one is that false negative results of 24-hour pH monitoring in patients with signs and symptoms of LPR may be caused by the presence of HGM islets. These important findings should be kept in mind during the examination and follow-up of patients for LPR disease for a possible diagnosis of HGM islets.

Declaration of conflicting interests

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