Significance of Extra-Esophageal Symptoms in Pediatric Gastroesophageal Reflux Disease

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Abstract

Introduction   Current practice guidelines in gastroesophageal reflux disease (GERD) often require invasive diagnostic testing.

Objective   The aim of the present study was to evaluate the significance of extra-esophageal symptoms and reliability of a screening risk score that is simple to use.

Methods   A longitudinal retrospective single-institution cohort study. Setting: A university clinical hospital tertiary referral center. The present study enrolled pediatric patients with symptoms suggestive of GERD: epigastric pain, occasional nausea, regurgitation, tasting acid in the oral cavity, chronic cough, hoarseness of voice, frequent throat clearing. The patients underwent 24-hour esophageal pH monitoring and fiber-optic laryngoscopy. The correlations between the local findings, anamnestic and objective measurement data were analyzed.

Results   The present study evaluated 89 pediatric patients. Patients with asthma presented significantly more often with adjoining gastrointestinal symptoms ($p = 0.0472$). Patients that were obese were linked to a higher rate of reports of gastrointestinal symptoms ($p = 0.0495$). After the patients had been assigned to newly developed risk groups, obesity showed to be significantly more frequent in patients placed in higher risk groups ($p < 0.0001$) for a positive GERD diagnosis.

Conclusion   Patients with leading symptoms of asthma presented significantly more often with adjoining gastrointestinal symptoms. Obesity showed to be significantly more frequent in patients placed in higher risk groups for a positive GERD diagnosis.

Keywords
► diagnostics
► obesity
► pediatric gastroesophageal reflux disease
► screening

Introduction

Pediatric gastroesophageal reflux disease (GERD) is characterized by backflow of gastric contents into the esophagus, with acid-induced and pepsin-mediated injury to the mucosa causing troublesome symptoms, affecting up to 3.3% of the pediatric population.[1] The manifestations of GERD have been labeled as either esophageal or extra-esophageal syndromes (EESs).

Among the latter, atypical manifestations of GERD, including chronic cough and pediatric laryngopharyngeal reflux (PLPR) have been considered significant by general physicians, pediatricians and otorhinolaryngologists.[2] In particular, there are increasing evidence linking the growing prevalence of PLPR among GERD patients.[3] There is evidence that PLPR is associated with rhinosinusitis, laryngitis, pneumonia, and asthma in children, but the comorbidities are still frequently overlooked

by otorhinolaryngologists and pediatricians.[4] Children with GERD often experience extra-esophageal symptoms that can be intermittent.[5] Controversies remain regarding the confirmation of the diagnosis of extra-esophageal GERD manifestations in general. At present, insufficient data are available on the assessment of GERD symptoms and on the characteristics of the symptom complex in these patients. In October 2009, the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) published new clinical practice guidelines for the diagnosis and management of reflux in the pediatric population, updating and unifying their previous guidelines as a means of improving uniformity of practice and quality of patient care. One of the most frequent deviations from the NASPGHAN/ESPGHAN recommendations concerned the use of diagnostic modalities. Previously published studies show symptom description to be unreliable and nonspecific.[6] Current practice guidelines in GERD often require invasive diagnostic testing. The aim of the present study was to evaluate the prevalence of extra-esophageal symptoms and the reliability of a novel screening score that is simple to use.

Methods

The present study was conducted as a retrospective longitudinal cohort study. It encompassed pediatric patients who presented with extra-esophageal GERD symptoms (epigastric pain, nausea, regurgitation, acid in the oral cavity, chronic cough, dysphonia, frequent throat clearing) to the pediatric gastroenterologist first, who were then evaluated by an otorhinolaryngologist. The 24-hour dual-probe monitoring procedure was performed in all pediatric patients with extra-esophageal symptoms clearly present in their patient history as part of a department diagnostic protocol. Initially, data from 121 pediatric patients who underwent 24-hour esophageal pH monitoring and fiber optic laryngoscopy were evaluated. Out of these, 32 patients were excluded from the study due to incomplete treatment data and informed consent forms. The correlations between local findings and anamnestic data and objective data obtained by 24-hour dual-probe monitoring were analyzed. The present study was conducted from January 1st, 2007, to December 31st, 2012, in a tertiary pediatric and otorhinolaryngology referral center.

The present study and its protocol were designed and conducted adhering to the 1983 Helsinki Declaration, and informed consent was obtained from all of the patients' parents and legal guardians. After fasting, 24-hour double-probe pH monitoring was performed with the use of a nasal catheter and pH recorder (Flexisoft III, Oakfield Instruments Ltd, Witney, UK).[7] All of the patients were on their usual diet during monitoring. A positive diagnosis of GERD was observed if there was a pH value < 4 for more than 5% of the total recording time. Three or more episodes of pH < 4 in the proximal probe and distal probe simultaneously, or 1% of the total recording time showing pH < 4 in the proximal probe were accepted as PLPR. The measures calculated included reflux, Boix-Ochoa and DeMeester-Johnson indexes, and number of acid reflux events

lasting > 5 minutes. The measurements were performed by the same pediatric gastroenterologist. The otorhinolaryngologic examination was performed by the same otorhinolaryngologist to reduce interobserver variability, through fiber-optic laryngoscopy (4-mm flexible optic fiber, Karl Storz, Tuttlingen, Germany) that assessed the upper airway from the nasal vestibule to the infraglottic area. The patients' parents gave written informed consent for the diagnostic testing.

Obesity was factored in as an independent predictive factor if the patient's body mass index (BMI) was at least two standard deviations (SDs) above the World Health Organization (WHO) growth reference median. The diagnosis of asthma was established through spirometry examinations (reduced forced expiratory flow higher than 25–75% of the Forced Vital Capacity [FVC]).

The statistical analysis was performed using the MedCalc software (MedCalc Software, Ostend, Belgium), version 11.2.1. The data for the cohort were expressed as ratios due to the fact that it was composed of less than 100 patients ($n = 89$). The associations between variables were assessed using the Fisher exact test, Mann–Whitney test and Kruskal–Wallis test for nonparametric paired samples. All of the tests of statistical significance were performed using a two-sided 5% type-I error rate.

Results

The present study included 89 pediatric patients with a median age of 12. There were 56 girls and 33 boys. Out of these patients, 52 had positive diagnostic criteria for GERD, and 50 of these 52 had positive criteria for PLPR. When gastrointestinal comorbidity was analyzed, 15/89 complained of epigastric pain, 14/89 had occasional nausea, 10/89 experienced regurgitation, and 3/89 complained of tasting acid in the oral cavity.

Data showed that the moderate and severe forms of GERD were most prevalent, and that boys tended to have GERD significantly more often than girls (Mann–Whitney U test, $p < 0.0001$), and scored significantly higher on the pH monitoring tests (Mann–Whitney U test, $p < 0.0001$). Patients with leading symptoms of asthma and asthma + cough were statistically significantly correlated with higher GERD grades (Kruskal–Wallis test, $p = 0.0493$). They also presented significantly more often with adjoining gastrointestinal symptoms in our cohort (Kruskal–Wallis test, $p = 0.0472$). Patients that had obesity as a comorbidity factor were linked to a significantly higher rate of reports of gastrointestinal symptoms (Mann–Whitney U test, $p = 0.0495$).

A risk score encompassing clinical findings, gastrointestinal symptoms, comorbidities and obesity was then developed. After the patients had been assigned to the newly-developed risk groups, a significant correlation with a positive GERD diagnosis was found among the groups (Kruskal–Wallis test, $p = 0.0262$) (►Table 1, ►Fig. 1). When adding obesity to the scoring table as an independent factor, an even higher rate of corresponding risk distribution among the risk groups and GERD severity categories was evident (Kruskal–Wallis test, $p = 0.0109$) (►Fig. 2). Obesity alone showed to be significantly more frequent in patients placed in higher risk categories

Table 1 Gastroesophageal reflux disease (GERD) diagnostic probability scoring tool

Upper respiratory symptoms and local findings (oropharyngoscopy and nasal fiber optic laryngoscopy)	Chronic cough Chronic throat clearing Dysphonia Halitosis Oropharyngeal redness and granulation Posterior laryngitis Vocal nodules	If present +1
Gastrointestinal symptoms	Nausea Gastric or epigastric pain Vomiting Malnourishment	If present +1
Comorbidity	Asthma Recurrent laryngitis	If present +1
Obesity	Body-mass index > 2 standard deviations above the World Health Organization growth reference median	If present +1
Score	Low GERD risk: 0/1 points Moderate GERD risk: 2 points High GERD risk: 3-4 points	Total _____

(Kruskal–Wallis test, $p < 0.0001$) (►**Fig. 3**). Finally, when analyzing the patients with gastrointestinal symptoms, it became apparent that they were more frequently allotted to higher risk groups (Kruskal–Wallis test, $p < 0.0001$) (►**Fig. 4**).

Discussion

Although a clinical entity that has been increasingly recognized in recent years, pediatric GERD and its associated symptom complex continues to pose more questions than answers. It is often connected with failure to thrive, chronic cough, dysphonia and laryngeal spasm.[8] The extra-esophageal symptom complex is often diagnosed by noting atypical laryngoscopic findings: erythema, edema, ventricular obliteration, postcricoid hyperplasia and pseudosulcus. However,
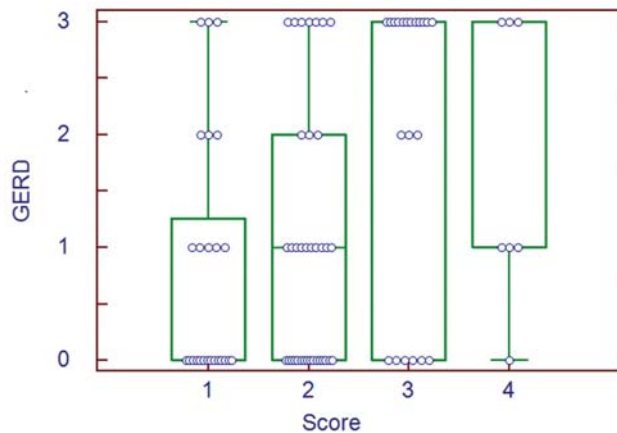

Fig. 2 Correlation between positive gastrointestinal symptoms and rising risk scores in the newly proposed screening score (Kruskal-Wallis test; $p < 0.0001$; $n = 89$).

Fig. 3 Correlation between obesity as an independent risk factor and rising risk scores in the newly proposed screening score (Kruskal-Wallis test; $p < 0.0001$; $n = 89$).

Fig. 1 Correlation between rising gastroesophageal reflux disease (GERD) grades and the newly proposed screening score (Kruskal-Wallis test; $p = 0.0109$; $n = 89$).
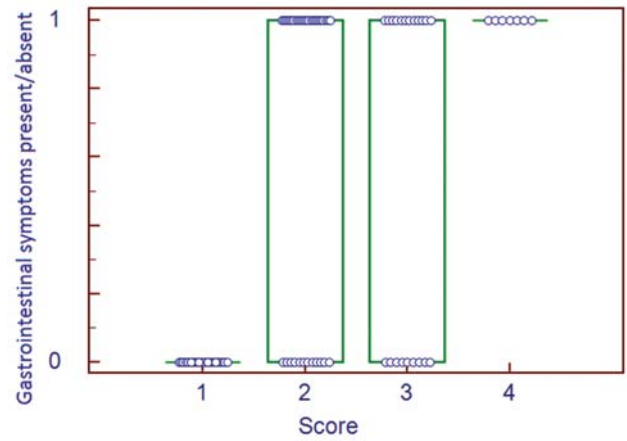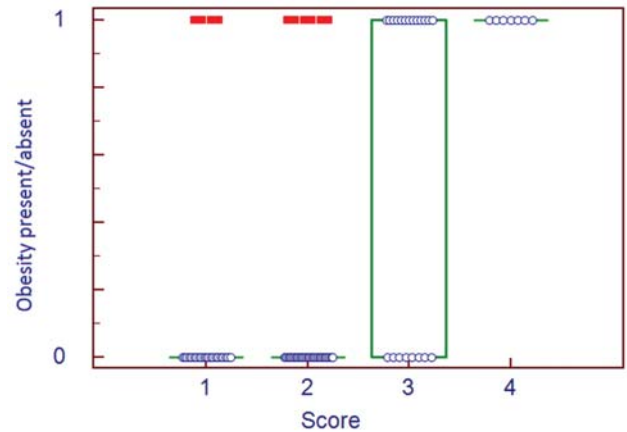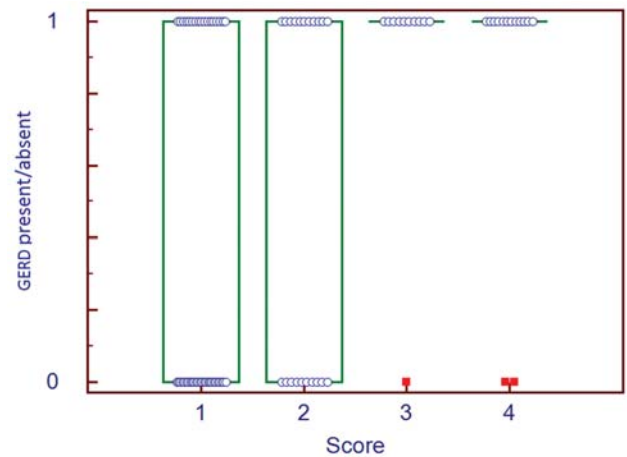

Fig. 4 Correlation between GERD diagnosis through 24-hour pH monitoring and probability scoring using the newly proposed screening score (Kruskal-Wallis test; $p = 0.0017$; $n = 89$).

these findings are also common in healthy volunteers, and this largely limits their diagnostic value.[9] Gastroesophageal reflux disease is considered an important factor in perpetuating laryngeal inflammation.[10] Few studies shed light on the characteristics of reflux episodes and adjoining gastrointestinal symptoms in those patients. Numerous controversies encompass the clinical manifestations, diagnostics, interpretation of findings and treatment.[11,12] This is even more of a challenge when considering that the most frequent deviation from the NASPGHAN/ESPGHAN recommendations are diagnostic modalities for GERD. According to a recent study,[13] the vast majority of pediatricians do not perform specific testing and diagnose solely based on patient history-taking, even in young children and infants. A study[14] surveyed North American pediatric health care providers in 2007 and found that 31% of them diagnosed GERD without performing specific testing, irrespective of age. A study[15] performed in 2012 found a similar attitude among 59% of the surveyed French pediatricians. Even when extra-esophageal manifestations have been suspected based on 24-hour dual-probe esophageal pH monitoring results, it may still be inaccurate, since its sensitivity is low and the incidence of false-negative results is as high as 25% to 50%.[16–18] The limitations of diagnosing GERD solely based on patient symptoms, without the 24-hour esophageal pH testing, remain a major hindrance in achieving a timely diagnosis and subsequent symptom control.[19] In addition, many GERD patients present with atypical symptoms.[20] Most frequently, respiratory symptoms are present but difficult to describe objectively. A variety of otorhinolaryngologic symptoms may be identified, with a suggested correlation with asthma.[21] Our study diagnosed 50 out of 52 GERD patients (total cohort: $n = 89$) with PLPR through 24-hour esophageal probe pH monitoring. Esophageal probe pH monitoring was performed in all of the patients because they were referred to our institution by pediatric gastroenterologists who had previously suspected a possible GERD/PLPR diagnosis. In 42 out of 89 patients, the following was noted: epigastric pain (15/89), nausea (14/89), regurgitation (10/89), and acid aftertaste in the oral cavity (3/89) (►Fig. 1). Patients with asthma and chronic cough (48/89) showed a noted propensity for higher GERD levels. Out of 50 patients with a positive GERD diagnosis, 25 had reported gastrointestinal symptoms. Boys tended to have more advanced GERD levels, according to 24-hour esophageal pH monitoring results, but accounted for only 1/3 of the patients. All of the patients had respiratory symptoms at the initial evaluation, with the most frequent being an injected and granulated oropharynx accompanied by posterior laryngitis (54/89). To date, very few studies have correlated the clinical presentation in PLPR and GERD and the diagnostic accuracy by objective testing. Most published studies favor fiber-optic laryngoscopy as a method of upper-airway clinical assessment, but few attempts have been made to create a structured risk score using available respiratory and gastrointestinal findings, especially in the pediatric population.[10,11,17,18] The results of our study, as well as those of previously published studies, show that the diagnosis confirmation rate can be improved without subjecting the patient to unnecessary testing.[22]

With the help of data gathered in our study, patient symptoms and factors that have been correlated to extra-esophageal symptoms in our patient cohort were used to develop a risk score to reduce unnecessary testing and help administer proper and cost-effective treatment[23] (►Table 1). When allocating the patients into risk groups, four major criteria were used; respiratory symptoms and findings (otorhinolaryngologist evaluation); gastrointestinal symptoms (gastroenterologist evaluation); respiratory comorbidity (asthma or recurrent laryngitis); and presence of obesity. The otorhinolaryngologist noted the presence of chronic cough, throat clearing, dysphonia, halitosis, oropharyngeal redness and granulation, posterior laryngitis or vocal nodules. The gastroenterologist noted the presence of nausea, gastric or epigastric pain, vomiting or malnourishment. Respiratory comorbidity was also noted by either examiner, mainly asthma or recurrent laryngitis. Obesity was factored in if the patient's BMI exceeded 2 SDs above the WHO growth reference median.[24] Every group (gastrointestinal symptoms, respiratory symptoms, comorbidity and obesity) scored one point or zero points, and depending on the cumulative score (0–4), the diagnosis of GERD was considered (►Table 1). If at least one positive symptom from the symptom group was present, a point was added. In the end, the patients were divided into 3 risk groups: patients that had a high probability score for GERD (3–4 points); patients that had a moderate probability score for GERD (2 points); and patients that had a low probability score for GERD (0–1 point). The risk score showed that in our appropriate patient groups, 25 patients had a low risk for GERD, 36 had a moderate risk, and 28 had a high risk for GERD. The patient groups showed significant correlation with a positive GERD diagnosis, with obesity as an independent factor that improved scoring reliability (Kruskal–Wallis test, $p = 0.0109$) (►Figs. 1, 2, 3). A strong correlation is shown with GERD grading as well, which confirms that the scoring system functions well for GERD risk stratification (Kruskal–Wallis test, $p = 0.0020$). (►Fig. 2) A one-sheet score based on additive categories encompassing all of the benchmarks of the initial patient evaluation ensures a helpful assessment of the GERD risk, and could prove useful in the everyday clinical setting. The management of GERD in children includes lifestyle changes, pharmacologic therapy, and surgery. Among the pharmacologic agents, proton pump inhibitors (PPIs) are confirmed superior to histamine-2 receptor antagonists (H2RAs) to heal erosive esophagitis and relieve symptoms; however, the dramatic increase in the patterns of prescription of PPIs during the past several years has raised concerns related to their appropriate use and associated cost.[25] Proton pump inhibitors were administered to all of the patients diagnosed with moderate and severe GERD by 24-hour double-probe pH monitoring in our study, with favorable follow-up results. The treatment seems to demonstrate symptom reduction as well as improvements in the concomitant diseases, such as PLPR.

Conclusions

Extra-esophageal symptoms should always be considered when dealing with GERD as a chronic disease with a variety

of presentations. The present study investigated the relationships between clinical symptoms and objective findings, and it stress the need for a comprehensive appraisal of both gastrointestinal and respiratory symptoms in the everyday clinical practice.

Conflict of Interests
The authors have no conflict of interests to declare.

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