

Gastroesophageal reflux and asthma in childhood: a study on their relationship using esophageal PH monitoring

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Abstract

Objectives: This study aims at verifying the prevalence of gastroesophageal reflux in asthmatic children, and at determining the sensitivity and specificity of the reflux index for the diagnosis of gastroesophageal reflux disease.

Methods: Sixty-nine children, aged 1-5 years, with asthma, were studied by 24-hour pH monitoring. The patients were randomly selected.

Results: Ages varied from 12.4 to 63.1 months, mean age = 30.79 months, and 62.3% were males. Gastroesophageal reflux was observed in 68.1% of the children. The patients were divided into two groups, moderate and severe asthma, and gastroesophageal reflux was diagnosed in 58.5 and 82.1% of the cases, respectively. Occult gastroesophageal reflux occurred in 31.8% of the cases. The reflux index showed a sensitivity of 89.4%, specificity of 95.5%, positive predictive value of 97.7% and negative predictive value of 80.8%.

Conclusions: The results of this study indicate a relationship between gastroesophageal reflux and asthma, and suggest that the reflux index as a single parameter of pH monitoring has good sensitivity and specificity for the diagnosis of gastroesophageal reflux disease.

J Pediatr (Rio J). 2007;83(6):535-540: Asthma, gastroesophageal reflux, child, pH monitoring.

Introduction

Gastroesophageal reflux (GER) may be manifested by respiratory symptoms alone (occult GER), such as chronic coughing,¹ aspiration pneumonia, asthma, laryngeal spasm, apnea, laryngeal stridor, pulmonary dysplasia and cyanotic crises.² Nocturnal wheezing or coughing, with inadequate response to medical treatment for asthma, negative family history of atopia and early onset of bronchial hyperreactivity characterize patients who should be studied for GER. Wheezing can be

the only manifestation of reflux in some children, indicating occult GER.²

Asthma is a chronic inflammatory pulmonary disease primarily characterized by airway obstruction, which might be resolved spontaneously or by treatment.³ Asthma is a complex condition comprising genetic, infectious, endocrinologic, psychological and immunologic factors at variable levels. Exposure to environmental allergens is one of the most

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Fundação de Amparo à Pesquisa de Minas Gerais supplied the equipment used in the study.

This article originated from a Masters' thesis.

No conflicts of interest declared concerning the publication of this article.

Suggested citation: Teixeira BC, Norton RC, Penna FJ, Camargos PA, Lasmar LM, Macedo AV. Gastroesophageal reflux and asthma in childhood: a study on their relationship using esophageal PH monitoring. *J Pediatr (Rio J)*. 2007;83(6):535-540.

Manuscript received Jan 31 2007, accepted for publication Sep 19 2007.

doi 10.2223/JPED.1736

important risk factors for triggering asthma in individuals with a predisposition for the disease and is considered a causal factor.³

The relationship between GER and asthma was firstly described in the 19th century, by William Osler: "attacks may be due to direct irritation of the bronchial mucosa or (...) indirectly, too, by reflex influences from stomach (...)"⁴ It is known that GER is more often observed in asthmatic patients than in the general population.⁵

GER may cause chronic respiratory disease by two mechanisms: vagal response and tracheal aspiration of gastric contents.⁶

Distal esophageal acidification leads to reactive bronchial obstruction, by means of vagal innervation sensitive to the acid present in the esophagus, and this is the main mechanism by which wheezing is triggered in patients with GER.^{7,8} In the embryogenesis of the esophagus and bronchial tree, there is a common innervation to both structures. Some studies have demonstrated that instillation of acid in the distal esophagus triggers bronchial obstruction and that this reflex mechanism is abolished by atropine.⁹ Patients with atopic symptoms present vagal hyperreactivity, leading to further reactive bronchial obstruction due to presence of acid in the distal esophagus.

Aspiration of gastric contents change pulmonary resistance and cause reactive airway obstruction.¹⁰

On the other hand, asthmatic patients present reduced lower esophageal sphincter (LES) pressure and take longer to perform esophageal clearance.⁶ More frequent reflux episodes are observed during respiratory physiotherapy. Presence of thoracic deformities also favors GER.

Mishra et al.¹¹ showed that exposure to inhaled allergens induces onset of esophagitis, which is determined by presence of eosinophils in the esophagus. The same was not observed when exposure to allergens occurred through oral or intragastric routes. Therefore, it might be concluded that hypersensitivity of the esophagus occurs simultaneously with pulmonary inflammation.

PH monitoring registers esophageal acidification, for a long period, while the patient indulges in his daily activities.¹² Respiratory symptoms were predominant among the indications for esophageal pH monitoring in children.^{13,14} Sensitivity of this exam ranges from 87 to 93.3%, and its specificity from 92.9 to 97%. Bauman et al.¹⁵ found positive predictive value of over 90% and negative predictive value of less than 50%.

This study aims at verifying prevalence of GER in asthmatic children, as well as determining the relationship between prevalence of GER and asthma severity using esophageal pH monitoring. It also intends to evaluate sensitivity and specificity of the reflux index as a single parameter of esophageal pH monitoring for the diagnosis of GER.

Methods

Study design, setting and population studied

This is a cross-sectional study involving asthmatic children, seen at the Pediatric Pulmonology Outpatient Clinic, Teaching Hospital, Universidade Federal de Minas Gerais and at the Pediatric Pulmonology Outpatient Clinic, Campos Salles Healthcare Clinic of the Municipal Health Authority of Belo Horizonte, Brazil.

Esophageal pH monitoring was performed by the researchers in children who met the inclusion criteria for this study. Children were admitted to hospital for 24 hours, in a specific bed for this examination, accompanied by a guardian, and were kept under medical and nursing supervision.

Inclusion criteria

To be included in the study, the child must meet the following criteria:

- age group - 1 to 5 completed years;
- symptoms compatible with daily manifestations of asthma before initiating preventive treatment;
- presence of asthma symptoms at night, once a week or more often;
- two admissions to hospital due to wheezing in the past 6 months, or two monthly episodes that improved with bronchodilators and/or steroids;
- use of inhaled steroids for prevention;
- positive family history of atopia and/or bronchial asthma;
- chest X-ray with signs suggesting asthma (hyperinflation) and ruling out other diseases that mimic asthma, such as cardiopulmonary malformations, other chronic lung diseases, etc.;
- diagnosis performed for more than 6 months.

Exclusion criteria

Children with acute exacerbation of asthma were not submitted to tests.

Statistical aspects

Sample size and sampling plan.

It is estimated that, in average, 4,000 patients are seen every year at the Pediatric Pulmonology Outpatient Clinic, Teaching Hospital, Universidade Federal de Minas Gerais and at the Campos Salles Healthcare Clinic; of these, asthmatic children account for 75% of the cases. Approximately 8% of these patients (240 children) met the inclusion criteria mentioned above. Considering a prevalence of GER of 50% in asthmatic patients and an α error of 5%, a sample size of 69 children was calculated for this study. The patients were randomly selected, part of them from the Pediatric Pulmonology Outpatient Clinic, Teaching Hospital, Universidade de Minas

Gerais, and part from Campos Salles Healthcare Clinic. Selection was based on a random table produced by the Epi-Info software version 6.04D.

During the study, it was necessary to recruit a new group of patients because of dropouts: children who did not attend the exams to which they had been referred and patients whose tests were interrupted due to acute wheezing episodes or accidental removal of the pH monitoring probe. A new selection of 16 patients was randomly made using Epi-Info 6.04D, according to the same inclusion criteria, and the patients were referred to the Pediatric Pulmonology Outpatient Clinic, Teaching Hospital, Universidade Federal de Minas Gerais.

Statistical tests

Statistical analysis consisted in calculating prevalence of GER in the whole population studied, considering a confidence interval (CI) of 95%, and, also, separately, in each of the groups with moderate or severe asthma. Chi-square analysis with Yates correction was used to check whether this difference was statistically significant or not. Frequency distributions were also calculated for variables in the protocol.

Considering the DeMeester index as the gold standard parameter for the diagnosis of GER, the sensitivity, specificity, negative and positive predictive values of the reflux index were calculated.

Study protocol

The asthmatic children were selected based on the inclusion criteria, and, then, divided into two groups: those with moderate asthma or those with severe asthma. This classification was based on the frequency of night symptoms:

- moderate asthma: presence of night symptoms one to three times a week;
- severe asthma: presence of night symptoms more than three times a week.

For esophageal pH monitoring, the protocol determined by the ESPGAN¹⁶ was followed.

The DeMeester score was used to define pathological GER.¹⁷ The following items have to be considered when calculating the DeMeester index: number of reflux episodes in 24 hours, number of reflux episodes greater than 5 minutes in 24 hours, duration of the longest reflux episode and reflux index. The duration of the longest reflux episode is important, since this parameter is related to esophageal clearance.

A reflux episode occurs when esophageal pH drops below a certain cutoff point (pH 4) for at least 15 seconds, and it ends when pH achieves a value above that cutoff point. If pH drops again below the cutoff point within 15 seconds, it is not considered a new episode, but a continuation of the previous one.¹⁶

The reflux index is obtained by dividing the total registered time during which esophageal pH persisted below 4 by

the total registered period (in minutes). The result is expressed as the percentage of time elapsed with pH below 4. The reflux index is considered abnormal if it is over 5%, in patients more than 1 year old, or over 10%, in those below this age.

Some medications were discontinued to perform pH monitoring: prokinetics, 48 hours before; antihistamines, 72 hours before; and proton pump inhibitors, 1 week before. Tests were postponed in children with acute manifestations of bronchial obstruction.

Tests were carried out by the researchers using one type of esophageal pH monitoring equipment: Flexilog, by Oakfield Instruments, model 2020. Esophageal pH monitoring was performed with one or two-channel antimony electrodes, with an external reference electrode, and calibrated, before and after each test, in standardized solutions.

Calculation of the correct position of the pH monitoring probe was made by two methods: first, by Strobel's formula, and later, by chest X-ray (in order to check position).

A local anesthetic was applied to one of the nostrils to introduce the probe. The test was then performed after checking its correct position.

Nutritional status was determined by height for age and weight for age z scores.

After written and/or oral explanation of the test, the guardians of the children participating in the study filled in and signed a consent form. This study was approved by the Department of Pediatrics and the Research Ethics Committee of Universidade Federal de Minas Gerais and by the managers of Campos Salles Healthcare Clinic.

Results

Sixty-nine pH monitoring tests were performed in the asthmatic children selected for the study. Eighteen children were referred from Campos Salles Healthcare Clinic and the remainder from the Pediatric Pulmonology Outpatient Clinic, Teaching Hospital, Universidade Federal de Minas Gerais.

There were 16 dropouts during the study: six children did not attend the tests; two were excluded for presenting wheezing during pH monitoring; and eight did not conclude the test due to accidental removal of the probe.

The main aspects of the children studied are specified in Table 1.

Forty-one children (59.4%) had moderate asthma and 28 (40.6%) had severe asthma.

GER was observed in 47 of the asthmatic children by pH monitoring (68.1%; CI95% 55.1-79.1). When patients were distributed into two categories – those with moderate and those with severe asthma – GER was diagnosed in 24 (58.5%) and in 23 (82.1%) children, respectively. This difference was

Table 1 - Main features of the population studied

Males	62.3%
Age variation	12.4 to 63.1 months
Mean age	30.79 months
Standard deviation	14.59 months
Median	28.11 months
Nutritional status	2 children (2.9%) presented severe chronic malnutrition
Moderate asthma	41 children (59.4%)
Severe asthma	28 children (40.6%)
Age at onset of respiratory symptoms	1 to 30 months
Median	4 months

not statistically significant according to the chi-square analysis with Yates correction ($p = 0.071$).

There were no respiratory symptoms during pH monitoring.

GER symptoms were observed in 36 (52.2%) patients: vomiting (40%), regurgitations (30%), irritability (14%),

sleep disorder (12%), heartburn (5%), dysphagia (5%), failure to thrive (3%) and hematemesis (2%). GER symptoms were predominant after meals in 20 (57%) children, in the supine position in 26 (72%), and associated with $\text{pH} < 4$ in 24 (67%) children.

Occult GER (with no gastrointestinal symptoms or positive history) was observed in 31.8% of the subjects.

The reflux index was the most sensitive single esophageal pH monitoring parameter for the diagnosis of GER in the patients studied. It demonstrated sensitivity of 89.4% (CI95% 76.1-99.6), specificity of 95.5% (CI95% 75.1-99.8), positive predictive value of 97.7% (CI95% 86.2-99.9), and negative predictive value of 80.8% (CI95% 60.0-92.7%).

Discussion

From 1966 to 2000, 222 articles were published addressing GER associated with bronchial asthma; of these, 44 were pediatric studies initiated as of 1971. These studies have shown prevalence of GER in children with bronchial asthma ranging from 50 to 75.5%, by using 24-hour pH monitoring (Table 2).

Prevalence of GER in this study was similar to that found in the literature. Sheikh et al.²¹ studied GER in younger children (< 1 year old), in whom bronchial obstruction may occur due to other causes apart from bronchial asthma. Gustafsson¹⁸ and Tucci¹⁹ studied small populations. In neither of these studies were the children submitted to random selection or rigid exclusion criteria. Moreover, in both studies they were submitted to pH monitoring during acute asthma crisis, which may compromise results. In our study, acute respiratory symptoms were exclusion criteria.

Wheezing or cough episodes reduce LES competence and increase thoracic negative pressure, thus allowing reflux to occur.⁷ The risk of GER is higher in patients who have suffered

Table 2 - Relationship between gastroesophageal reflux and bronchial asthma in children as determined by 24 hour pH monitoring

Author	% relationship between GER and asthma	Population studied
Gustafsson ¹⁸	50%	42 children aged 9-20 years with moderate and severe asthma
Tucci ¹⁹	75.5%	36 children aged 18-178 months with non-controlled asthma
Balson ²⁰	73.4%	79 children aged 2-17 years with asthma
Sheikh ²¹	64%	84 children, mean age of 8.74 months, with daily wheezing

GER = gastroesophageal reflux.

from asthma for longer periods and in those in use of theophyllines. Use of bronchodilators reduces LES pressure,⁵ resulting in GER.

Taking into account the separation between moderate and severe asthma, GER was observed in 58.5 and 82.1% of the children, respectively. This difference was not statistically significant, but it suggests some relationship between GER and frequency of night respiratory symptoms.

The "frequency of night asthma symptoms" criterion was used to separate groups, since there are more episodes of reflux leading to respiratory symptoms at night (in decubitus). During sleep, LES pressure decreases and cough and salivation reflexes are reduced. Al-Assom et al. found that the probability of having GER in an asthmatic patient is nearly eight times higher if he/she has nocturnal respiratory symptoms.⁷

The data obtained in this study confirm the literature because more reflux episodes occurred when patients were lying down. According to Vandenplas & Hauser,¹² most reflux episodes occur during the postprandial period, at night and in the supine position.

Every child in this study had positive family history of atopic diseases. Pastorino et al.²² found a positive family history of atopia in 61.6% of the asthmatic children studied. Positive family history of atopia is an important piece of information for the clinical diagnosis of asthma, particularly in children with wheezing in the first 2 years of life.

GER symptoms were demonstrated in 52.2% of the children, and the most common were regurgitations and vomiting. In this study, it was observed that 31.8% of the patients did not present GER symptoms but had altered pH monitoring. Gonzales et al.²³ showed that 30% of patients with reflux and asthma had no symptoms of GER. Sheik et al.²¹ showed that 44% of asthmatic patients had silent GER.

Glass electrodes are more accurate, more expensive and have a longer half-life than antimony electrodes;²⁴ however, time to respond to pH changes is adequate in both electrodes. It is preferable to use an internal rather than an external reference because the difference of potential between skin and mucosa induces a 0.3-0.6 pH unit error. In pediatric studies, the external reference is used with no harm to test result.¹⁶

The pH monitoring probe may have more than one channel (electrode), placed at different points in the esophagus. Arana et al.²⁵ concluded that pH monitoring with simultaneous distal and proximal evaluation is not advantageous to the diagnosis of GER, not even in patients with respiratory symptoms and suspicion of microaspiration.

Johnson & DeMeester described for the first time the parameters of pH monitoring and established a score system, producing the well-known DeMeester score, used for diagnosing GER. This index presents some limitations, such

as cutoff point value (pH4). Small pH variations (0,2-0,4) above four are not detected as reflux episodes.

In this study, reflux index was the most sensitive and specific single parameter for the diagnosis of GER in asthmatic children.

The ESPGAN¹⁶ has found that the reflux index and the number of reflux episodes that last over 5 minutes are little affected by equipment. However, the number of reflux episodes and the duration of the longest episode seem to depend on technical factors.

The reflux index is the simplest isolated parameter for differentiating physiological from pathological GER, having sensitivity of 94%.²⁶ Vincent et al.²⁷ concluded that the reflux index is the most useful single parameter for diagnosing GER in patients with respiratory symptoms.

The results obtained in this study indicate a relationship between GER and asthma in children aged 1-5 years. Therefore, esophageal pH monitoring is an important complementary diagnostic method in difficult-to-control patients.

Nasopharyngeal pH monitoring is another method for determining the relationship between GER and chronic respiratory disease.²⁸

Unfortunately pH monitoring only identifies acid reflux. Bioelectrical impedance might be a complementary method for diagnosing GER disease.^{29,30} Mattioli et al.²⁹ observed that, in children with typical and atypical GER respiratory symptoms, the incidence of reflux detected through esophageal bioelectrical impedance was twice as high as the incidence detected through esophageal pH monitoring.

Based on these observations, further studies on the treatment of GER in these children are required to determine whether control of the reflux episodes improves the respiratory symptoms of asthma and vice-versa.

Acknowledgments

The authors wish to thank the staff of the Pediatric Pulmonology Outpatient Clinic of Hospital das Clínicas - Universidade Federal de Minas Gerais and of Campos Salles Healthcare Clinic for their assistance. This study was supported by grants from Fundação de Amparo à Pesquisa do Estado de Minas Gerais.

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