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Hypersensitive esophagus: can it be classified as a subgroup of gastroesophageal reflux disease?

Hipersensitif özofagus: gastroözofageal reflü hastalığının bir alt grubu olarak sınıflandırılabilir mi?

Sedef ÖZDAL KURAN, Ülkü DAĞLI, Canan ALKIM, Dilek OĞUZ, Burhan ŞAHİN

Türkiye Yüksek İhtisas Hospital, Department of Gastroenterology, Ankara

Background/aims: *Gastroesophageal reflux disease is one of the most common gastrointestinal diseases of adulthood. Hypersensitive esophagus is a new term which defines patients with reflux symptoms, negative endoscopic findings and normal acid contact time on 24 hour pH analysis, although there is a convincing relationship between symptoms and acid reflux episodes on pH analysis- positive symptom index. In this study, the frequency of hypersensitive esophagus among patients with heartburn was determined and demographic findings, symptoms, manometric and pHmetric findings were compared among hypersensitive esophagus, non-erosive reflux disease, erosive reflux disease and normals.* ***Methods:*** *Patients admitted to hospital with heartburn and without any cardiac, severe gastric or duodenal pathologies (except minimal antral gastritis) and with no abnormal manometric findings suggestive of esophageal motility disorders were included in the study. All patients were questioned about age, height, weight, educational status and intestinal and extraintestinal reflux related symptoms. Upper endoscopy, esophageal manometry and 24 hour pH monitoring were performed respectively.* ***Results:*** *Of the 44 patients (17 male, 27 female) included in the study, seven (16%) had hypersensitive esophagus, 15 (34%) had non-erosive reflux disease, seven (16%) had erosive reflux disease and 15 (34%) had normal findings. The female ratio in the hypersensitive esophagus and normal groups was higher while the male ratio was higher in erosive reflux disease. There was no significant difference among groups according to age, body mass index and symptoms. There was also no significant difference according to manometric findings. De Meester scores were significantly lower in hypersensitive esophagus and normal groups while symptom index was highest in the hypersensitive esophagus group. Reflux was observed especially in the upright position in all groups.* ***Conclusion:*** *The ratio of hypersensitive esophagus, gastroesophageal reflux disease and no pathology in patients with heartburn was 16%, 50% and 34% respectively. It would be appropriate to accept hypersensitive esophagus as a subgroup of reflux disease as it has both symptoms and some manometric and pHmetric changes.*

Key words: Gastroesophageal reflux disease, hypersensitive esophagus, acid sensitive esophagus.

Amaç: *Gastroözofageal reflü hastalığı erişkin yaş grubunda gastrointestinal sistemin en sık karşılaşılan hastalıklarından biridir. Hipersensitif özofagus son yıllarda tartışılan, endoskopisi ve 24 saatlik pH metresi normal ancak semptom indeksi %50'nin üzerinde olan olguları içeren bir klinik tablodur. Çalışmamızda retrosternal yanması olan olgular arasında bu tablonun sıklığını saptamayı, hipersensitif özofagusu olan olguları, gastroözofageal reflü hastalığı ve normal bulgular tesbitedilen olgular ile demografik özellikleri, semptomları, manometrik bulguları ve 24 saatlik pH metrik profilleri açısından karşılaştırmayı planladık.* ***Yöntem:*** *Polikliniğe retrosternal yanma yakınması ile başvuran, koroner arter hastağı olmayan, endoskopide mide, bulbus ve duedenum 2. kıta patolojisi (antral gastrit hariç) bulunmayan ve manometrik olarak primer özofagus motor hastalığı olmayan 44 olgu çalışmaya alınmıştır. Olguların yaşları, vücut kitle indeksleri, eğitim düzeyleri, semptomları kaydedilmiştir. Tümüne özofagogastroskopi, özofagus manometrisi ve 24 saatlik pH moniterizasyonu uygulanmıştır.* ***Bulgular:*** *44 olgunun (17 erkek, 27 kadın) 7'sinde (%16) hipersensitif özofagus, 15'inde (%34) noneroziv reflü hastalığı, 7'sinde (%16) eroziv reflü hastalığı, 15'inde (%34) normal bulgular saptanmıştır. Gruplar arasında yaş, vücut kitle indeksleri, eğitim ve semptomlar yönünden farklılık bulunmamıştır. Hipertansif özofagus ve normal gruplarda kadın, eroziv reflü hastalığında erkek cinsiyet daha fazla bulunmuştur. Alt özofagus sfinkter ve gövde dinlenim basınçları, kontraksiyon amplütüdü ve süresi arasında istatistiksel fark izlenmemekle birlikte; hipertansif özofagus olan olgularda alt özofagus sfinkter hipotansif sınırda ve diğerlerinden daha düşük bulunmuştur (Hipertansif özofagus:7,6±4,4 mmHg; non-eroziv reflü hastalığı: 12,4±10,8 mmHg, eroziv reflü hastalığı:10,6±8,6 mmHg, Normal: 18,0±12,6 mmHg). 24 saatlik pH metrik değerlendir-mede eroziv reflü hastalığında De Meester skoru en fazla iken; semptom indeksi, hipertansif özofagus grubunda belirgin olarak fazla bulunmuştur. Reflüler özellikle ayakta pozisyonda fazladır. Distal reflüde, hipertansif özofagus olan olgular, pozisyon değişimine en belirgin reflü artışı ile yanıt verenmişlerdir.* ***Sonuç:*** *Retrosternal yanma ile başvuran olgularda hipersensitif özofagus %16, gastroözofageal reflü hastalığı %50, normaller %34 olarak saptanmıştır. Hipertansif özofagus gerek bazı manometrik özellikleri, gerekse pH metrik özellikleri açısından gastroözofageal reflü hastalığı içerisinde sınıflandırılması uygun olan bir gruptur.*

Anahtar kelimeler: Gastroözofajiyal reflü hastalığı, hipersensitif özofagus, asit sensitif özofagus.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is one of the most common clinical conditions affecting the gastrointestinal tract (1). Reflux disease has a wide clinical spectrum including symptoms such

Address for correspondence: Dr. Sedef ÖZDAL KURAN
Türkiye Yüksek İhtisas Hastanesi, Gastroenteroloji Kliniği, Ankara
Tel: 0312-310 30 80/1334

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as heartburn, regurgitation, chest pain and less commonly asthma, hoarsness,cough and halitosis (2). According to findings of the Gallup survey of adults in the United States, 44% of the population were found to suffer from heartburn at least once monthly (3). Patients with GERD symptoms may have endoscopic findings ranging from normal endoscopy (endoscopy negative) to severe ulcerative esophagitis, Barrett's esophagus and strictures (4). Until recenty, our understantanding of GERD was largely limited to patients with erosive esophagitis (5). However, nonerosive reflux disase (NERD) is more common than erosive reflux disease (ERD) among patients with reflux symptoms. There is no generally accepted clinical definition of NERD in the literature but it is often defined as typical GERD symptoms caused by excessive intraesophageal acid diagnosed by 24 hour pHmetric test and with no visible esophageal mucosal injury found at endoscopy (5).There is also another group of patients with reflux symptoms but negative endoscopic findings and normal acid contact time on 24 hour pH analysis, although there is a convincing relationship between their symptoms and acid reflux episodes on pH analysis- positive symptom index. The term hypersensitive esophagus or acid sensitive esophagus is used to describe these individuals (4). In a French study, acid sensitive esophagus prevalence was found as 12.5%, with 81% of patients having negative endoscopy findings (6). Another study from Scotland showed hypersensitive esophagus prevalence to be 6.7% (7). There is little information available regarding acid sensitive esophagus. In this study, patients with reflux symptoms were evaluated according to their endoscopic, manometric and pHmetric findings. We compared demographic, symptomatic, manometric and 24 hour pHmetric differences between patients with NERD, ERD, hypersensitive esophagus and normal findings.

MATERIALS AND METHODS

Between January and July 2001, 44 patients presenting with a main complaint of heartburn for at least three months and occurring more than three times a week were included in the study. Only those on no medication such as proton-pump inhibitors or histamine-receptor blockers, without any cardiac, severe gastric or duodenal pathologies (except minimal antral gastritis) and with no abnormal manometric findings suggestive of esophageal motility disorders were included in the study. All patients were questioned about age, height, weight, educational status and intestinal and extraintestinal reflux related symptoms. Upper endoscopy, esophageal manometry and 24 hour pH monitoring were performed respectively.

Esophageal manometry was performed using Synetics medical microcapillary infusion system, PC polygraph HR and eight channel Dent sleeve catheter. Findings were analysed by polygram upper GI edits, version 6.2 computer program.

Twenty four hour ambulatory pH monitoring was performed using Synectics Digitrapper MKIII, and double channel, 15 cm antimony catheter. The esophageal pH catheter was placed 5cm above the upper border of the manometrically determined lower esophageal sphincter. Findings were evaluated by microsoft Esophagogram version 2.04. They were accepted as pathologic if acid contact time was more than 1% of total time for proximal refluxes and De Meester score was more than 14.72 for distal refluxes.

Symptom index (SI) is a numerical value and can be defined as the number of times the symptom occurs when pH is lower than 4, divided by the total number of times the symptom is reported. This quotient is then multiplied by 100 to give the percentage of symptom episode that correlated with gastroesophageal reflux. SI is accepted as positive if it is more than 50% (8).

$$SI = 100 \times \frac{\text{Number of symptoms with pH} < 4}{\text{Total number of symptoms}}$$

Patients were divided into four groups according to their endoscopic and 24 hour ambulatory pH monitoring findings

Group 1: Hypersensitive esophagus (HE): Patients in this group had normal endoscopy and 24 hour pHmetry findings but positive SI

Group 2: Endoscopy-negative reflux disease (NERD): Patients in this group had normal endoscopy findings but reflux on pHmetry

Group 3: Endoscopy-positive reflux disease (ERD): Patients in this group had esophagitis endoscopically and reflux on pHmetry

Group 4: Normals (N): Patients in this group had normal endoscopy and 24 hour pHmetric findings and negative SI

All groups were compared according to their demographic, manometric and pHmetric values.

Table 1. Demographic findings of patients

	HE	*NERD*	*ERD*	*N*	*P value*
Patient number	7	15	7	15	
Male/female ratio					
(female%)	2/5*	8/7	5/2*	2/13*	p<0.05
	71.4	46.7	28.6	86.7	
Age (years)	45±14.5	44±12.7	48.9±14.0	43.2±11.5	p>0.05
BMI(Kg/m^2)	28.6±1.8	25.9±3.5	26.0±2.6	27.1±4.3	p>0.05

*Statistically significant ratios (high female ratio were significant for HE and normal groups; high male ratio were significant for ERD group)

Statistical analysis was performed according to SPSS statistics computer program and one-way variance analysis, Spearsman's correlation analysis, Chi-square test and Kruscal-Wallis variance analysis were used.

RESULTS

A total of 44 patients (17 male, 27 female) were included in the study of whom seven (16%) had HE, 15 (34%) had NERD, seven (16%) had ERD and 15 (34%) had normal findings. The female ratio in the HE and normal groups was significantly higher than others (p<0,05).There was no significant difference according to age and body mass index. These parameters are shown in Table 1.

There was no significant difference between groups according to level of education. Although it was not significant, HE and normal groups of patients had a lower educational level (no primary school education than others). They comprised 71.4% of HE , 66.6% of the normal group, 40% of NERD and 28.6 % of ERD groups. Patients were questioned about intestinal and extra-intestinal reflux related symptoms and findings are shown in Table 2 and 3. There was no difference between

Table 2. Gastro-intestinal reflux-related symptoms of patients

	HE		**NERD**		**ERD**		**N**		**P value**
	n	*%*	*n*	*%*	*n*	*%*	*n*	*%*	
Regurgitation	3	42.9	9	60.0	6	85.7	11	73.3	p>0.05
Dysphagia	1	14.3	5	33.3	1	14.3	8	53.3	p>0.05
Chest pain	6	85.7	4*	26.7	5	71.4	13	86.7	*p<0.05
Dyspepsia	3	42.9	8	53.3	4	57.1	11	73.3	p>0.05
Spastic colon	0	0	2	13.3	2	28.6	3	20.0	p>0.05

*Chest pain ratio was lower than the others

Table 3. Extra-intestinal reflux related symptoms of the patients

	HE		**NERD**		**ERD**		**N**	
	n	*%*	*n*	*%*	*n*	*%*	*n*	*%*
No symptom	4	57.1	9	60.0	5	71.4	7	46.7
Cough			1	6.7			4	26.7
Hoarseness	2	28.6					1	6.7
Snoring			4	26.7	1	14.3	2	13.3
Hoarsness+snoring			1	6.7				
Cough+halitosis					1	14.3		
Cough+snoring	1	14.3					1	6.7

Table 4. Manometric findings

	HE	*NERD*	*ERD*	*N*	*P value*
LESP (mmHg)*	7.6±4.4	12.4±10.8	10.6±8.6	18.0±12.6	p>0.05
M*	10	10	8	16	
Esophageal body pressure (mmHg)	–5.3±6.6	-6.5±5.3	-5.9±4.6	–8.86±6.1	p>0.05
M	-5	-6	-5	-7	
Contraction amplitude (mmHg)	59.2±36.5	68.8±32.0	66.7±26.8	64.2±33.7	p>0.05
M	48.5	66.8	66.5	55	
Contraction duration (sec)	4.9±0.9	5.1±0.8	5.2±0.9	4.8±0.7	p>0.05
M	4.6	5.2	5.24	4.5	

Table 5. De Meester scores and symptom index according to 24 hour ambulatory pH monitoring

	HE	*NERD*	*ERD*	*N*	*P value*
De Meester	7.2±3.7*	22.0±18.2	36.4±15.5	0*	p<0.001
Symptom Index	61.9±18.5	35.3±34.6	50.9±41.6	0*	p<0.001

*Statistically significant

groups except that chest pain was found to be less common in NERD patients.

Manometric findings, De Meester scores and SI are shown in Table 4 and 5. There was no significant difference between groups according to manometric findings, but lower esophageal sphincter (LES) pressures were lower in HE, NERD and ERD groups (lowest was HE) than the normal group. De Meester scores were significantly lower in HE and normal groups and symptom index was highest in the HE group.

Twenty four hour pHmetric findings were evaluated as distal and proximal findings, values were also compared according to supine and upright position changes. Tables 6 and 7 show the distal and proximal number of acid refluxes, acid contact times and fractions of times pH was less than four. The number of distal and proximal refluxes were significantly lower in the normal group than others (p<0.001). Reflux duration and acid contact time were shorter in HE and normal groups and highest in the ERD group for distal parameters (p<0.001).

Table 6. 24 hour pHmetric findings (distal values)

	HE	*NERD*	*ERD*	*N*	*P values*
Number of distal refluxes	31.0±24.0	69.3±57.9	80.9±81.9	15.7±14.7*	p<0.001
M†	41	43.5	73	10	
Distal reflux duration (sec)	21.8±19.1*	79.3±66.0	114.4±77.1*	13.0±12.4*	p<0.001
M	26	36.0	117	10	
Fraction of time for distal refluxes					
M	1.7±1.4*	5.7±4.6	9.14±4.9	0.9±0.9*	p<0.001
	1.6	2.7	8.6	0.7	

* Values of HE and normal groups were significantly lover than others; value of ERD was also significant

†M: Median

Table 7. 24 hour pHmetric findings (proximal values)

	HE	*NERD*	*ERD*	*N*	*P values*
Number of proximal refluxes	0.1±0.4*	13.9±13.4	6.7±13.5	0.7±2.0*	p<0.001*
M	0	8	2	0	
Proximal reflux duration(sec)	0*	8.2±13.4	3.7±5.7	0.1±0.5*	p<0.001*
M	0	8	2	0	
Fraction of time for proximal refluxes	0*	0.6±0.9	0.5±0.8	0.01±0.05*	p<0.001*
M	0	3	0.2	0	

*Statistically significant

Effects of positional changes on reflux pattern were also evaluated for distal and proximal values (Table 8,9). Reflux number, duration and distal or reflux were higher in the upright position than supine position for every group according to distal parameters. The number of refluxes, duration of refluxes and time for reflux time were lower in the HE and normal group and highest in the ERD group for supine position of distal refluxes. Only the normal group had signiicantly lower values than others for the upright position. The difference between supine and upright reflux fraction time was compared in each group and a significant increase in all reflux parameters during the upright position was found compared with the supine position in the HE group. The same parameters were also evaluated for proximal values. There were no proximal refluxes in the HE group and very few for the normal group while proximal refluxes were observed in the ERD and NERD groups, with the number of proximal refluxes being higher in the NERD than the ERD and this increase was significant in the NERD group. All reflux parameters were higher in the upright than supine position. There was also an increase in all parameters for ERD but this was not significant.

DISCUSSION

Hypersensitive esophagus has been defined recently and there is no consensus as to whether it should be accepted as a subgroup of reflux disease. In this study, the similarities and differences among HE, NERD, ERD and normal patients with a main complaint of retrosternal pain was evaluated by comparing demographic, symptomatic, manometric and pHmetric findings.

It was found that seven (16%) patients had HE, 15 (34%) had NERD, seven (16%) had ERD and 15 (34%) had normal findings with the female ratio being significantly higher in HE and normal groups. Although no significant difference was found according to educational level, the HE and normal group of patients had a lower educational

Table 8. Changes in distal reflux values for supine and upright position according to 24 hour ambulatory pH monitoring

	Reflux during supine position			**Reflux during upright position**			
	Number	*Duration*	*Fraction of time*	*Number*	*Duration*	*Fraction of time*	*P value*
HE	1.6±2.1* ‡	2.0±2.8* ‡	0.5±0.6* ‡	29.3±22.7‡ ‡	23.8±17.2‡ ‡	3.3±4.6 ‡	p<0.01 ‡
NERD	20.0±27.2	34.7±44.1	5.8±7.2	37.8±39.3	43.2±39.1	5.7±4.6	p>0.05
ERD	29.0±25.2 *	41.6±29.7 *	8.7±4.9*	59.6±60.8	73.0±65.4	9.13±9.5	p>0.05
N	3.6±10.8* ‡	3.8±8.9*	0.9±1.9*	10.9±9.7*‡	9.1±9.5*	1.1±1.1*	p<0.05‡
P value	P<0.001*	p<0.001*	p<0.001*	p<0.001*	p<0.001*	p<0.001*	

*(for columns) HE and normal groups had statistically lower values than others, ERD group had statistically higher values than others

‡(for rows)Reflux changes during upright and supine position were statistically significant

Table 9. Changes in proximal reflux values for supine and upright position according to 24 hour ambulatory pH monitoring

	Reflux during supine position			Reflux during upright position			
	Number	*Duration*	*Fraction of time*	*Number*	*Duration*	*Fraction of time*	*P value*
HE	0*	0*	0	0.4±1.1*	0*	0*	p>0.05
NERD	2.1±5.4	3.2±9.1	0.4±1.2	10.8±11.3	5.9±6.4	0.8±0.9	p<0.05
	‡	‡	‡	‡	‡	‡	‡
ERD	1.7±4.1	0.3±0.8	0.04±0.1	6.1±10.6	3.8±5.0	0.5±0.9	p>0.05
N	0*	0*	0	1.8±4.9*	0.5±1.2*	0.04±0.1*	p>0.05
P value	p<0.001*	p<0.05*	p>0.05	p<0.001*	p<0.001*	p<0.001*	

*(for columns) HE and normal groups had statistically lower values than others

‡(for rows)Reflux changes during upright and supine position were statistically significant

level than others. It has been observed in the literature that female patients and those with low socioeconomic level have more functional gastrointestinal symptoms than others (9,10,11). Patients in the normal group had more intestinal and extraintestinal symptoms than others but this difference was not significant. According to studies which evaluate the effects of stress and psychological status on reflux related symptoms, reflux severity and manometric findings, it has been shown that there are no objective manometric and pHmetric changes but that the perception of symptoms or symptom severity was increased by stress (5,4,12). It has been suggested that the chronically anxious patient faced with stress might perceive low intensity esophageal stimuli as a painful reflux symptom and it has also been shown that patients with reflux symptoms but normal endoscopy, pHmetry and negative symptom index (similar to our normal group of patients) have significantly higher levels of anxiety (5,13).

In this study, there were no significant differences among groups according to manometric findings which evaluated LES and intraesophageal pressures, contraction amplitude and durations. It is of interest however, that the mean values of LES pressure and contraction amplitude in the HE group were the lowest among groups (7.6±4.4 mmHg, 59.2±36.5 mmHg). The mean LES pressure was also lower than normal LES pressure. It is known that LES pressures of patients with ERD are lower than NERD (5) although the etiology of the low basal LES pressures in ERD has not been clearly understood. There may be a relationship between inflammation, inflammatory mediators (especially arachidonic acid) and LES pressures according to studies based on animal models in which arachidonic acid and mediators induce LES contraction and relaxation (14). These results may partially explain low LES pressures in ERD patients but it does not explain occurrence of the lowest LES pressure in the HE group. Visceral hypersensitivity or chemoreceptor sensitivity in the esophagus is thought to be one of the possible factors in the perception of heartburn in HE. There may be some mediators which cause visceral hypersensitivity and arachidonic acid may be one of them. The same mediators which cause an increase in perception of pain may also cause low LES pressure. However, more detailed studies must be undertaken in order to prove this hypothesis.

In the present study, the highest De Meester score was found in ERD while the symptom index which shows the perception of reflux related pain was found to be highest in the HE group. This suggests that acid is mainly responsible for mucosal destruction in reflux disease but that some factors other than acid or increased sensitivity to acid affect the perception of symptoms. Animal models of afferent nerve sensitization have shown that acid can sensitize esophageal nerve ending (chemoreceptors) directly or via inflammatory mediators. Altered pain perception by increased chemoreceptor sensitivity to acid has been shown in NERD patients (5) Increased chemoreceptor sensitivity or visceral hyperalgesia is recently believed to be one of the most important factors in functional gastrointestinal disorders (4). On the other hand, non-acid related stimuli such as duodenogastroesophageal reflux, mechanosensitivity

and reflux content (intraduodenal fat content) may cause heartburn in patients (5).

Reflux was observed especially in the upright position in all groups during evaluation of the effect of position on reflux pattern. Transient LES relaxation, which is an important factor in reflux pathogenesis, occurs especially in the upright position, which may account for this finding (14). There were no proximal refluxes in the HE group, but the response to positional changes in this group was significant distally. There were very few refluxes in the supine position but the increase in reflux number, duration and fractional time was very significant in the upright position.

In conclusion, some important manometric and pH metric changes were found in HE patients compared to those with normal findings. Their LES pressures and contraction amplitudes were lower than ERD patients and they had a significant increase in distal reflux in the upright position. It is suggested that HE should be accepted as a subgroup of reflux disease because it not only has symptoms but also some manometric findings and pH metric changes.

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