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ORIGINAL ARTICLE

Nocturnal Reflux in Children and Adolescents with Persistent Asthma and Gastroesophageal Reflux

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Background. A higher frequency of nocturnal gastroesophageal reflux (GER) in adult patients with respiratory symptoms has been demonstrated. The aim of this study was to determine the prevalence of nocturnal GER by using prolonged intraesophageal pH monitoring and compare it with spirometry results in children with persistent asthma. **Methods.** Thirty-eight patients with persistent asthma for at least 2 years were studied. Gastrointestinal symptoms suggestive of GER were considered as regurgitation, heartburn, and abdominal pain. All patients underwent prolonged intraesophageal pH study and spirometry. GER was considered positive when a reflux index (RI) was higher than 5%. Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁), forced mid-expiratory flow rate (FEF_{25–75%}), and FEV₁/FVC ratio were measured. **Results.** Median age was 10 years of age (range 5 to 15) and 58% were male; GER prevalence was 47.3%. Median (range) of reflux index during supine and upright periods from GER patients were, respectively, 8.7% (3.2 to 23.6) and 10.5% (5.2 to 15.0) ($p = 0.913$), and only FEF_{25–75%} was below the predicted value: 54.5% (39.4 to 96.9). Reflux index was not significantly correlated with FVC, FEV₁ and FEF_{25–75%}. **Conclusions.** A high prevalence of GER was found in children and adolescents with persistent asthma, equally distributed in the supine (nocturnal) and upright positions. There was no correlation with pulmonary function test.

Keywords asthma, gastroesophageal reflux, spirometry, esophageal pH monitoring, child, adolescent

INTRODUCTION

Gastroesophageal reflux disease (GERD) and asthma are common diseases in childhood. Recently, it has been proposed that their association might be more than a casual occurrence. The causal relationship is still unclear, although two pathophysiological mechanisms have been proposed to explain esophageal acid-induced bronchoconstriction: the “reflex” (esophageal-bronchial vagal reflex) and “reflux” (microaspiration of acid contents into the airways) theories (1).

Prevalence of gastroesophageal reflux (GER) among asthmatic adults has ranged from 32% to 80% (2) and 50% to 75% in asthmatic children (3–7). In adult patients with “difficult-to-control” asthma, GER seemed to be the most likely exacerbating factor; however, treatment of GERD does not seem to improve asthma control (8) or pulmonary function (9).

GER has been addressed as one of the mechanisms of nocturnal asthma, which is characterized by an exaggeration in the normal variation of lung function circadian rhythm and is associated with increased morbidity and inadequate asthma control; however, there is a lack of evidence showing improvement in nocturnal asthma after GERD improvement (10).

Nocturnal GER seems to be more frequent in patients with respiratory symptoms, asthma, and obstructive sleep apnea syndrome (11, 12). Yet, the real role of nocturnal reflux as an exacerbating factor for asthma onset is controversial (13), and studies regarding nocturnal GER in children and adolescents with asthma are sparse. Therefore, this study intended to evaluate the prevalence of GER during upright and supine (nocturnal) periods in children and adolescents with persistent asthma through prolonged intraesophageal pH monitoring and compare GER symptoms and pulmonary function tests in children with and without GER.

PATIENTS AND METHODS

This study was approved by the Ethical Committee of Hospital de Clinicas de Porto Alegre. Informed and written consent was obtained from the patients and caretakers.

This was a cross-sectional study and patients were consecutively enrolled from two tertiary-care outpatient clinics specialized in Pediatric Respiratory Disease in Porto Alegre, Brazil. All patients were often reviewed on a regular basis as part of their long-term follow-up.

Inclusion criteria were (a) children and adolescents between 5 and 18 years of age, set as a minimum age with ability to perform spirometry (14); (b) patients were on a asthma treatment for at least 2 years before the study (7); (c) requirement of a combination of short- and long-acting bronchodilators and inhaled corticosteroids or leukotriene modifiers for the management of asthma for at least 30 days

This work was performed at the Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul (Porto Alegre, RS, Brazil).

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before the enrollment in the study; and (d) no use of medications to control gastric acidity in the past (antacids, H₂-blockers, proton-pump inhibitors). The diagnosis and classification of asthma severity were established according to the Guidelines for the Diagnosis and Management of Asthma, National Institute of Health (15). Exclusion criteria were the presence of other chronic respiratory diseases, cardiac diseases, or neurological diseases.

All parents and patients answered a questionnaire to identify demographic data, asthma symptoms, and presence of gastrointestinal symptoms suggestive of GER, such as heartburn, regurgitation, and abdominal pain (16). All patients underwent prolonged intraesophageal pH monitoring, and they were further separated in two groups (with and without GER).

Prolonged intraesophageal pH monitoring

Digitrapper MK III equipment and software Polygram for Windows 2.03 version (Synetics Medical, Sweden) were utilized. After an overnight fast, a one-channel antimony pH probe with an external Ag/AgCl reference electrode was positioned in the distal esophagus. Placement of pH sensor between the eighth and tenth thoracic vertebrae was verified with a plain chest radiograph. All asthma medications were maintained uninterrupted. Patients and caretakers were asked to fulfill a diary regarding meal times, sleep times and occurrence of symptoms, such as cough, wheezing, dyspnea, heartburn, regurgitation, and abdominal pain.

The parameters analyzed were the number of episodes of acid reflux; percentage of time pH under 4 in relation to total period of the study (total reflux index), in relation to bedtime (supine reflux index) and to upright position during the day (upright reflux index); number of reflux episodes lasting more than 5 minutes; and duration of the longest reflux episode. Presence of GER was defined when total reflux index was greater than 5% (7, 16).

Pulmonary function test

It was assessed by a forced spirometry (Jaegar Flow Pro, Erich Jaeger GmbH, Germany) in the morning before

the pH study, following a 12-hour washout period of sympathomimetic and anticholinergic medications. Parameters considered for analysis were forced vital capacity (FVC), forced expiratory volume in one second (FEV₁), forced mid-expiratory flow rate (FEF_{25–75%}), and FEV₁/FVC ratio. American Thoracic Society American Thoracic Society standardization of spirometry and acceptability criteria was applied (17, 18).

Statistical analysis

Demographic data are presented as median and 25% to 75% quartiles or absolute values. Mann-Whitney U test, Fisher's exact test, and Spearman's rho sum of ranks were used to compare frequencies of GER, clinical outcomes, and spirometry results between groups with and without GER. Data were analyzed using software Statistic Package for Social Sciences for Windows version 10.0 (SPSS Inc, USA). Statistically significant values were considered when $p < 0.05$.

RESULTS

Thirty-eight patients were enrolled in the study. The prevalence of GER among the asthma patients was 47.3%. Table 1 shows the baseline characteristics of both groups. The groups were similar in age and gender. Asthma features, such as symptom onset before 1 year of age, symptoms lasting longer than 7 days per month, emergency room visits, exercise-induced symptoms, passive smoking, and dose of inhaled steroids were similar in either groups.

Nine patients (50%) of GER group had asymptomatic GER. There was no significant difference in the presence of gastrointestinal symptoms between groups with or without GER. Additionally, they had not reported respiratory symptoms or gastrointestinal symptoms during the pH monitoring in either groups.

Results of spirometry did not show significant differences between either groups for FVC ($p = 0.273$), FEV₁ ($p = 0.640$), and FEV₁/FVC ratio ($p = 0.501$) and they were within the predicted values.

TABLE 1.—Baseline characteristics of asthma patients with and without GER.

Variables	With GER (n = 18)	Without GER (n = 20)	p value
Age, yr [†] (range)	9.5 (7–11)	10.0 (8–12)	0.708*
Male: Female (proportion)	10:8	12:8	0.520 [‡]
<i>Frequency of asthma features</i>			
Symptom onset before 1 year of age	12 (67%)	12 (60%)	0.745 [‡]
Symptoms lasting > 7 days/month	7 (39%)	12 (60%)	0.475 [‡]
Emergency room visits over last 12 months	4 (22%)	7 (35%)	0.485 [‡]
Exercise-induced symptoms	5 (28%)	6 (30%)	0.999 [‡]
Passive smoking	2 (11%)	1 (5%)	0.595 [‡]
Current dose of inhaled steroids (μg) [‡]	400 (200–500)	400 (300–500)	0.775 [‡]
Gastrointestinal symptoms [§]	9 (50%)	8 (40%)	0.913 [‡]
<i>Spirometry results as percent of predicted pre-BD treatment</i>			
FVC [‡]	84.1% (70.3–98.9)	89.0% (79.9–94.6)	0.273*
FEV ₁ [‡]	84.0% (65.7–99.1)	80.1% (71.5–87.6)	0.640*
FEF _{25–75%} [‡]	54.5% (39.4–96.9)	47.1% (35.8–84.4)	0.804*
FEV ₁ /FVC ratio [‡]	83.1 (71.3–91.9)	78.1 (69.7–88.3)	0.501*

FVC = forced vital capacity; FEV₁ = forced expiratory volume in 1 second; FEF_{25–75} = forced mid-expiratory flow.

*Mann-Whitney U test, [‡]Fisher's exact test.

[§]Vomiting; heartburn; abdominal pain.

[‡]Data presented as median (25–75% quartiles).

TABLE 2.—Results of esophageal pH monitoring analysis with positive GER.

Variables	Supine GER (n = 18)	Upright GER (n = 18)	<i>p</i> value*
Duration of study (min)	527 (476–589)	742 (653–793)	
Reflux index (%)	8.7 (3.2–23.6)	10.5 (5.2–15.0)	0.913
No. of episodes of reflux	21 (16.0–30.5)	48 (29.5–80.5)	0.002
No. of episodes lasting > 5'	2 (0.5–3.5)	2 (1.5–6.0)	0.107
Longest episode of reflux (min)	19 (3.5–47.5)	15 (7.5–25.0)	0.332

Data presented as median (25–75% quartiles).

*Wilcoxon Signed Ranks Test.

The FEF_{25–75%} values were reduced in both groups without significant difference ($p = 0.804$). There was no significant correlation between FVC ($\rho = -0.081$; $p = 0.627$), FEV₁ ($\rho = -0.031$; $p = 0.851$), FEF_{25–75%} ($\rho = -0.014$; $p = 0.936$) values and reflux index of all patients of the study.

Patients with GER had a median (25–75% quartiles) reflux index of 9.0% (5.7–18.9) and those without GER had 2.5% (1.4–3.7) ($p < 0.001$). Table 2 shows the results of pH monitoring during bedtime and daytime from patients with positive GER pH study. There was no significant difference between reflux index of patients with GER during supine and upright position.

DISCUSSION

This study demonstrated a high prevalence of GER in children and adolescents with persistent asthma; however, without a predominance of either supine (nocturnal) or upright position GER pattern. Moreover, no correlation was found between results of prolonged pH monitoring and spirometry. These data are different from other few studies that evaluated nocturnal GER in a subset of children and adolescents with asthma (19, 20).

Although controversial, nocturnal GER has been referred to as a trigger for asthma onset in adults with asthma (21). It has also been related to a longer period of esophagus acidification (22) and increased intrathoracic pressure leading to reflux episodes and subsequent respiratory symptoms (11). In this study, although reflux index was not different during upright and supine period, the number of reflux episodes was higher during upright compared to supine period. Episodes of GER that were predominantly short and that had a daytime occurrence were found in pediatric patients with asthma (6).

In comparison with other studies that found 50% to 75% prevalence of GER in children (3–7), this study showed a lower prevalence (47.5%), which could be explained by differences in inclusion criteria considering the assessment of severity of asthma, since patients were enrolled according to the presence of persistent asthma regardless its stratification as mild, moderate, or severe.

In this study, the prevalence of gastrointestinal symptoms was similar in patients with and without GER. Symptoms such as abdominal pain, heartburn, and regurgitation were found in 50%. Other studies found absence of gastrointestinal symptoms in 44% of wheezing babies (23) and in 63% of children with chronic respiratory symptoms (24). Similar results were reported in asthmatic adults since symptoms of GER could be absent in as many patients as 25% to 62% (25). Although abdominal pain is not considered a typical

symptom of GER, it was taken into account due to the inability of 5-year-old children to complain of heartburn (26). Therefore, pH monitoring was justified by the lack of a reliable score for clinical diagnosis of GER in children. The initial age of 5 years for enrollment in this study was defined considering the minimum age children could perform reproducible spirometry (14).

This study found similar spirometric results among patients with and without GER and no correlation between severity of reflux and pulmonary function tests. Others studied the relationship between GER and pulmonary function tests considering a bronchoconstriction response (27) and decreased expiratory peak flow after intraesophageal acid challenge in asthmatic adults (28).

Asthmatic children with good asthma control did not seem to have a spirometry improvement after a 12-week treatment with omeprazol (16). Likewise, all patients from our study had spirometric results close to predicted values for FVC and FEV₁. The lack of differences in the spirometric results between patients with and without GER from this study might be a consequence of an adequate pharmacological management of asthma. Improved FEV₁ values were obtained in asthmatic adults after an 8-week treatment with omeprazol; however, that was a heterogeneous group of patients with asthma (29). Gibson et al. have concluded in their meta-analysis that subgroups of asthmatic patients with GER may have benefit from GER treatment; however there was no overall improvement in asthma (30).

The possible role of non-acid reflux has been suspected because only 51% of adult asthmatic patients who presented classical GER symptoms were found to have GERD during the pH monitoring (2). Conversely, a high prevalence of GER diagnosed by pH monitoring (62%) in adult asthmatic patients without GER symptoms (25) might suggest that GER can be present, although GER symptoms are absent. This study did not evaluate the presence of nonacid reflux because the technique of esophageal impedance-pH monitoring was not used (31). In children, the relationship between non-acid reflux and respiratory complications is yet to be clarified (32). However, possible non-acid reflux might act as an adjuvant factor, and it may explain the lack of association between spirometric and esophageal pH monitoring in this study.

Several studies suggested that silent GER may worsen asthma (23, 25, 29), particularly nocturnal asthma (33). Among several mechanisms relevant to trigger nocturnal asthma, nocturnal reflux seems to have an important role (10). Nocturnal GER might be worsened by a delayed esophageal clearance and a decreased upper esophageal sphincter resting pressure with sleep onset that might predispose to microaspiration (13, 33). The association between nocturnal asthma and nocturnal GER is controversial (19, 20, 34). In this study, none of the patients presented nocturnal symptoms of asthma.

In conclusion, a high prevalence of GER was found in children and adolescents with persistent asthma, equally distributed in the supine (nocturnal) and the upright positions. There was no correlation between GER and spirometry. Further studies are necessary to better clarify the relationship between nocturnal GER and asthma in children.

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