Gastroesophageal reflux disease in asthmatic children and its relation with atopy

Astımlı çocuklarda gastroözefageal reflü hastalığı ve atopi ile ilişkisi

Özge YILMAZ[1], Erhun KASIRGA[2], Şebnem KADER[3], Senem ALKAN[3], Hasan YÜKSEL[1]

[1] Department of Pediatric Allergy and Pulmonology, Faculty of Medicine, Celal Bayar University, Manisa, Turkey
Celal Bayar Üniversitesi Tıp Fakültesi, Çocuk Allerji ve Pulmonoloji Bilim Dalı, Manisa, Türkiye

[2] Department of Pediatric Gastroenterology, Faculty of Medicine, Celal Bayar University, Manisa, Turkey
Celal Bayar Üniversitesi Tıp Fakültesi, Çocuk Gastroenteroloji Bilim Dalı, Manisa, Türkiye

[3] Department of Pediatrics, Faculty of Medicine, Celal Bayar University, Manisa, Turkey
Celal Bayar Üniversitesi Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Manisa, Türkiye

ABSTRACT

Objective: The aim of this study was to determine frequency of gastroesophageal reflux disease (GERD) and influence of GERD treatment on respiratory findings in atopic and nonatopic children with asthma.

Materials and Methods: Thirty two nonatopic, 24 atopic children with asthma were enrolled in this retrospective study. GERD related respiratory symptoms and asthma severity parameters six months prior to and after pH monitoring were recorded. 24 hour pH monitoring results were also recorded.

Results: Frequency of proximal GERD was 71.9% in atopic and 70.8% in nonatopic group (p= 0.93). Distal GERD frequencies were similar (66.7% and 68.8% in atopic and nonatopic groups respectively, p= 0.87). All parameters improved in nonatopic children after GERD treatment (p≤ 0.01). However, only respiratory symptoms and hospitalization improved in atopic children (p= 0.002 and p= 0.007 respectively).

ÖZET

Giriş: Bu çalışmanın amacı, atopik ve nonatopik astımlı çocuklarda gastroözefageal reflü hastalığı (GÖRH) sıklığını ve solunum yolu bulgularına GÖRH tedavisinin etkisini belirlemektir.

Gereç ve Yöntem: Bu retrospektif çalışmaya 32 nonatopik, 24 atopik astımlı çocuk alındı. GÖRH ile ilişkili solunum sistemi belirtileri ve astım ağırlığı parametreleri pH monitörizasyondan önceki ve sonraki altı ay göz önüne alınarak kaydedildi. Ayrıca, 24 saatlik pH monitörizasyon sonuçları da kaydedildi.

Bulgular: Proksimal GÖRH sıklığı atopik grupta %71.9, nonatopik grupta %70.8 saptandı (p= 0.93). Distal GÖRH sıklığı gruplar arasında benzerdi (sırasıyla atopik ve nonatopik gruplarda %66.7 ve %68.8, p= 0.87). Nonatopiklerde GÖRH tedavisi sonrasında tüm klinik parametrelerde düzelme mevcuttu (p≤ 0.01). Ancak, atopiklerde, sadece solunum sistemi belirtileri ve hastaneye yatışta düzelme görüldü (sırasıyla p= 0.002 ve p= 0.007).

Yazışma Adresi/Address for Correspondence
Doç. Dr. Hasan YÜKSEL
16/17 Sokak No: 7 C Blok Daire: 3 Bornova-İzmir, Türkiye
e-posta: hyukselefe@hotmail.com

Conclusion: Similar frequencies of GERD in atopic and nonatopic children may suggest role of asthma in development of GERD. However, improvement in all clinical parameters in nonatopic but not in atopic children might indicate that gastroesophageal reflux is the causal event in the association of asthma and GER in nonatopic children whereas it is the result in atopic ones. These findings need to be supported by further prospective cohort studies.

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Key words: Atopy, gastroesophageal reflux disease, asthma, children

Sonuç: Atopik ve nonatopik çocuklarda benzer GÖRH sıklığı olması, GÖRH gelişiminde astımın rolüne işaret ediyor olabilir. Ancak nonatopik çocuklarda tüm klinik parametrelerde GÖRH tedavisi ile düzelme olurken, atopik çocuklarda bunun gözlenmemesi; GÖRH'nin nonatopiklerde astım ve GÖR ilişkisinde nedensel rolü olduğunu ancak atopiklerde sonuç olarak ortaya çıktığını düşündürebilir. Bu sonuçların daha ileri prospektif kohort çalışmalarla desteklenmesi gereklidir.

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Anahtar kelimeler: Atopi, gastroözefageal reflü hastalığı, astım, çocuk

INTRODUCTION

Asthma that is one of the most common chronic diseases of children, is characterized by variable airflow obstruction that changes over a short period of time and is associated with respiratory mucosal eosinophilic inflammation in diagnosis[1,2]. Atopy to inner or outer environmental allergens is demonstrated in most cases of childhood asthma[3]. Gastroesophageal reflux (GER) is the passive regurgitation of gastric contents retrograde into the esophagus and is regarded pathological [gastroesophageal reflux disease (GERD)] when associated with findings of esophagitis or respiratory symptoms like cough[4-6].

Association of GERD and respiratory symptoms, especially asthma, is complex and multifactorial[7]. Although there is a high frequency of co-existence of these two diseases, the exact mechanism underlying the association is not clear. Some of the proposed mechanisms include the influence of vagally mediated neurogenic reflex triggered by increased acidity of esophagus and the influence of microaspirations of gastric contents into the bronchial tree leading to increased airway inflammation[6,8]. Moreover, it has been shown that agents used in asthma treatment such as albuteral, decreases lower esophageal sphincter pressure aggravating GER[9].

It has been shown in a previous study that treatment of gastroesophageal reflux disease improves asthma in nonatopic children[7,10]. However, since most cases of childhood asthma is atopic and since the direction of association between asthma and GER is not fully explained yet, it is important to evaluate GER in children with atopic asthma. Therefore, the aim of this study was to compare the frequency of GERD and the influence of GERD treatment on respiratory findings in atopic and nonatopic children with asthma.

MATERIALS and METHODS

Study Population

Thirty two nonatopic and 24 atopic children aged between four and 16 years who had been diagnosed as asthma were included in this study. Diagnosis of asthma was based on history of recurrent cough and wheezing with prolonged expiration time which demonstrated clinical reversibility with short effective bronchodilator therapy, beta-2 agonist[7]. Atopy was determined according to serum allergen specific immunoglobulin-E values in children less than 5 years of age and skin prick test results in the ones above 5 years of age. Serum levels of immunoglobulins were normal; purified protein derivative (PPD) and sweat chloride test were negative in all the patients. None of the children included in the study had body mass

index above 20 to avoid the GER provoking influence of obesity.

Study Design

Records of all children with asthma who had undergone pH monitoring during the four year period between 2004 and 2008 were reviewed. Their age at the time of pH monitoring, gender, respiratory findings associated with gastroesophageal reflux (such as wheezing and cough), total days of requirement for inhaled steroids, total days of inhaled bronchodilator and parenteral steroid use, total number of respiratory exacerbations and total days of hospitalizations were recorded during the six months period prior to and after the pH monitoring were recorded. Patients diagnosed as having GERD according to the results of 24 hour pH monitoring and the ones who had received treatment were recorded.

pH Monitoring

A standard protocol is followed for 24 hour pH monitoring that is carried in the Pediatric Gastroenterology Department. The protocol requires stopping anti-reflux treatment for one month before the procedure and all medications which might interfere with the results are stopped one week before. Then an antimony catheter with a diameter of less than 2.1 mm and 2 sensors are placed nasally following an overnight fast. The sensors of the catheter are 10 cm apart to measure pH in the proximal and distal esophagus. Position of the catheter is verified by chest X-ray to be 2-3 cm above the diaphragm[11]. Measurements of pH are recorded using a pH recorder (MMS Orion II, MMS, Enschede, Netherlands). Patients receive regular feeds during recording and daily activities are resumed as normal. Parents recorded the meal times and position of the patients using the buttons on the recorder. Recorded pH data are downloaded in an IBM compatible computer and analyzed by software (EsopHogram Software System) Orion Medical Measurement Systems Software Version 8.3, Build 1147 (MMS, Enschede, Netherlands). Fraction of time with pH for proximal and distal esophagus was considered abnormal if more than 1% and more than 4% respectively[12-14].

Evaluation of Disease Severity

Clinical response to treatment was determined by evaluating the presence of symptoms, total days of bronchodilator, parenteral steroid use and total number of days of hospitalization requirement as well as the number of asthma exacerbations. Symptoms that were evaluated included vomiting, wheezing, hoarseness, recurrent pneumonia, sore throat, chronic cough, regurgitation. Total numbers of symptoms 6 months prior to and after GERD treatment were recorded.

Statistical Analysis

Statistical analyses were performed by SPSS 13.0 (Chicago IL) computer program. Mann Whitney U test, Wilcoxon test and Pearson's Chi Square test was used for the statistical analysis. Nonparametric tests were used because the values were not normally distributed. P values less than 0.05 were regarded as statistically significant.

RESULTS

Subject Characteristics

Mean age of the atopic group was 9.2 ± 2.7 years while that of the nonatopic group was 8.1 ± 2.3 years. Age means of the two groups were not significantly different (p= 0.06). Number of the males in atopic and nonatopic groups were 18 vs 16 respectively (p= 0.55).

Comparison of Clinical Parameters Before and After Gastroesophageal Reflux Treatment

Gastroesophageal reflux treatment was initiated in 18 children in the atopic group and 24 children in the nonatopic group. All of the children had received lansoprozole. In the atopic group 1 child had also received domperidon, 7 children had received alginic acid (Gaviscon Liquid suspension®, Ali Raif Co, Turkey) while 7 children had received treatment with

all three agents. In the nonatopic group, 2 children had also received domperidon, 16 children had also received alginic acid (Gaviscon Liquid suspension®, Ali Raif Co, Turkey) and 6 had received treatment with all agents. Treatment modalities were not found to be significantly different between the groups (p= 0.568).

Comparison of the clinical parameters between the two groups before treatment revealed a significant difference in the days of hospitalizations (0.5 ± 1.5 vs. 4.1 ± 7.2 in atopic and nonatopic groups respectively, p= 0.020). However there was no significant difference in the number of symptoms, days of bronchodilator and parenteral steroid use, number of exacerbations and number of hospitalizations between the two groups after GER treatment (p= 0.381, p= 0.188, p= 0.859, p= 0.679, p= 0.450 respectively) (Table 1).

Comparison of the clinical parameters among the groups themselves before and after treatment displayed significant improvement in all in the nonatopic group (p≤ 0.01 for all). On the other hand, only number of symptoms

and days of hospitalizations had improved in the atopic group (1.5 ± 0.8 vs. 0.3 ± 0.4, p= 0.002 and 0.9 ± 0.9 vs. 0.3 ± 0.6, p= 0.007 respectively) (Table 1).

Comparison of pH Monitoring Results in the Two Groups

Frequency of proximal GER in the atopic and nonatopic groups were 71.9% vs. 70.8% respectively and there was no significant difference between the two groups (p= 0.93). Similarly, the frequency of distal GER were similar between the two groups (66.7% vs. 68.8% in atopic and nonatopic groups respectively, p= 0.87) (Figure 1). Mean proximal and distal GER indices in the atopic group was 3.6 ± 4.6 and 9.2 ± 9.9 respectively while those in the nonatopic group were 2.1 ± 1.5 and 7.0 ± 5.4 respectively (p= 0.61 and 0.99 respectively) (Table 2).

DISCUSSION

Association of GERD and asthma has been demonstrated clearly however, the interaction of the two diseases and the causal direction has not been explained fully yet[6,8,9]. Reflex and reflux theories indicating vagal stimulation by esopha-

Table 1. Clinical characteristics of the atopic and nonatopic groups before and after gastroesophageal reflux treatment (mean ± standard deviation)

	Group	Before treatment	After treatment	p*
Number of symptoms	Atopic	1.5 ± 0.8	0.3 ± 0.4	**0.002**
	Nonatopic	1.5 ± 0.7	0.1 ± 0.4	**0.000**
	p	**0.787**	**0.381**	
Days of bronchodilator requirement/6 months	Atopic	3.5 ± 4.2	1.8 ± 4.3	**0.374**
	Nonatopic	6.3 ± 8.8	0.5 ± 1.5	**0.000**
	p	**0.441**	**0.188**	
Days of parenteral steroid requirement/6 months	Atopic	0.8 ± 1.7	0.2 ± 0.5	**0.496**
	Nonatopic	2.2 ± 3.9	0.3 ± 1.2	**0.015**
	p	**0.174**	**0.859**	
Number of asthma exacerbations/6 months	Atopic	0.9 ± 0.9	0.3 ± 0.6	**0.007**
	Nonatopic	1.2 ± 0.9	0.4 ± 0.6	**0.000**
	p	**0.315**	**0.679**	
Days of hospitalizations/6 months	Atopic	0.5 ± 1.5	-	**0.317**
	Nonatopic	4.1 ± 7.2	0.1 ± 0.4	**0.005**
	p	**0.020**	**0.450**	

p*: Comparison of before and after treatment values in each group.
p: Comparison of the groups with each other.
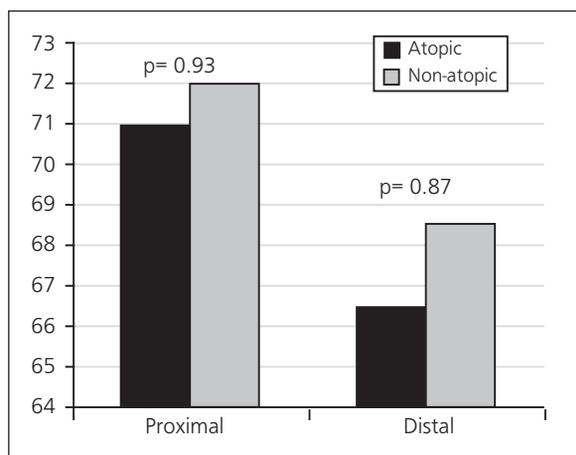
Figure 1. Frequency of proximal and distal GER in atopic and non-atopic groups.

Table 2. Mean proximal and distal gastroesophageal reflux indices (%) in atopic and nonatopic groups

GER Indices	Atopic group	Nonatopic group	p
Proximal (%)	3.6 ± 4.6	2.1 ± 1.5	**0.608**
Distal (%)	9.2 ± 9.9	7.0 ± 5.4	**0.987**

geal reflux leading to bronchoconstriction and microaspirations respectively have been suggested as possible mechanisms of development of asthma findings in patients with GERD[15-19]. Moreover, it has been shown that agents used in asthma treatment including albuteral decreases lower esophageal sphincter pressure aggravating GER[9]. Most cases of childhood asthma are atopic but influence of GER and its treatment on asthma findings in atopic children with asthma have not been assessed before.

The clinical picture of chronic recurrent cough, recurrent lower respiratory problems, wheezing, rhonchi and prolonged expiration time responsive to bronchodilator administration was defined as asthma in this study[20]. GERD is defined as total distal reflux index (RI) > 4 in distal esophagus determined by the most suitable diagnostic tool for GERD, that is the 24 hour pH monitoring with a sensitivity and specificity above 90%[5,21,22].

It has been shown before that both pressure changes in thorax due to respiration problems in asthma and decrease of lower esophageal pressure due to the medical treatment agents used in asthma might contribute to GER[9,20,23]. Similar frequency of GERD in atopic and nonatopic children with asthma might be a stronger clue for a major role of asthma in GERD development in these children instead of the GERD contributing to asthma. The finding that eosinophilic infiltration into the esophagus is present in GER might point out a role of allergic sensitization in pathogenesis of this disease[24]. Moreover, GER can also be a manifestation of eosinophilic esophagitis which has been associated with sensitization to aeroallergens[25]. Prevalence of asthma and other allergic diseases are higher in patients with eosinophilic esophagitis and exposure to inhalant allergens promotes eosinophilic esophagitis[24-26]. This finding highlights the role of sensitization to inhalant allergens to gastrointestinal symptoms like GER and suggests the presence of a common mechanism regulating eosinophilic inflammation in the respiratory tract and esophagus[24]. The patients in this study have not undergone esophageal biopsy therefore eosinophilic infiltration could not be evaluated. However, considering that systemic eosinophilic inflammation is established in allergic diseases, children with atopic asthma might also have esophageal eosinophilic infiltration[27]. The frequency of GER was similar in atopic and nonatopic children with asthma in our study, however, rate of improvement with GER treatment was lower in asthmatic children with aeroallergen sensitivity. Eosinophilic infiltration in the esophagus might have contributed to this resistance to treatment.

Improvement in asthma symptoms in nonatopic children with asthma like GERD has been demonstrated before[7,10]. This is consistent with the findings of our current study. Eosinophilic infiltration of airways is a major component of asthma[2]. Moreover, increased

eosinophil infiltration in the sputum of GER patients with asthma has been demonstrated before[8]. However, since nonatopic children with asthma did respond to treatment, this does not seem to blunt therapy responsiveness. However, increase in the eosinophilic infiltration associated with GER and the one associated with aeroallergen sensitization in the airways as is the case for atopic asthma, might have blunted the favorable clinical response to GER treatment in children with atopic asthma.

The major limitation of this study was the retrospective study design which might have led to the loss of information on some symptoms. Since this information was obtained from patient records, they could only be gathered if recorded but could not be specifically questioned from the patient. Moreover, if control pH monitorization in patients unresponsive to GERD treatment was performed, we could have concluded if the reason for unresponsiveness is failure to control GERD or the persistence of respiratory findings despite GERD control. Moreover, lack of endoscopic findings limited our interpretation about esophageal eosinophilic infiltration in atopic children with asthma who did not respond to GERD treatment.

In conclusion, the results of our study indicate coexistence of GERD and asthma in atopic and nonatopic children with asthma similar to many previous studies. However, similar frequency of GERD in nonatopic children who do not have any other risk factor for asthma and in atopic children who have allergy as the major risk factor for asthma might suggest the role of asthma for development of GERD. Moreover, failure of the asthma findings to respond to GERD treatment in atopic children but not in non-atopic children might be an indicator of atopy as the determinant of asthma control even in the ones with GERD further suggesting asthma as the initiating event in the association of GERD and asthma.

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