



Frequency of gastroesophageal reflux disease in nonatopic children with asthma-like airway disease

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Summary Gastroesophageal reflux disease (GERD) is commonly associated with asthma; however, frequency in nonatopic children with asthmatic symptoms is unknown. The aim of this study was to determine the frequency of gastroesophageal reflux (GER) in nonatopic children with asthma-like airway disease that recur despite conventional asthma treatment and to evaluate the clinical response to lansoprazole treatment. Twenty-five nonatopic children aged between 1 and 16 years who have asthma-like airway disease and 25 healthy children were included in the study. All cases underwent 24 h pH monitoring with dual sensor catheters. Additionally, acid suppressor treatment was administered to patients diagnosed as having GERD and clinical response was evaluated.

Major symptoms encountered in the patient group included wheezing and cough (88%, and 32%, respectively). Reflux episodes were more common in distal esophagus during the prone position (reflux index (RI) of 11.5 ± 10.3 vs. 16.2 ± 9.4 during supine vs. prone). All distal esophageal parameters were significantly higher in the patient group except number of reflux episodes lasting longer than 5 min (RI of 13.3 ± 13.1 vs. 3.9 ± 2.9 in the patient vs. control groups, respectively). There was a significant improvement in symptoms and requirement for medication with treatment (number of systems decreased from 2.3 ± 0.6 to 0.4 ± 0.6 , $P = 0.00$).

In conclusion, GERD is significantly more common in nonatopic children with asthma-like airway disease compared to the controls and clinical improvement is significant after acid suppressor treatment. Thus, we suggest that children followed-up with the diagnosis of nonatopic asthma with recurrent exacerbations despite adequate asthma treatment have a high frequency of GER and that lansoprazole treatment may be considered early in management.

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Introduction

Prevalence of asthma symptoms in children reaches up to 30% in some populations.¹ The pathophysiology of this disease depends on airway hyperresponsiveness and airflow limitation.² Only around 10% of asthmatic children have been reported to be nonatopic.³ Allergen exposure is an important factor in exacerbations of respiratory symptoms in children with atopic asthma. However, other factors like gastroesophageal reflux disease (GERD) may be contributing to asthmatic exacerbations in nonatopics because this factor is absent. GERD, which is the passive regurgitation of gastric contents retrograde into the esophagus may be associated with asthma.⁴⁻⁶ However, exact causal relationship has not been confirmed between asthma and GERD.⁴ Most suitable diagnostic tool for GERD is 24 h pH monitoring with a sensitivity and specificity above 90%.^{5,7,8} The relationship between asthma and GERD has been detected in many studies by 24 h pH monitoring.^{7,9-11} However, these studies have not been conducted on a specific subgroup of asthmatic patients and a more precise relationship can be detected if the study population is limited to specific subgroups.

Many different categories of drugs like H₂ receptor antagonists, antacids, prokinetics, and proton pump inhibitors (PPIs) may be used in the treatment of GERD.^{12,13} Among these, PPIs constitute the most effective treatment option for GERD.¹³⁻¹⁶ It has been reported that lansoprazole produce greater symptom relief than omeprazole.¹⁷ Thus, lansoprazole therapy was given to nonatopic children with asthma-like airway disease and GERD in our study.

Therefore, the aim of this study was to detect the frequency of GERD in a subgroup of nonatopic children who have asthma-like airway disease that recur despite asthma treatment and also to evaluate the influence of lansoprazole treatment on asthma severity.

Material and methods

Study population

Twenty-five nonatopic children (16 boys and 9 girls) aged between 1 and 16 years (mean $\pm$ SD of 72.6 ± 38.1 months) who have asthma-like airway disease with recurrent exacerbations despite conventional asthma therapy (such as inhaled steroids, bronchodilator, etc.) directed by international consensus report were included in this prospective

study.¹⁸ It was carried out during the period between January 2003 and October 2004.

Inclusion and exclusion criteria

Diagnosis of asthma-like airway disease was based on history of recurrent cough and wheezing with prolonged expiration time which demonstrated clinical reversibility with short effective bronchodilator therapy, β_2 agonist. Absence of atopy was confirmed by normal immunoglobulin E values in children less than 5 years of age and negative skin prick test in the ones above 5 years of age. Immunoglobulin levels 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

All patients and control subjects underwent 24 h pH monitoring. Patients diagnosed as having GERD according to the results of 24 h monitoring received acid suppressor treatment (lansoprazole). Then, the results of this treatment were evaluated on the basis of symptoms, requirement of bronchodilator, systemic steroid use, days of hospitalizations and number of acute asthmatic attacks.

pH monitoring

All cases underwent 24 h pH monitoring according to a standard protocol. None of the subjects had received anti-reflux treatment during the last 1 month. Moreover, 1 week before the procedure all medications which might interfere with the results were discontinued. Then an antimony catheter with a diameter of less than 2.1 mm and two sensors were placed nasally following an overnight fast. The sensors of the catheter were 10 cm apart to measure pH in the proximal and distal esophagus. Position of the catheter was verified by chest X-ray to be 2-3 cm above the diaphragm.⁹ Measurements of pH were recorded using a pH recorder (Digitrapper Mk 3, Synetics Medical AB, Stockholm, Sweden). Patients received regular feeds during recording and daily activities resumed as normal. Parents recorded the meal times and position of the patients using the buttons on the recorder. Recorded pH data were downloaded in an IBM compatible computer and analyzed by a software (EsopHogram Software System). Fraction of time with pH for proximal and distal esophagus was

considered abnormal if more than 1% and more than 4%, respectively.^{19–21}

Results of the 24 h pH monitoring of an asymptomatic group was obtained from a previous study by Aydoğdu et al.²² Age means of the patient and control groups were not statistically different (72.7 ± 38.1 and 92.6 ± 43.3 months, respectively; $P = 0.09$). The same protocol was used for pH recordings with the pH recorder of the same brand. Similar to our study, an antimony catheter with two sensors was used; however, since only distal sensor parameters were recorded at that time, gastroesophageal reflux (GER) parameters of the distal sensor of the patient group were compared to those of this control group.²²

Treatment

Patients diagnosed as having GER received treatment with PPIs, namely lansoprosol at a dose of 1 mg/kg/day taken 2 h before meals for 3 months. All the children and families were informed about conservative measures of GER control. Patients received inhaled steroid, fluticasone propionate 125 mcgr/dose by 12 h intervals, as anti-asthmatic treatment. The ones who were hospitalized received nebulized salbutamol and parenteral steroids namely intravenous dexamethasone for treatment of the acute exacerbations.

Evaluation of disease severity

Clinical response to treatment was evaluated by evaluating the presence of symptoms, days of bronchodilator, parenteral steroid and 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 and laryngitis.^{9,23–25} Post-treatment evaluation was performed during the 3-month period after initiation of GER treatment. Pre-

treatment evaluation was performed according to the patient records of the same months of the previous year to avoid seasonal influence like air pollution, and viral infections on asthma symptoms.

Statistical analysis

Statistical analyses were performed by SPSS 11.0 (Chicago IL) computer program. Paired samples *t*-test, independent samples *t*-test and Pearson's χ^2 -test was used for the statistical analysis. *P* values less than 0.05 were regarded as statistically significant.

Results

Gastroesophageal reflux related pulmonary symptoms

Symptoms encountered in the patient group included vomiting, wheezing, recurrent lower respiratory tract infection, chronic cough in 4%, 88%, 16% and 32%, respectively (Table 1).

pH monitoring

Analysis of the GER parameters in the patient group revealed that the number of reflux episodes were more common during prone position compared to that during supine in both proximal (101.6 ± 55.8 /patient vs. 34.9 ± 23.2 /patient, $P = 0.09$) and distal (208.3 ± 143.9 /patient vs. 48.8 ± 44.8 /patient, $P = 0.00$) esophagus. This difference was not statistically significant except for total number of reflux episodes in distal esophagus. However, in the proximal esophagus, all other parameters like number of reflux lasting longer than 5 min, reflux index (RI) and longest episode of reflux were higher when supine (1.8 ± 1.2 /patient, 5.8 ± 5.6 /patient, 6.2 ± 7.6 /patient, respectively). Contrarily, number of reflux episodes lasting longer

Table 1 Distribution of gastroesophageal reflux related symptoms among children with asthma-like airway diseases.

Symptom	Present		Absent		Total
	<i>n</i>	%	<i>n</i>	%	
Vomiting	1	4	24	96	25
Wheezing	22	88	3	13	25
Recurrent LRTI*	4	16	21	84	25
Chronic cough	23	32	2	8	25

*LRTI, lower respiratory tract infection.

Table 2 Comparison of GER parameters of the distal esophagus between patient and control groups.

Parameter	Control group	Patient group	P*
# of reflux episodes	94.4 ± 68.1	248.9 ± 203.4	0.00
# of reflux episodes > 5 min	1.6 ± 1.6	5.4 ± 4.3	0.08
Reflux index	3.9 ± 2.9	13.3 ± 13.1	0.01
Longest episode of reflux	7.0 ± 4.6	18.3 ± 13.8	0.02

*P value was accepted as significant less than 0.05.

Table 3 Analysis of the response to treatment in children with asthma-like airway disease according to the symptom score, bronchodilator and steroid requirement and duration of hospitalization (Mean ± sd).

Parameter	Before treatment	After treatment	P*
Number of symptoms	2.3 ± 0.6	0.4 ± 0.6	0.00
Bronchodilator use*	8.3 ± 6.8	1.4 ± 3.4	0.00
Systemic steroid use (day/patient)	5.3 ± 5.4	0.4 ± 1.2	0.00
Asthma attack (number/patient)	1.5 ± 1.1	0.3 ± 0.6	0.00
Hospitalization (day/patient)	9.1 ± 7.7	0.5 ± 2.2	0.00

*P value was accepted as significant less than 0.05.

than 5 min and RI in distal esophagus were higher when prone (2.6 ± 2.1 /patient, 16.2 ± 9.4 /patient, respectively). Longest episode of reflux in distal esophagus occurred when supine (16.1 ± 9.6 /patient).

Comparison of the distal esophageal parameters among control and patient groups revealed that total RI, total number of reflux episodes and longest duration of reflux were significantly higher in the patient group; number of reflux episodes lasting longer than 5 min was also higher in the patient group, though statistically insignificant (Table 2).

Asthmatic medication

Symptoms, days of bronchodilator and/or steroid requirement and number of asthma exacerbations as well as in-hospital days per patient decreased with acid suppressor treatment. The decrease in all these parameters were highly significant ($P = 0.00$) (Table 3).

Discussion

GER which is the passive regurgitation of gastric contents retrograde into the esophagus is termed as pathological GERD when it results in poor weight gain, signs of esophagitis, persistent respiratory

symptoms and neurobehavioral changes.^{4,5} Respiratory symptoms associated with GERD mainly include cough, dyspnea and wheezing.²³ Association of GERD and respiratory symptoms, especially asthma, is complex and multifactorial. Asthma includes variable airflow obstruction that changes over a short period of time associated with demonstration of respiratory mucosal eosinophilic inflammation in diagnosis. Therefore, 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-like airway disease in this study.²⁶

Smaller group of asthmatic children have been reported to be nonatopic. There is evidence that some differences in airway inflammatory mechanisms exist between atopic and nonatopic asthmatic children. Exposure to environmental allergens is not the major contributing factor in appearance of symptoms in nonatopic asthmatics. These children experience exacerbations of disease more commonly in response to viral infections, environmental irritants and endogenous risk factors such as GER, etc. and nonatopic asthma seems to have a better prognosis.^{3,26} It is reported that frequency of GERD in asthmatic children ranges between 59–75%.^{10,11,27} However, considering that over 90% of childhood asthma is atopic in whom exacerbations are provoked by allergen exposure, this frequency might be higher in the small group with

nonatopic asthma which does not have a risk factor as obvious as allergen sensitization.³

In this study, frequency of GERD was 76% in our group of asthmatic nonatopic children who have no other provocative factor for airway hyperreactivity. GERD was defined as total distal RI > 4 in distal esophagus determined by the most suitable diagnostic tool for GERD, that is the 24 h pH monitoring with a sensitivity and specificity above 90%.^{5,7,8} This was significantly higher than that in the control group (48%, $P = 0.04$). This is an expected phenomenon when the results of previous studies indicating the coexistence of asthma and GERD are considered. Therefore, GER may be one of the contributing factors to exacerbations in nonatopic asthma. The diagnosis of GER depended on the results of 24 h pH monitoring, therefore nonacid reflux could not be determined; however, the most sensitive and specific diagnostic modality for GER is still pH monitoring and previous literature had also focused on the effects of acid reflux. Moreover, treatment with PPIs would not lead to improvement of symptoms associated with non-acid reflux, therefore it was not taken into consideration of this study.

Despite determination of this association, most of the time, it cannot be determined if asthma-like findings are consequences of GERD or vice versa. Vagal reflex mechanism which increases airway resistance in response to the increase in esophageal acidity, neural enhancement of bronchial reactivity and microaspirations leading to epithelial damage are accused in the pathophysiology of esophageal acid induced bronchoconstriction.^{4,5,17,28,29}

Higher frequency of GERD in nonatopic patients with asthma-like airway disease with recurrent exacerbations despite adequate anti-asthmatic treatment suggests the role of this pathology in the development of bronchoconstriction. However, some authors have proposed that this phenomenon depends on the high frequency of respiratory symptoms and reflux by themselves.³⁰ To avoid misleading results, not only frequency of GERD but also response of asthma severity to anti-reflux treatment was evaluated in this study. In our patient group, significant reduction in respiratory symptoms, bronchodilator and steroid requirement, number of asthmatic attacks and need for hospitalization after acid suppressor treatment contributes to the theory that GERD induces bronchoconstriction. A control group that did not receive treatment was not included in this study due to ethical concerns. Therefore, placebo effect should be considered due to lack of the control group and due to the waxing and waning clinical progress of asthma. However, the expected im-

provement in asthma symptoms in a placebo group in clinical trials has been reported to be lower than 30% in childhood. Thus, the significant improvement in our study cannot be attributed to the placebo effect.³¹

Similar results were obtained in a previous study which reported a significant reduction in the requirement of anti-asthmatic medications in children with persistent symptoms.²⁷ This is also supported by the reduction of chronic symptoms and requirement of anti-asthmatic treatment after effective control of GER in another study.³² However, there is still debate about the issue and there is literature denying an improvement in lung function and asthma symptoms with anti-reflux treatment.³⁰ Results of our study indicate that sufficient control of GERD lead to a significant decrease in severity of asthma-like airway disease in nonatopic patients. Opposite results reported by some previous studies may be attributed to inefficient control of GERD as well as other pathological conditions lying under the respiratory symptoms in patients.^{33,34} Moreover, time of the year during which pre- and post-treatment severity of disease was evaluated may lead to a bias if not standardized. In this study, pre-treatment severity was assessed according to the patient records of the previous year during the same months as post-treatment to avoid seasonal variation caused by air pollution, crowding and increased frequency of viral infections.

Moreover, distribution of symptoms among our patients emphasizes an important point in that, gastrointestinal complaints may be absent in these nonatopic patients with an asthma-like respiratory disease. Vomiting which was present in 4% of the patients was the only gastrointestinal complaint reported. This, as reported by previous studies necessitates a high index of suspicion for GERD in nonatopic patients with an asthma-like airway disease even in the absence of gastrointestinal symptoms.⁸ Therefore, asthma-like respiratory disease as the only presentation of GERD makes this pathology a topic of pediatric respiratory diseases along with gastroenterology.

In conclusion, GERD is an important factor in development of asthma-like respiratory disease in nonatopic children and should be suspected especially in patients with exacerbations of asthma despite adequate conventional asthma treatment because relief of this disorder contributes significantly to the control of the respiratory symptoms. Thus, we suggest that in this subgroup of patients with asthma-like respiratory disease lansoprazole may be tried initially.

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