Chapter 12
Evaluation of Laryngopharyngeal Reflux in Pediatric Patients with Asthma Using a New Technique of Pharyngeal pH-Monitoring

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Abstract There is a debate about the association between asthma and gastroesophageal and/or laryngopharyngeal reflux (LPR). Pharyngeal pH-monitoring is a new technique that allows a physician to assess whether reflux passes the upper esophageal sphincter barrier. The aim of the study was to assess the prevalence of LPR in children with difficult-to-treat asthma. The present study was an open, prospective one. A total of 21 subjects of the mean age 12.7 years were enrolled in the study. All children were asked to fill out a Reflux Symptoms Index questionnaire and a 24-h pharyngeal pH monitoring was performed, using the Dx-pH Measurement System. The LPR was diagnosed in 13 (61.9%) children. There was a positive correlation between LPR diagnosis and the degree of asthma control. The LPR was more frequent in children treated with a higher than lower doses of fluticasone ($p = 0.019$, OR = 17.3) and in those using montelukast compared with non-users ($p = 0.008$, OR = 19.0). The mean Reflux Symptoms Index score was almost twice greater in children with LPR than in those without it (13.2 *vs*. 6.8, respectively, $p = 0.003$). We conclude that the prevalence of laryngopharyngeal reflux in children with difficult-to-treat asthma is substantial.

Keywords Asthma • Children • Laryngopharyngeal reflux • pH monitoring • Reflux symptoms index

12.1 Introduction

In children, gastroesophageal reflux disease (GERD) is defined as the passage of gastric contents into the esophagus, which causes troublesome symptoms and complications (Vandenplas et al. 2009). When the refluxate arises into the pharynx, the condition is often called pharyngeal or laryngopharyngeal reflux (LPR). Many studies, mainly observational, have demonstrated an association between asthma and GERD by esophageal pH-monitoring or pH-impedance. In a recent review assessing the extraesophageal symptoms of gastroesophageal disease in children, the prevalence of diagnosed asthma in children

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with GERD was 13.2%, compared with 6.8% in controls (Tolia and Vanndenplas 2009). In children with asthma, GERD is diagnosed in 19–65% of them (Debley et al. 2006; Barakat et al. 2006). The discrepancy in the results is probably related to the methodology used to identify GERD and different definitions of GERD and asthma used by the authors.

Patients with asthma are probably more predisposed to GERD than healthy people. The known predisposing factors include autonomic dysregulation, an increased pressure gradient between the thorax and the abdomen, altered crural diaphragmatic function, airway obstruction, medication used in asthma therapy and lifestyle (Harding and Sontag 2000). The mechanisms by which refluxate aggravates asthma are the following: (i) airway inflammation due to aspirated gastric contents, with damage to the upper airway epithelium resulting in the release of cytokines and adhesion molecules, (ii) airway hyper-responsiveness triggered by lower airway aspiration of minute amounts of acid refluxate that may aggravate asthma by increasing bronchomotor responsiveness to other stimuli, (iii) vagally mediated bronchial or laryngeal spasms, in which the decrease of pH in the esophagus is associated with an increase in airway resistance, and (iv) neurally mediated inflammation (Vandenplas et al. 2009; Harding and Sontag 2000).

To-date, a 24-h pH-monitoring is considered the gold standard for the diagnosis of GERD, but it is unable to detect non-acid refluxate. Despite the use of a dual-channel probe, it is still impossible to assess precisely the proximal extent of reflux. A more modern technique, pH-monitoring combined with multichannel, intraluminal impedance (pH-MII), allows to detect both acid and non-acid reflux episodes and also makes it possible to identify the nature (liquid, gas. or mixed liquid–gas) of the refluxate and the proximal extent of the reflux. The lack of normal ranges for children limits the value of this test in pediatrics. However, none of these techniques examine whether reflux really crosses the upper esophageal sphincter barrier, which is crucial in the pathogenesis of gastroesophageal reflux in asthma.

Pharyngeal pH-monitoring is a new technique that allows assessing whether the mechanisms mentioned above are really present in the reflux-asthma association. This technique has some advantages compared with classic pH-monitoring or pH-monitoring combined with MII. Firstly, pH-monitoring takes place in the pharynx, the most proper place for the diagnosis. Secondly, thanks to the flashing LED diode located at the tip of a probe, it can be easily placed in the oropharynx with no need of X-ray imaging or esophageal manometry. Thirdly, a novel pH sensor has been designed specifically to monitor pH in the pharynx. This sensor detects aerosolized or liquid acid, resists drying, and does not require contact with fluid or tissue for electrical conduction. The probe has a teardrop shape with the sensor oriented downward to avoid becoming covered with food or mucus. Finally, because of wireless signal transmission, the recorder may be up to 4 m from the patient and can be placed safely on a bedside table during the night. Although this technique is new, normal values have been well established in several studies (Sun et al. 2009; Chheda et al. 2009). The aim of the present study was to estimate the prevalence of laryngopharyngeal reflux in pediatric patients with difficult-to-treat asthma.

12.2 Methods

The protocol for this study was approved by the Bioethics Committee of the Warsaw Medical University in Warsaw, Poland. This was an open, prospective study to evaluate the frequency of laryngopharyngeal reflux in children with asthma. From April to September 2010, patients over 6 years of age with difficult-to-treat asthma (defined according to GINA 2009) (GINA 2009) diagnosed at the Department of Pediatric Pneumology and Allergy, were referred to the Department of Pediatric Gastroenterology and Nutrition, Warsaw Medical University in Warsaw, Poland for the evaluation of laryngopharyngeal reflux. A total of 21 subjects (13 males) of the mean age of 12.7 years (range 7–17 years) were enrolled in the study. All patients (or their parents) were asked to fill out a Reflux Symptoms Index (RSI)

questionnaire. The questionnaire assessed the severity (0 = no problem, 5 = severe problem) of the following nine symptoms: hoarseness or problems with one's voice, clearing one's throat, excess throat mucus, difficulty swallowing food, liquids or pills, coughing after eating or after lying down, breathing difficulties or choking episodes, troublesome cough, sensation of something sticking in one's throat or a lump in the throat, heartburn, chest pain, indigestion or stomach acid coming up (Belafsky et al. 2002).

12.2.1 Pharyngeal pH-Monitoring

The 24-h pharyngeal pH-monitoring test was performed using a Dx-pH Measurement System (Restech, San Diego, California), consisting of a disposable catheter-based probe (containing an antimony sensor and reference electrodes) that connects to a wireless transmitter and a separate data recorder, which periodically saves data to a removable memory card (SD). The special design of the probe allows it to function properly in the pharynx without drying; it is moisturized with water vapour from the exhaled air. The catheter was placed transnasally and positioned in the oropharynx (approximately 10 mm below the uvula) with visual confirmation using a light-emitting diode (LED) located on the tip of the probe. Patients were asked to maintain their normal daily activities or eating habits and to record meal periods, changes in body position (supine and upright) and chief complaints digitally by pressing buttons on the recorder and manually in a daily activity log.

The data from the card were transferred to a computer with the Restech Dx-pH DataView Lite analysis software installed. Each record was manually reviewed and compared with a paper log to remove errors and artefacts. Meal times with the 5-min pre- and postprandial periods were excluded from the analysis. An acid reflux event was defined as a drop in the pH level in the oropharynx below 5.0 in the upright and 5.5 in the supine position. Recordings were automatically analyzed with DataView software, which calculated the composite score (RYAN score) based on the percentage of time below baseline pH, the number of reflux episodes and the duration of the longest episode in each body position. According to the criteria proposed by DeMeester, an abnormal value in the RYAN score indicated a diagnosis of laryngopharyngeal acid reflux.

12.2.2 Sample Size

On the basis of the literature (Khoshoo et al. 2003; Teixeira et al. 2007) we estimated the mean prevalence of GERD in pediatric patients with asthma at 62% (confidence interval 56–68%). We used a sequential test to verify the null hypothesis that the prevalence of GERD in asthma is within this interval (power of the test 80%). The sequential test is a type of statistical method that allows assessing the prevalence of a disease without examining a large number of patients; however, the assessment is less precise. During the study, the result of each consecutive examination (LPR diagnosis or not) was put into the statistically generated program, which determined (after each patient) whether to continue the study.

12.2.3 Statistical Analysis

We performed a statistical analysis, considering the anthropometric parameters, spirometry, degree of asthma control, medications, reported symptoms (RSI), level of total IgE and variables of pH-metric measurements in two groups of patients: with and without laryngopharyngeal reflux. Anthropometric

differences between both groups of patients were tested with logistic regression and using the Mann–Whitney method. Akaike's information criterion was used as a measure of the fit of the model. The significance of the Dx-pH characteristics (22 variables) was investigated with a multiple hypothesis testing procedure based on a permutation method (Troendle 1995). Fisher's exact test was used in case of contingency tables with small expected frequencies. Results were regarded as statistically significant at $p<0.05$. Cohen's kappa coefficient was used as a measure of agreement between LPR diagnosis and RSI. The bias-corrected bootstrap (BCa) method was used to construct a 95% confidence interval for the regression coefficients. All data were analysed using R 2.2.1 version (www.r-project.org).

12.3 Results

Demographic data are shown in Table 12.1. Laryngopharyngeal reflux was diagnosed in 13 (61.9%) children, so the prevalence of LPR was between 56% and 68%. No association among LPR diagnosis and anthropometric data (sex, age, height and BMI) was found.

We found a positive correlation between LPR diagnosis and the degree of asthma control. Ten of the 13 (77%) LPR-diagnosed patients and only 1 of the 8 (12.5%) LPR-negative had their asthma at the fourth level of asthma treatment ($p=0.012$). There were no significant intergroup differences regarding the age of asthma diagnosis and the total IgE level. The analysis of correlation between LPR diagnosis and medications used showed that the LPR was more frequent in the users of higher than lower fluticasone doses ($p=0.020$, OR = 17.3) and in those using montelukast treatment ($p=0.008$, OR = 19.0).

The evaluation of Reflux Symptom Index revealed that the score >11 had no correlation with LPR diagnosis; the mean RSI score was almost two times higher in the LPR group (13.2 *vs*. 6.75, $p=0.003$). No specific symptom listed in the RSI was related to LPR diagnosis. Table 12.2 shows the details of RYAN scores and RSI scores. Additional analysis revealed that a combination of symptoms of difficulty swallowing, sensation of a lump or mass in the throat and heartburn or chest pain was almost 14 times higher in the LPR group (3.5 *vs*. 0.25, $p=0.001$). A cut-off value of RSI ≥2 for these three symptoms resulted in LPR diagnosis based on the RSI being compatible with the diagnosis based on pH-monitoring ($p=0.001$ using the Fisher test; Cohen's kappa coefficient 0.78, $p=0.001$).

Table 12.1 Characteristics of patients

	LPR (+)	LPR (−)	p
	(n = 13)	(n = 8)	CI95 (56%, 68%)
Age (year)	13.2 ± 3.06	12.1 ± 3.08	0.19
Sex (female/male)	9/4	4/4	0.62
Weight (kg)	47.8 ± 20.7	45.4 ± 18.7	0.94
Height (cm)	152.2 ± 15.7	152.5 ± 16.1	0.24
BMI (kg/cm^2)	19.8 ± 5.9	18.9 ± 4.4	0.97
Total IgE (U/mL)	352 ± 206	262 ± 82	0.89
Asthma			
Third level of control	3	7	0.012
Fourth level of control	10	1	
Medications			
Fluticasone 200 μg/day	3	7	0.019
Fluticasone 500 μg/day	9	1	
Montelukast	10	1	0.008

LPR (+) laryngopharyngeal reflux positive group, *LPR* (−) laryngopharyngeal reflux negative group

Table 12.2 RYAN score and Reflux Symptom Index score

	LPR (+)	LPR (−)	p
RYAN score			
Upright	22.2 ± 16.4	2.1 ± 0	<0.001
Supine	20.7 ± 19.2	3 ± 1.6	NS
RSI score			
n	10	8	–
Mean	13.2 ± 6.4	6.8 ± 3.6	0.003
Score >11	4	2	NS
Hoarseness or a problem with your voice	2.0	1.3	NS
Clearing your throat	2.5	1.4	NS
Excess throat mucous	1.3	1.1	NS
Difficulty swallowing food, liquids or pills	0.5	0	NS
Coughing after eating or after lying down	0.9	1.1	NS
Breathing difficulties or choking episodes	1.8	0.6	NS
Troublesome or annoying cough	1.2	1.1	NS
Sensations of something sticking in your throat or a lump in your throat	1.5	0	NS
Heartburn, chest pain, indigestion, or stomach acid coming up	1.5	0.2	NS

RSI reflux symptoms index

12.4 Discussion

The study demonstrates that the incidence of laryngopharyngeal reflux diagnosed by 24-h pharyngeal pH-measurement in children and adolescents with difficult-to-treat asthma lies between 56% and 68%; the incidence is higher than previously assessed.

The data regarding the role of gastroesophageal reflux or pharyngeal reflux in asthma are differential, but most studies have reported a higher prevalence of GERD in children with asthma compared with healthy controls (Debley et al. 2006; Chopra et al. 1995). According to a systematic review published in 2010, the estimates of the prevalence of GERD in children with asthma varies between 19% and 80%, giving a pooled, sample-size-weighted average prevalence of 22.8% (Thakkar et al. 2010). The authors found serious methodological limitations in previously published studies, of which only five had control groups. The variations in the results were probably related to the methodology used to identify GERD and to different definitions of asthma employed. Twelve of the studies measured esophageal pH (but only one included a control group), three studies included endoscopic evaluation, two studies used two different questionnaires, one study used scintigraphy, and one study used barium swallowing. The definition of asthma used was not reported in most of the studies; only five studies provided criteria for asthma diagnosis. Moreover, these studies varied according to age groups and timing in relation to the patients' symptoms. None of these studies directly assessed pharyngeal reflux. From the medical standpoint, evaluating the results of these studies could lead to confusion.

Thus far, there are only limited data to confirm the relationship between the presence of refluxate in the pharynx or larynx and asthma, mainly because of lack of proper diagnostic tools (Stapleton and Brodsky 2008). According to NASPGHAN/ESPGHAN (Vandenplas et al. 2009) recommendations, pH-monitoring is the gold standard in diagnosing GERD. The 24-h pH-monitoring procedure allows monitoring the pH level at 5 cm above the lower esophageal sphincter, but it can only register acid reflux episodes, whereas the non-acid episodes can cause some extraesophageal symptoms of GERD. Even the use of dual-probe pH-monitoring (the second channel is located above the upper

oesophageal sphincter) does not allow assessing the non-acid reflux episodes and the actual upward extension of a bolus. In the pediatric population, the proper location of the upper channel is often undone because of the varying, age-dependent length of the esophagus.

Regarding the unproven clinical utility of pH-monitoring in the detection of extraesophageal symptoms (including asthma) in GERD, there is a need for more sensitive and accurate techniques for defining proximal reflux in the esophagus. Pharyngeal pH-monitoring is a new technology that detects episodes of reflux in the pharynx and provides information about the correlation between episodes of reflux and symptoms. To-date, only a few studies evaluating extraesophageal symptoms of GERD using this technique have been performed, but the usefulness of pharyngeal pH-monitoring in adult patients with laryngopharyngeal symptoms has been established (Golub et al. 2009; Wiener et al. 2009; Friedman et al. 2011). Moreover, all studies have emphasized that the new catheter is easy to use and more comfortable because of the tip's location in the upper oropharynx (Stordal et al. 2006), which we confirmed in our pediatric population.

Our study revealed that the level of asthma control (intensity of treatment) is correlated with the prevalence of a pathological reflux. It conforms to the previously reported association between those two conditions (Stordal et al. 2006). The study shows that the Reflux Score Index was about twofold higher in patients with reflux than without it. However, a total score ≥11 was not consistent with a reflux diagnosis based on the RYAN score ($p = 0.51$). The lack of correlation between RYAN and RSI scores observed could be a result of the differences between adults and children, or even adolescents, and suggests the need to develop new symptom scores for younger age groups.

Our study evaluated the diagnostic value of a new, promising technique, pharyngeal pH-metry, in the work-up of two common childhood diseases. We chose a group of difficult-to-treat asthma patients because of the potential role of GERD in the pathogenesis of this common disease in the pediatric population. A limitation of the study is the lack of a control group. However, due to ethical issues it is very difficult to perform pharyngeal pH-metry in a group of healthy children. That is the reason why there is no normal value for different age groups, either for pH-monitoring alone or for pH-monitoring combined with impedance. The sample size was small, but it was similar to that in some other published studies (Sun et al. 2009) and the statistical methods were appropriately adjusted.

Conflicts of Interest: The authors declare no conflicts of interest in relation to this article.

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