

PERSISTENT UPPER RESPIRATORY DISEASES IN CHILDREN: ROLE OF GASTROESOPHAGEAL REFLUX STUDIED USING INTRALUMINAL IMPEDANCE AND PH

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Abstract

Background: A variety of signs and symptoms of otolaryngological complaints have been attributed to gastroesophageal reflux disease (GERD). However, proof of such an association is sparse. Recent studies suggest that in some cases GERD may be connected with upper respiratory diseases in children, and this paper explores the connection. The aim of the study was to estimate the incidence of GERD among children with persistent upper respiratory disease by inserting an electrode into the esophagus. Reflux can be detected as changes in intraluminal resistance brought on by liquid inside the esophagus, and pH measurements can be used to classify the reflux as acidic or nonacidic.

Material and Methods: This was a multicenter, prospective study of children (4–11.5 years old) with persistent upper respiratory disease. Chronic diseases such as allergy, asthma, cystic fibrosis, or congenital anomalies were excluded. The diagnosis of chronic upper tract disease was made by a single laryngologist. All children underwent a 24-hour multichannel intraluminal impedance and pH (MII-pH) study. The diagnosis of GERD was made with BioVIEW analysis software after manual review by a single investigator.

Results: Exactly 31 consecutive patients (17 boys, 14 girls, mean age 6.8 years) were enrolled in the study. A diagnosis of GERD was made in 11/31 (35%) patients. A total of 1172 reflux episodes were detected by MII-pH, and 759 (65%) of them were acid, 413 (35%) were nonacid. The most common symptoms were mouth breathing (28/31), snoring (22/31), fetor ex ore (13/31), hawking (4/11), and apnea (2/11). None of the patients declared gastroenterological symptoms of GERD.

Conclusions: The incidence of GERD in children with persistent upper respiratory diseases was high (35%) in our group, but not as high as has been previously assessed. More than 1/3 of reflux episodes were non-acid. Reflux should be taken into consideration as a probable etiology of persistent upper respiratory diseases in children. 24-h pH and impedance monitoring is a more precise way of diagnosing GERD than classic pH-metry.

Key words: upper respiratory diseases • children • acid reflux • non-acid reflux • extra-esophageal reflux

ПОСТОЯННЫЕ РЕСПИРАТОРНЫЕ ЗАБОЛЕВАНИЯ ВЕРХНИХ ДЫХАТЕЛЬНЫХ ПУТЕЙ У ДЕТЕЙ: РОЛЬ ГАСТРОЭЗОФАГЕАЛЬНОГО РЕФЛЮКСА, ИЗУЧЕННОГО С ИСПОЛЬЗОВАНИЕМ ВНУТРИПРОСВЕТНОГО ИМПЕДАНСА И PH-МЕТРИИ

Резюме

Введение: Множество признаков и симптомов оториноларингологических жалоб было приписано болезни гастроэзофагеального рефлюкса (ГЕРБ). Однако, не представлено точных доказательств такой закономерности. Недавние исследования предполагают, что в некоторых случаях ГЕРБ может быть связан с респираторными заболеваниями верхних дыхательных путей у детей. Представленная работа исследует данную связь. Цель исследования состояла в том, чтобы оценить уровень ГЕРБ среди детей с постоянными респираторными заболеваниями верхних дыхательных путей, помещая электрод в пищевод. Рефлюкс может быть обнаружен в виде изменений внутриполостного давления, являющегося результатом появления жидкости в пищеводе, а pH-метрия может быть использована для классификации рефлюкса как кислого или некислого.

Материал и методы: Данное исследование было проведено в нескольких центрах. В нем участвовали дети (4–11,5 лет) с постоянными респираторными заболеваниями верхних дыхательных путей. Были исключены хронические болезни, такие как аллергия, астма, муковисцидоз и врожденные аномалии. Одним ларингологом был поставлен диагноз хронической болезни верхнего тракта. Все дети подверглись 24-часовому многоканальному внутрипросветному импедансу и рН-метрии (МПИ-рН). Диагноз ГЕРБ был поставлен аналитическим программным обеспечением BioVIEW после того, как один исследователь провел проверку.

Результаты: В исследовании участвовало 31 пациент (17 мальчиков, 14 девочек, средний возраст 6,8 лет). Диагноз ГЕРБ был поставлен у 11/31 (35%) пациентов. В общей сложности было обнаружено 1172 рефлюксов с помощью МПИ-рН, при этом 759 (65%) из них были кислотные, 413 (35%) были некилотные. Наиболее распространенные признаки это – дыхание через рот (28/31), храп (22/31), неприятный запах (13/31), откашливание (4/11) и одышка (2/11). Ни один из пациентов не указал гастроэнтерологических признаков ГЕРБ.

Заключения: Частота появления ГЕРБ у детей с постоянными респираторными заболеваниями верхних дыхательных путей была высокой (35%) в нашей группе, но не настолько высокой как ранее предполагалось. Больше 1/3 случаев рефлюкса были некилотными. Рефлюкс должен быть рассмотрен как признак вероятной этиологии постоянных респираторных заболеваний верхних дыхательных путей у детей. 24-х часовой контроль с помощью рН-метрии и импеданса является более точным способом диагностики ГЕРБ, чем классическая рН-метрия.

Ключевые слова: респираторные заболевания верхних дыхательных путей • дети • кислотный рефлюкс • некилотный рефлюкс • экстраэзофагеальный рефлюкс

PERSISTENTES ENFERMEDADES DE VÍAS RESPIRATORIAS ALTAS EN NIÑOS: PAPEL DE REFLUJO GASTROESOFAGICO ESTUDIADO USANDO IMPEDANCIA INTRALUMINAL Y PH

Extracto

Introducción: Una variedad de signos y síntomas de quejas otolaringológicas han sido atribuidos a la enfermedad de reflujo gastroesofágico (GERD). Sin embargo, la prueba de tal asociación no está presentada. Los estudios recientes sugieren que en algunos casos GERD puede estar relacionado con enfermedades de vías respiratorias altas en niños, y este estudio explora la conexión. El objetivo del estudio era estimar la frecuencia de GERD entre niños con la persistente enfermedad de vías respiratorias altas insertando un electrodo en el esófago. El reflujo puede ser descubierto como cambios de la resistencia intraluminal provocada por el líquido dentro del esófago, y las medidas de pH pueden ser usadas para clasificar el reflujo como ácido o no ácido.

Material y Métodos: El estudio tuvo lugar en muchos centros. Participaron los niños (4-11,5 años) con la persistente enfermedad de vías respiratorias altas. Las enfermedades crónicas, como alergia, asma, fibrosis quística, o anomalías congénitas fueron excluidas. El diagnóstico de la enfermedad respiratoria crónica fue hecho por un laringólogo. Todos los niños se sometieron a una impedancia intraluminal multicanal y pH estudio (MII-pH) de 24 horas. El diagnóstico de GERD fue hecho con el software de análisis BioVIEW después de la revisión manual por un investigador.

Resultados: Exactamente 31 pacientes consecutivos (17 muchachos, 14 muchachas, edad media 6,8 años) fueron matriculados en el estudio. Un diagnóstico de GERD fue hecho en el 11/31 (35%) pacientes. Un total de 1172 episodios de reflujo fue descubierto por el MII-pH, y el 759 (65%) de ellos eran ácidos, el 413 (el 35%) no eran ácidos. Los síntomas más comunes eran respiración por la boca (28/31), ronquido (22/31), olor malo(13/31), tos (4/11), y ahogúo (2/11). Ninguno de los pacientes declaró síntomas gastroenterológicas de GERD.

Conclusiones: La frecuencia de GERD en niños con enfermedades de vías respiratorias altas era alta (35%) en nuestro grupo, pero no tan alta como ha sido creído antes. Más que 1/3 de los episodios del reflujo no eran ácidos. El reflujo debería ser tenido en cuenta como una etiología probable de persistentes enfermedades de vías respiratorias altas en niños. Las 24 horas de pH y impedancia son un modo más preciso de diagnosticar a GERD que el pH-metría clásica.

Palabras claves: enfermedades de vías respiratorias altas • niños • reflujo ácido • reflujo no ácido • reflujo extraesofágico

Background

The child who is “always sick” is a common problem for different medical specialists. The diagnosis and management of persistent respiratory tract infection in children

presents a significant challenge for doctors. An increasing number of studies have indicated that gastroesophageal reflux disease (GERD) could be related to various extra-esophageal disorders such as chronic sinusitis, otitis media with effusion, chronic cough, and, recently, adenoid and

tonsil hyperplasia and persistent upper respiratory disease [1]. Laryngologists may find extra esophageal symptoms and signs in children with GERD. In children with laryngeal symptoms, the prevalence of GERD is unknown, but may be more than 60% [2,3]. Because of the proximity of the trachea to the esophagus, the respiratory tract is vulnerable to the effects of GERD. Upper respiratory disease often coexists with adenoids and tonsil hypertrophy in children. The most common symptoms of adenoid hyperplasia include snoring, nasal congestion/mouth breathing, noisy breathing, rhinorrhea, recurrent otitis media, and sleep disturbance. In children, the true incidence of adenoid hyperplasia is difficult to assess, but it seems to occur in 11% of symptomatic school children [4].

Although the role of gastric refluxate in the development of upper tract diseases is still unknown, we do know that acid exposure results in edema and secretion in respiratory mucosa [5]. Moreover, minimal but chronic acid exposure can turn a minor laryngeal injury into subglottic stenosis [6].

So far there is limited data to confirm the relationship between the presence of refluxate in the pharynx or larynx and extra-esophageal symptoms of GERD, and lack of a proper diagnostic tool could play a part. Until now, studies have detected only those reflux episodes with $\text{pH} < 4$, but it is possible that not only acidic but also alkaline and neutral reflux episodes are responsible for irritation and hypertrophy of mucosal tissues [7,8]. There is evidence that infants and children have a much higher proportion of reflux, but of the non-acidic type that cannot be detected by classic pH-monitoring [9]. Monitoring of the esophagus with a pH probe has been the gold standard for measuring acid reflux, but it has the major limitation that it cannot detect non-acid reflux, and this might underlie some extra-esophageal symptoms of GERD. Moreover, even use of dual probe pH-monitoring does not allow measurement of reflux episodes with pH above 4.0 or the actual upward extent of the bolus.

Combined multiple intraluminal impedance (MII) and pH-monitoring is a relatively new technology that provides a more detailed description of esophageal events: it detects acid and non-acid reflux episodes and measures the upward extent of the bolus and its physical length. Many consider it the new gold standard for evaluation of GERD in adults [10].

The aim of this study was to assess the prevalence of gastroesophageal reflux disease in children with persistent upper tract infection by using the combination of MII and pH-monitoring.

Material and Methods

Exactly 31 children (17 males and 14 females) with a mean age of 6.8 years (range 4 to 11.5 years) with respiratory symptoms were examined by a single laryngologist at the Institute of Physiology and Pathology of Hearing, Kajetany, Poland and chosen for further diagnosis by a gastrologist. Patients with persistent, recurrent upper respiratory tract infections (more than 10 episodes per year) were referred to the Department of Pediatric Gastroenterology and Nutrition, Medical University of Warsaw for evaluation of GERD. Excluded were children with congenital

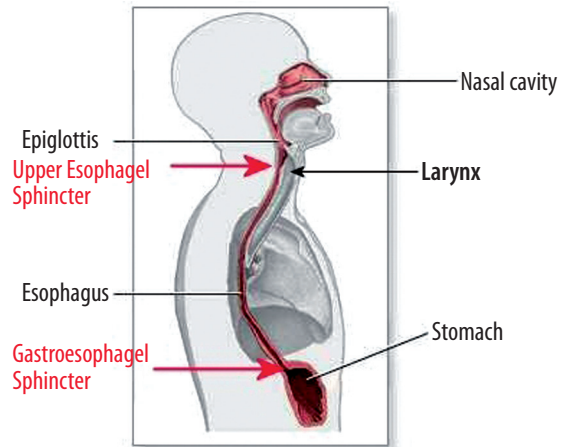


Figure 1. Oesophagus.

anomalies, allergy, systemic diseases (including diabetes), leukemia, and malnutrition; similarly, they were excluded if they had received in the previous 2 weeks drugs that might affect motor function of the gastrointestinal tract or might reduce gastric acid production (i.e. H_2 -receptor antagonists, proton pump inhibitors, antacids, cisapride, metoclopramide, theophylline, anticholinergic, neuroleptics, and sucralfate) (Figure 1).

To evaluate GERD, 24-hour multichannel pH/impedance was performed with an appropriate-to-age catheter (Sandhill Scientific Inc., Denver, CO, USA). The pH/impedance catheter consisted of a 2.3 mm polyurethane catheter incorporating 6 impedance segments (each 2 cm long) and a pH-measuring electrode. The configuration of this catheter allowed changes in intraluminal impedance at 3, 5, 7, 9, 15, and 17 cm above the lower esophageal sphincter (LES) to be recorded. In addition, pH was monitored at 5 cm above the LES. The pH sensor was placed at the level of the third vertebra above the diaphragm, a location determined from an X-ray. The data were collected by the Sleuth mobile recorder (Sandhill Scientific) (Figure 2).

Parents were asked to register any symptoms present during study, sleep, and meals using event marker keys on the recorder and to note them on a paper form. There were no diet restrictions during the study. Data were analysed by BioVIEW analysis software (ver. 5.4.3) and reviewed manually by a single investigator. Meal periods were excluded from the analysis. All reflux events were classified in three ways: as "pH/MII acid" when retrograde bolus movement was detected by an impedance drop and accompanied by a pH drop from above 4.0 to below; "pH/MII nonacid" when there was no pH drop during the impedance-detected retrograde bolus movement; and "pH only" if a pH drop from above 4.0 to below was observed for at least 5 seconds regardless of retrograde bolus movement. Gas, liquid, or mixed reflux events could also be distinguished by MII. A symptom was considered as related to the reflux event if, in terms of the pH-impedance trace, it occurred within a 2-minute window.

Abnormality was scored if any of the normal values set out in the study report by DeMeester was exceeded. The DeMeester score was obtained from 6 different



Figure 2. pH and impedance: combined multiple intraluminal impedance (MII) and 24-hour pH monitoring.

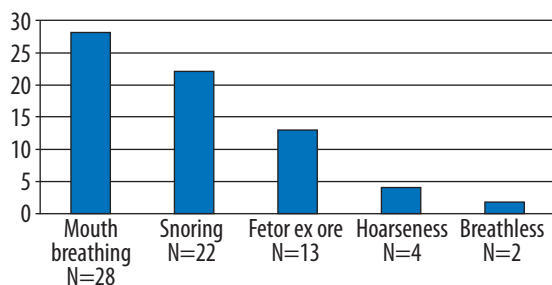


Figure 3. Symptoms index in the examined group of 31 children.

parameters: (1) total percentage time pH<4.0; (2) percentage time pH<4.0 in the upright period; (3) percentage time pH<4.0 in the recumbent period; (4) the total number of acid reflux episodes; (5) the total number of acid reflux episodes longer than 5 minutes; and (6) the duration of the longest acid reflux episode. Mean values and SD were calculated.

The study design was approved by the Bioethical Committee of the Medical University of Warsaw. For all patients written informed consent was obtained from at least one parent.

Results

Of the 31 subjects in the study, all had more than 10 episodes of recurrent respiratory tract infection (Figure 3).

The amount of upper respiratory tract infection (URTI) in the examination group, including nasopharyngitis, pharyngitis, tonsillitis, sinusitis, laryngitis, and otitis media, are described in Table 1.

Table 1. Frequency of upper respiratory tract infection (URTI) in the examined group of 31 children.

URTI	Amount [%] (n=31)
Nasopharyngitis	21 [68%]
Pharyngitis	16 [52%]
Tonsillitis	15 [48%]
Sinusitis	7 [23%]
Laryngitis	6 [19%]
Otitis media	18 [58%]

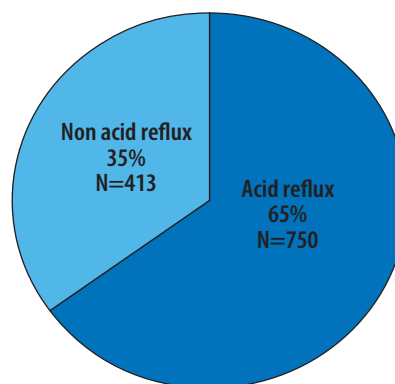


Figure 4. Episodes of gastro-oesophageal reflux N=1172.

Gastroesophageal reflux was diagnosed in 11 (35%) children. There were a total of 1172 reflux events (RE) detected by pH/impedance, and of these 413 (35%) were characterised as non-acid and 759 (65%) as acid (Figure 4).

1242 reflux events were detected by pH alone. Only 45.5% of all reflux events (70.2% of acid RE) found after pH/impedance trace analysis were also detected by pH-only analysis. During the 24-hour pH/impedance monitoring no symptoms were recorded by patients and/or their parents. Evaluation of the relationship between the character of a reflux event and its proximal height revealed that gas reflux events had approximately equal frequency of reaching either the medium or high esophageal zone.

Discussion

In this study we have shown that pH/impedance is a good tool in establishing an association between respiratory symptoms and gastroesophageal reflux in treated children with persistent symptoms. The results of our pilot trial demonstrate that in our examination group the prevalence of GERD in children with persistent upper respiratory diseases is 35%.

In two pediatric prospective studies, Keles et al. [11] and Turgor et al. [12] determined the incidence of GERD as 66.7% (20/30) and 56.7 (17/30) respectively; mean age of the patients was 6.5 years and 7.9 years, respectively. In both studies, 24-hour pH monitoring with a dual probe was used. 24-hour pH-monitoring with two electrodes on the catheter allows monitoring of the pH at the level of 5 cm (distal)

and 20 cm (proximal) above LES, but it still can register only acid reflux episodes. The lack of normative values and methodological variability in proximal esophageal pH measurements, especially related to the positioning of the upper pH probe, make interpretation of proximal pH data difficult [13]. Moreover, proximal pH-metry cannot provide any information on causality between refluxed gastric acid and symptoms, which was demonstrated previously in adults with laryngopharyngeal reflux disease [14]. Regarding unproven clinical utility of proximal pH monitoring, there is a need for more sensitive and accurate techniques for defining proximal reflux in the esophagus. The 24-hour pH/impedance monitoring is “the procedure of choice” in upper airway symptoms of GERD, because of its potential ability to detect acid and non-acid episodes of reflux and to differentiate between reflux episodes and acts of swallowing.

We reviewed studies assessing extraesophageal symptoms of GERD and we found our results similar to those of Lee et al. [15] (37.8% of their patients with laryngopharyngeal symptoms had GERD). Considering patients suffering from atypical symptoms of GERD, Bajbouj et al. [16] determined pathologic GERD in 61% of patients. Several factors could explain the difference between the results. Firstly, different extra-esophageal symptoms were assessed. A second possible reason is the difference between “pediatric” and “adult” GERD. Finally, in Asian countries the prevalence of GERD seems to be lower than in Western countries.

In our study, acid reflux episodes represented 2/3 of all reflux episodes, while in patients without GERD the proportion of acid and non-acid is equal. It seems that non-acid

reflux episodes are less frequency than acid refluxes, although non-acid refluxes may also play a role in the pathogenesis of persistent respiratory disease. However, similar findings were noted previously in studies that assessed other protracting extraesophageal symptoms of GERD – recurrent sinusitis, otitis, or hoarseness [17].

A limitation of the trial is a lack of a control group, but it is very difficult to perform pH/impedance monitoring in a group of healthy children. This is why there are no normal values for different age groups both for pH-monitoring alone or combined with impedance.

Despite treatment with antisecretory agents such as proton pump inhibitors, many patients continue to have respiratory symptoms that could be ascribed to GERD. The use of pH/impedance is a new tool in the evaluation of pediatric GERD. This measurement may give new insight into the pathophysiology of GERD. It is able to give information about acid and non-acid reflux, which should be useful in choosing treatments.

Conclusions

The incidence of gastroesophageal reflux disease in children with persistent upper respiratory diseases was high (35%) in our examination group, but it was not as high as has been previously assessed. More than 1/3 of reflux episodes were non-acid. Reflux should be taken into consideration as a probable etiology of persistent upper respiratory diseases in children. In diagnosing GERD, 24-h pH/impedance is a more precise technique than classic pH-metry.

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