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ORIGINAL ARTICLE

Diagnosis of laryngopharyngeal Reflux by Impedance with esophageal pHmetry in children with chronic dysphonia

Diagnóstico de Reflujo faringolaríngeo mediante Impedanciometría con pHmetría esofágica en niños con disfonía crónica

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What do we know about the subject matter of this study?

Laryngopharyngeal reflux is one of the most frequently described chronic inflammatory conditions of the larynx. However, most of these patients do not show classic symptoms of gastroesophageal reflux disease, making it difficult to diagnose or rule out it based on clinical manifestations only.

What does this study contribute to what is already known?

It is the first national pediatric report on children with chronic dysphonia which, using esophageal pH/impedance monitoring as a diagnostic tool, allows to confirm with greater certainty a causal relationship between suspicious laryngoscopic findings and laryngopharyngeal reflux.

Abstract

Laryngopharyngeal Reflux (LPR) is the retrograde flow of gastric or duodenal contents into the pharynx and larynx, causing inflammation in the upper aerodigestive tract. Traditionally, a pH monitoring study with an acid reflux index was used. The use of multichannel intraluminal impedance testing with pH monitoring (MII-pH) confirms a causal relationship between suspicious symptoms and LPR. **Objectives:** To evaluate LPR diagnosed by MII-pH in the pediatric population consulting due to chronic dysphonia and laryngoscopic findings suggestive of LPR, in addition, to measure the concordance between MII-pH and traditional pH monitoring. **Patients and Method:** Descriptive, prospective study of patients consulting at the Gastroenterology or Otorhinolaryngology polyclinic due to chronic dysphonia, whose nasofibrolaryngoscopy (NFL) was suggestive of LPR. The patients were hospitalized for a 24-hour MII-pH. Patients with a congenital or acquired morbid history were excluded. Pathological LPR was considered if there were 3 or more acid reflux episodes at the proximal level in MII-pH. The frequency of traditional pH monitoring and altered MII-pH and the concordance between both methods were evaluated. **Results:** 12 patients were recruited, 10 men, 6 to

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15 years old. On 9/12, pathological LPR was confirmed by MII-pH, of which 2/9 had traditional pH measurements in normal ranges and 7/9 altered pH measurements. In 3 patients, LPR was ruled out by normal proximal MII-pH. The concordance between MII-pH and traditional pH monitoring was acceptable (kappa 0.4). **Conclusions:** 75% of the patients with dysphonia and suggestive NFL showed objective evidence of pathological LPR. Since only with the clinical evaluation, NFL and conventional pH monitoring it is not possible to diagnose LPR, we recommend perform MII-pH for greater diagnostic certainty, avoiding unnecessary treatment, and with unwanted effects in 25% of cases.

Introduction

Laryngopharyngeal reflux (LPR) is defined as the retrograde flow of gastric or duodenal contents into the pharynx and larynx resulting in irritation and inflammation in the upper aerodigestive tract[1-3]. Pediatric LPR tends to be considered an unusual pathologic condition different from gastroesophageal reflux (GER) but remains an entity with more questions than answers[2,4].

For at least four decades, the otorhinolaryngological literature has described the existence of gastric reflux with extra-digestive laryngeal manifestations, however, the current conceptualization in a pediatric-gastroenterological approach was described by James Koufman as LPR only in the early 90'[5]. It is an increasingly well-known entity, with publications attempting to explain this pathophysiological disorder[1].

LPR is one of the most frequently reported chronic inflammatory conditions of the larynx, affecting 8-20% of the general population, 4-10% of patients consulting an otorhinolaryngologist, 1% of primary care patients, and up to 75% of patients with refractory ENT symptoms. LPR may affect 50-78% of the population with voice discomfort and 91% of cases of voice disorders in the elderly[6]. The prevalence of LPR in children is still unknown since there are little data on this subject[2].

The etiology is multifactorial, including upper esophageal sphincter dysfunction, time of exposure, and tissue sensitivity level[1,7]. There are reports that the laryngeal epithelium is more sensitive to reflux than the esophageal one. Only 3 episodes of LPR per week with pH less than 4, would be enough to cause damage at the laryngeal level, unlike GER which requires approximately 50 episodes per week to produce some degree of esophageal damage. The explanation for this greater epithelial sensitivity remains unclear, but it is believed that the presence of a low pH at the laryngeal level, along with the presence of pepsin, would generate a reaction that would increase the production of stress proteins, affecting epithelial repair, causing damage[1].

Immunohistochemical studies had described pepsin concentrations and carbonic anhydrase isoenzyme III depletion in laryngeal biopsy of documented cases of LPR[8]. In addition, we must include the participation of pancreatic enzymes in duodenal reflux[6].

Direct irritation by reflux can cause coughing and choking (laryngospasm) because sensitivity at the sensory nerves endings of the larynx is regulated by local inflammation[8]. This combination of factors can lead to vocal cords edema, contact ulcers, and granulomas that cause other symptoms associated with LPR, such as dysphonia, globus pharyngeus, and odynophagia[8]. Dysphonia is related to anatomopathological changes in the epithelium that are associated with other interacting factors.

Most patients with LPR do not show classic symptoms of GER disease, making it difficult to diagnose. In addition, they present non-specific symptoms, and the diagnosis is potentially confusing. Most of the laryngoscopic signs considered suggestive of LPR have poor specificity, as they can be found in up to 70% of asymptomatic subjects[9].

Although there is no ideal diagnostic test for LPR due to some limitations, techniques such as the 24-hr Multichannel Intraluminal Impedance-pH (MII-pH) monitoring have been developed, which allows monitoring of GER for evaluating the movement of liquids, solids, and air, regardless of the pH of the refluxed material (acid, weakly acidic, weakly alkaline)[10]. On the other hand, 24-hr Esophageal pH Monitoring evaluates only acid reflux[11].

Since 2002, the MII-pH (combination of 2 previous techniques) has been available with pediatric probes. The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) and the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) report that "MII-pH is better than traditional pH monitoring alone for the assessment of the temporal relationship between symptoms and GER"[12,13].

Before the use of 24-hr MII-pH, there was no way to demonstrate a causal relationship between suspected symptoms such as chronic cough of unknown cause, dysphonia, or recurrent laryngitis and LPR. The association of this diagnostic tool with laryngoscopic

findings suggestive of LPR is intended to increase diagnostic certainty, decrease overdiagnosis of LPR, and offer more appropriate treatment.

The objective of this research was to study the presence of LPR diagnosed by MII-pH in a pediatric population consulting due to chronic dysphonia and laryngoscopic findings suggestive of LPR, as well as to evaluate the concordance between the MII-pH and the traditional pH monitoring.

Patients and Method

Descriptive and prospective study of pediatric patients who consulted in the Gastroenterology or Otolaryngology polyclinic of the *Hospital San Juan de Dios* in Santiago, Chile, between November 2015 and November 2016, with chronic dysphonia and whose Nasofibrolaryngoscopy (NFL) was suggestive of LPR.

The patients who were included were those with history of dysphonia and whose NFL performed by an otorhinolaryngologist had reported some of the following findings: arytenoid erythema, laryngeal edema, granulomas, laryngeal pseudosulcus or sulcus, posterior commissure erythema, posterior pharyngeal wall with cobblestone appearance, and vocal fold nodules.

Patients with congenital, heart, digestive and orofacial malformations, history of thoracic or abdominal surgery (including esophageal surgery or fundoplication), cystic fibrosis, neuromuscular disorders, seizures, intellectual disability due to the risk of removal of MII-pH probe during hospitalization, and cerebral palsy were excluded.

Procedure

The patients were hospitalized for a 24-hour MII-pH study. Those who were on proton pump inhibitor treatment were instructed to discontinue it one week before. In all patients, a 24-hr recording was completed with the Digitrapper™ pH-Z monitoring system (24-Hour pH & Impedance Recorder) with impedance and pH sensor.

This study was performed by installing a small probe through a nostril into the esophagus that records, along with pH changes, the changes in electrical impedance between two contiguous electrodes during the passage of the food bolus through the esophagus, regardless of whether the contents are acid or non-acidic. The direction of bolus movement can be visualized by the presence of multiple electrodes placed sequentially in a catheter as well as establishing the height of reflux episodes[14].

Before placement, the equipment was calibrated with 2 different pH solutions (pH 7.0 and pH 4.0). A trans-nasal sensor previously moistened with distilled water was introduced to facilitate the passage through the nostrils. Lubricant gel was not used because its presence in the probe can decrease its accuracy during the test[12]. Using chest and abdominal plain X-ray, the position of the probe's pH sensor was verified at the level of the 2nd vertebra above the diaphragm.

The patients received the usual milk formulas and feeding appropriate to their age and development. The recordings were made while the patient was in the supine position during sleep and in the standing position (sitting, walking) during wakefulness. The idea was to reproduce as much as possible the normal activity of the home. Before starting the protocol, the parents of potential study subjects were contacted, explained what the study consisted of, and those who accepted to participate signed the informed consent form, which also stipulated the use of the data obtained and their publication. Patients older than 8 years signed assent (University of Chile – Medicine Faculty, Ethics Committee for Research on Human Subjects, Project N°122-2016, File Act n°1).

Parameters considered

Esophageal pH monitoring with reflux index (RI): Defined as the percentage of total recording time in which the esophageal pH is < 4 to determine pathological GER and reflects the cumulative exposure of the esophagus to acid[15]. Studies describe that RI measured by pH monitoring has a sensitivity and specificity of 50% and 82%, respectively[16].

DeMeester score: It is commonly used in the adult population and considers an overall score > 14.72 in the distal esophagus as abnormal acid exposure. This combined score is obtained by the sum of the calculation of each of its six components: number of reflux episodes in 24 hours, number of reflux episodes longer than 5 minutes in 24 hours, longest episode (minutes), % of total time with pH < 4.0, % of time with pH < 4.0 in standing position, and % of time with pH < 4.0 in the supine position[17].

Normal or altered pH monitoring was defined according to RI (normal ≤ 7) and the DeMeester score (normal ≤ 14.72 p95 in adults), considering the RI as the most relevant parameter.

MII-pH: Proximal GER was defined as a drop in impedance that reached 1 or 2 of the most proximal sensors of the impedance probe, categorized as acid, weakly acidic, or weakly alkaline according to the distal pH sensor recording. According to the reviewed literature, which suggests that 3 proximal refluxes of pH < 4 per week are enough to cause laryngeal epithelium damage, we defined as altered proximal MII-pH the presence of 3 or more episodes of acid reflux at the proximal level by MII-pH.

Statistical analysis

The frequency of altered pH monitoring and altered MII-pH was analyzed in the studied population. Descriptive statistics, median, and interquartile range (IQR) were used. Data were analyzed in Microsoft Excel spreadsheet version 2012. The concordance of traditional pH monitoring versus MII-pH for the diagnosis of LPR was evaluated through Cohen's Kappa index[18].

Results

Twelve patients were recruited, 10 were male, with a median age of 10 years and IQR of 4 (6 to 15 years).

The presence of normal pH monitoring based on RI and DeMeester score (4/12) did not rule out LPR, since half of these patients (2/4) had proximal reflux, which could not be detected if this test was not complemented with MII. On the other hand, of the patients with altered pH (8/12), 7/8 had altered proximal MII-pH and 1/8 had normal proximal MII-pH, therefore, having altered pH monitoring is not equivalent to the presence of LPR.

The above means that in 4 of the 12 patients, LPR would have been ruled out due to a normal pH monitoring based on acid RI and DeMeester score, 2 of them would have been false negatives, and 2 true negatives (Figure 1). In addition, 9/12 had proximal reflux detected by altered proximal MII-pH, of which 2/9 had a pH monitoring based on RI and DeMeester score within normal ranges and 7/9 had abnormal pH monitoring (Figure 1).

The agreement between traditional pH monitoring and MII-pH was acceptable (Kappa 0.4) (Table 1).

The most frequent findings in NFL both in the total number of patients and in those with altered proximal MII-pH were edema or erythema of the arytenoids and posterior commissure (Table 2).

Discussion

This study demonstrated that only 75% of patients with dysphonia and NFL suggestive of LPR show objective evidence (altered proximal MII-pH) of pathological LPR. This is in line with the studies of Dr. Rosen et al. who concluded that when MII-pH is combined, clinical decision making is modified in approximately 25% of patients compared with traditional signs and symptoms and pH monitoring[19].

By performing pH monitoring alone, two patients with LPR who were detected using proximal MII-pH would not have been diagnosed and one patient would have been overdiagnosed. Considering only the laryngoscopic findings for treatment with proton pump inhibitors would have meant overtreated three patients.

Although altered NFL suggestive of LPR was indeed an inclusion criterion in our study and, therefore, all children evaluated with symptoms suspicious of LPR such as chronic dysphonia were included, not all of them had proximal MII-pH compatible with LPR, so we can conclude that there are no signs and symptoms and NFL pathognomonic of LPR, nor is altered pH monitoring. On the other hand, normal pH monitoring based on the RI or DeMeester score does not rule out LPR, so it is necessary to include MII, which was evidenced by an acceptable but insufficient Kappa index.

Publications show that traditional pH monitoring, especially in the study of extra-digestive GER symptoms, has limitations such as poor identification of full column reflux and failure to correlate symptoms with esophageal acid events, making it an inadequate tool for the diagnosis of extraesophageal symptoms[20,21]. In addition, obtaining data in healthy controls is not ethically feasible due to the invasive nature of pH monitoring, hindering the determination of true "normal" values[16] plus the disadvantage that pH monitoring does not detect non-acid reflux episodes.

Finally, while correlation of symptoms with reflux events is one of the main indications for pH monitoring, patients and parents often do not report symptoms, a factor that affects symptom correlation[22]. In addition, there is a debate on which appropriate time frame should be considered as a symptom correlated with reflux[23].

In conclusion, there is not enough evidence to support the routine use of pH monitoring for the diagnosis of GER disease in pediatrics.

The DeMeester score is generally used more in adults than in children, which is considered a limitation. Studies carried out with 24-hr pH monitoring, based on the DeMeester score, have shown to have high diagnostic accuracy when the population studied consists of patients with a high prevalence of GER[17]. Despite this, we would like to emphasize that in our study we identified one patient who, having normal pH monitoring, had an altered DeMeester score, detecting proximal reflux by MII-pH.

LPR can affect both infants and young children, with different symptoms depending on age. Infants may present dysphagia, recurrent croup, subglottic stenosis, or chronic respiratory problems; school children with chronic cough, dyspnea, dysphonia, persistent sore throat, halitosis, and globus sensation; and older children may report chronic respiratory problems[4]. However, as found in our study, symptoms of LPR have been reported to be nonspecific and the diagnosis can be potentially confusing[3,8] because most

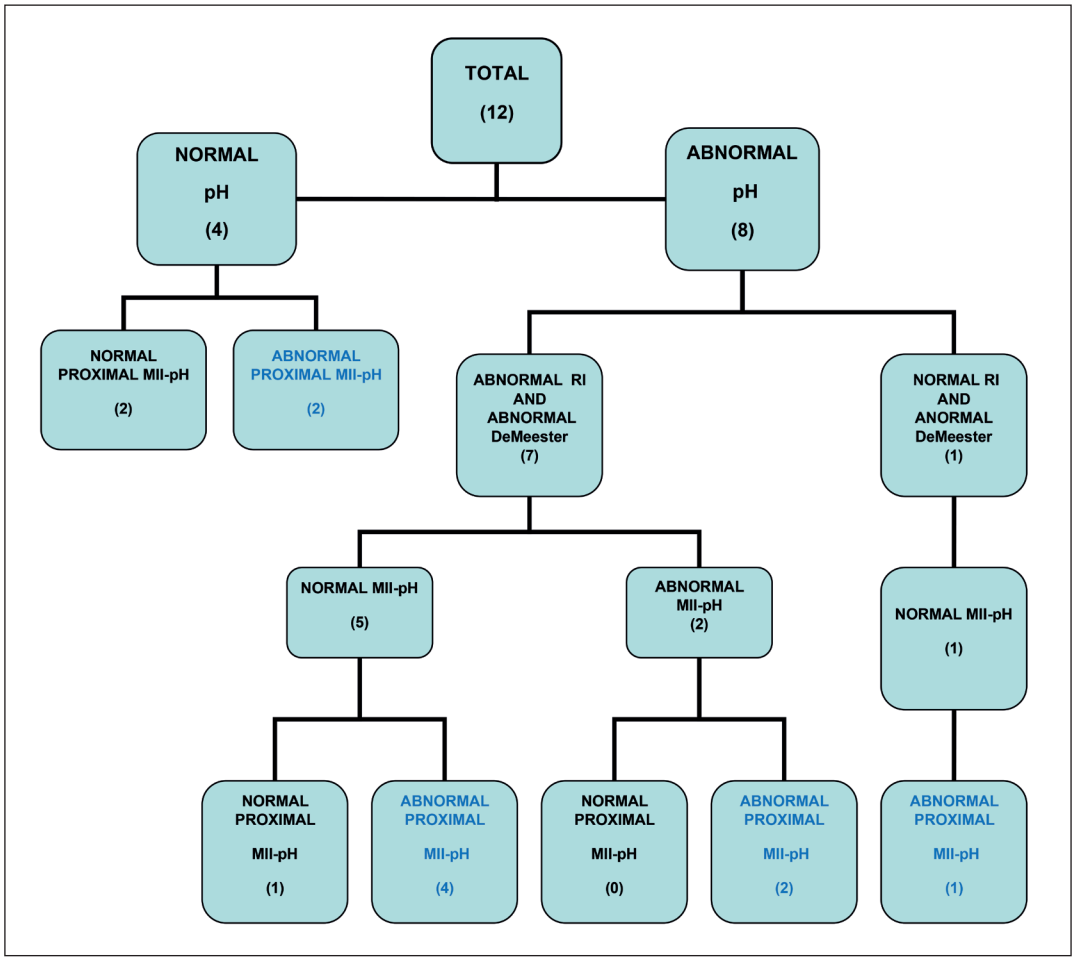

Figure 1. Distribution of patients according to pHmetry. pH = pHmetry. RI = Acid reflux index (normal < or = 7). DeMeester score= Normal < or = 14,72 (p95). MII-pH= Impedance with esophageal pH measurement

Table 1. Comparison between conventional pHmetry and Impedance with esophageal pHmetry

	Altered Proximal MII-pH	Normal Proximal MII-pH	Total
Acidic RI and/or DeMeester Score Altered	7	1	8
Acidic RI and/or Score DeMeester Normal	2	2	4
Total	9	3	12

Table 2. Nasofibrolaryngoscopy findings

NFL findings	Patients with altered proximal MII-pH (9)	Patients with normal proximal MII-pH (3)
Edema or erythema of arytenoids	8	1
Posterior commissure edema or erythema	7	2
Cobblestone posterior pharyngeal wall	2	1
Vocal cord nodules or outline of them	4	3

NFL = Nasofibrolaryngoscopy; MII-pH = Impedance with esophageal pH measurement.

patients with LPR do not show classic symptoms of GER disease and, in children, due to the intermittent pattern, even if symptoms such as chronic cough, frequent throat clearing with post-nasal drip, recurrent laryngitis, and laryngeal spasm have been observed[1].

On the other hand, findings suggestive of NFL include erythema and edema of the posterior commissure, arytenoid edema, medial arytenoid wall edema, vocal process granuloma, pseudo sulcus, posterior pharyngeal wall with a cobblestone appearance, and edema of the posterior wall of the cricoid cartilage[1]. Out of these findings, the most frequently described sign in patients with GER is edema and erythema of the posterior pharyngeal wall[1], consistent with the common findings in patients with LPR in our study, without being pathognomonic[8].

Among the limitations of this study, we highlight the small number of cases, making this a preliminary report, and the lack of a control group, which was not considered due to ethical limitations. Among the strengths of the study is its prospective nature.

Conclusions

In 75% of patients with chronic dysphonia and NFL suggestive of LPR, proximal reflux was detected with MII-pH, concluding that not every patient with dysphonia and NFL suggestive of LPR actually has it.

Only with clinical evaluation, a flexible endoscopic study of the larynx, and traditional pH monitoring it is not possible to confirm the diagnosis of LPR, so it is recommended to associate impedance to pH monitoring to achieve greater diagnostic accuracy of LPR, reducing overdiagnosis in 25% of cases.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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